Oesophageal and Gastric Cancer:

optimising care and outcomes in changing clinical practice

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Omslag:
Op de voorkant van dit proefschrift staat een slokdarm en een maag afgebeeld omringd door kersenbloesems. Kersenbloesem wordt beschouwd als het begin van de lente, maar het is ook een metafoor voor het leven: mooi, maar vergankelijk. Kersenbloesem is vooral populair in Japan, één van de landen waar maagkanker veel voorkomt.

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Contents

Chapter 1

Introduction

Introduction

Cancer is a major burden of disease worldwide. Every year, over 10 million people are diagnosed with cancer around the world and more than half of them eventually die from it.[1] As prevention and treatment of cardiovascular diseases improved, cancer became the number one killer in Europe and is on its way to become the number one killer in the United States and many other parts of the world.[2-5] As cancer is primarily a disease of the elderly and population aging continues in many countries due to increasing life expectancy, cancer will evolve to be the major health problem around the globe.[6]

Epidemiology of oesophageal and gastric cancer

Oesophageal and gastric cancer are in the top-10 most common cancers worldwide as well as in the top-10 causes of cancer-related death.[1] In the Netherlands, the incidence of oesophageal cancer is increasing while the incidence of gastric cancer is decreasing (Figure 1). Oesophageal cancer is currently the 8th most common cancer among males in the Netherlands. In 2016, 2800 patients were diagnosed with oesophageal or cardia cancer and 1250 patients were diagnosed with non-cardia gastric cancer.[7] Both remain devastating diseases with a 5-year overall survival rate of only 19%-25% in non-metastatic oesophageal cancer and 20-31% in non-metastatic gastric cancer.[8,9] Among patients with metastatic disease, more than half of the patients die within 7 months after diagnosis.[10,11]

Patients with oesophageal or gastric cancer are predominantly male and are of old age. At time of diagnosis, oesophageal cancer patients are on average 68, and gastric cancer patients 73 years old (Figure 2).[7] Due to the high age at diagnosis, a large proportion of the patients suffer from comorbidities. Two-third of the patients with oesophageal and gastric cancer has at least one comorbid condition.[12,13] The most common concomitant diseases are cardiovascular diseases and hypertension followed by chronic obstructive pulmonary disease and diabetes.[12]

The majority of malignant oesophageal tumours can be subdivided in two histological groups, i.e. squamous cell carcinoma and adenocarcinoma. Squamous cell carcinoma is predominantly seen in the proximal oesophagus, while adenocarcinoma develops mainly in the distal part of the oesophagus. Globally, squamous cell carcinoma is the predominant histologic subtype with the highest burden in Asia and Africa, while in the Western world, including the Netherlands, oesophageal adenocarcinoma is more common.[14] The incidence of oesophageal adenocarcinoma rapidly increased the last decennia in the Netherlands as well as in several other Western countries. As a result the incidence gap between oesophageal adenocarcinoma and oesophageal squamous cell carcinoma has widened (Figure 3).[15-17] Tobacco use and alcohol consumption are the most important risk factors for squamous cell carcinoma.[16] While the most important risk factors for oesophageal adenocarcinoma are obesity and gastro-oesophageal reflux disease.[16] A long-standing gastro-oesophageal reflux disease is a primary risk factor for the development of Barrett's oesophagus, which is linked to an even higher risk to develop oesophageal adenocarcinoma.[16]

A Barrett's oesophagus is currently the only known precursor for oesophageal adenocarcinoma.[16] In Barrett's oesophagus the squamous mucosa of the oesophagus is replaced by columnar epithelium (intestinal metaplasia), and oesophageal endoscopy shows

a displacement cranially of salmon coloured mucosa into the oesophagus. Barrett's epithelium can progress from non-dysplastic to low-grade dysplasia, to high-grade dysplasia and ultimately result in oesophageal adenocarcinoma.[18] However, yearly only 0.4% of the Barrett's oesophagus patients will progress to oesophageal adenocarcinoma.[19-21] Endoscopic surveillance is currently recommended in long-segment Barrett's oesophagus patients to reduce morbidity and mortality through early detection of dysplasia and cancer.[22] A contributing problem for the optimal management of Barrett's oesophagus surveillance is the occurrence of 'interval' and 'missed' cancers. One study in this thesis focusses on the risk of 'missed' (pre)cancerous lesions at index endoscopy among patients with a Barrett's oesophagus.

As shown in figure 1, the incidence of gastric cancer has been declining in Western countries, especially for non-cardia gastric cancer, probably due to the replacement of refrigerators instead of salt-preserved foods, a higher intake of fruit and vegetables and a lower prevalence of the Helicobacter pylori infection.[8,23-26] Helicobacter pylori is reported to be a risk factor for gastric cancer.[27] The prevalence of Helicobacter pylori has declined due to improved sanitation and eradication therapy. It causes the formation of precancerous lesions. By contrast, Helicobacter pylori infection is associated with a reduced risk of a Barrett's oesophagus and oesophageal adenocarcinoma.[28,29] The decreasing seropositivity for Helicobacter pylori might have contributed to the rising incidence of oesophageal adenocarcinoma.[28,29]

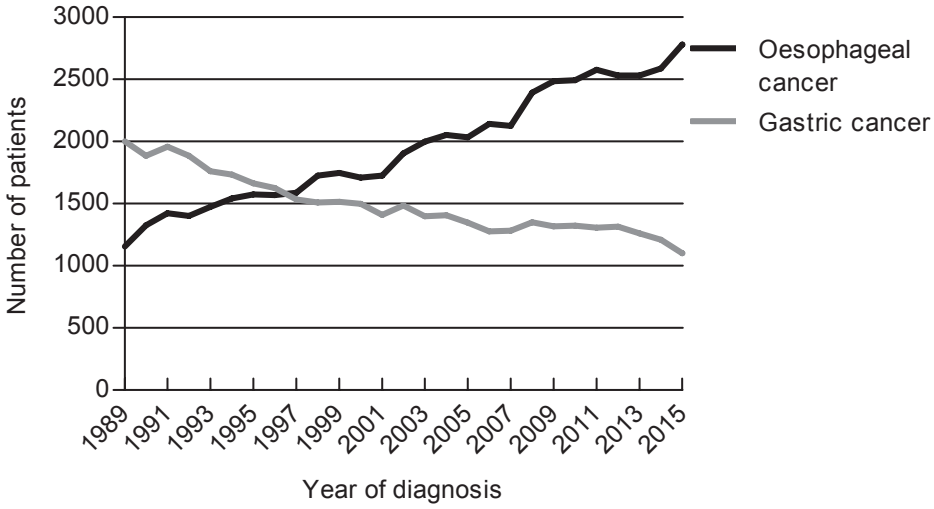

Figure 1 Absolute incidence of oesophageal and gastric cancer in the Netherlands by year of diagnosis. Source: Netherlands Cancer Registry. The numbers for 2016 are based on estimations.

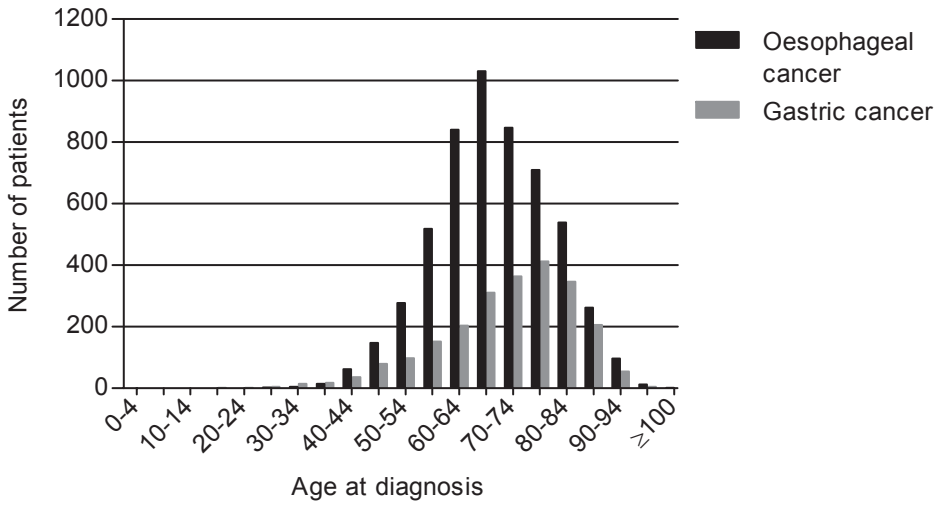

Figure 2 Age at diagnosis of patients with oesophageal and gastric cancer diagnosed in the Netherlands in 2014-2015 (n=5341 and n=2298, respectively). Source: Netherlands Cancer Registry.

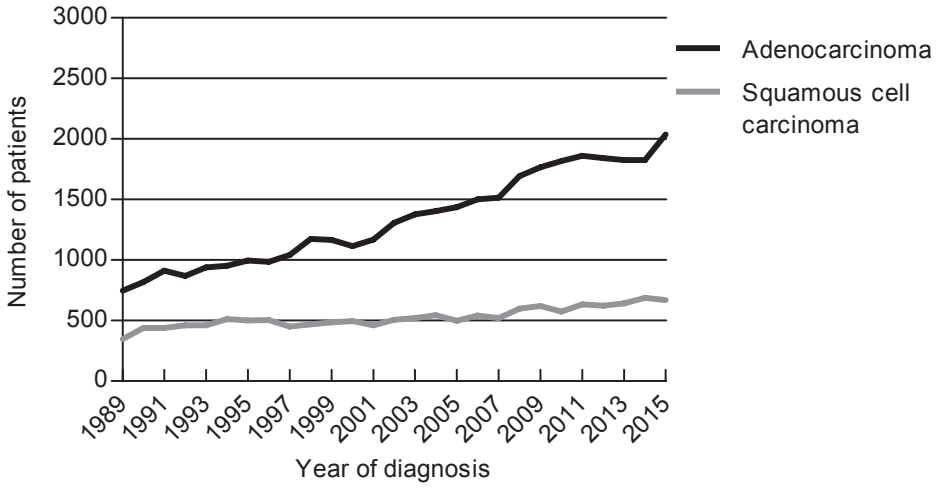

Figure 3 Incidence of oesophageal cancer in the Netherlands by year of diagnosis and morphology. Source: Netherlands Cancer Registry.

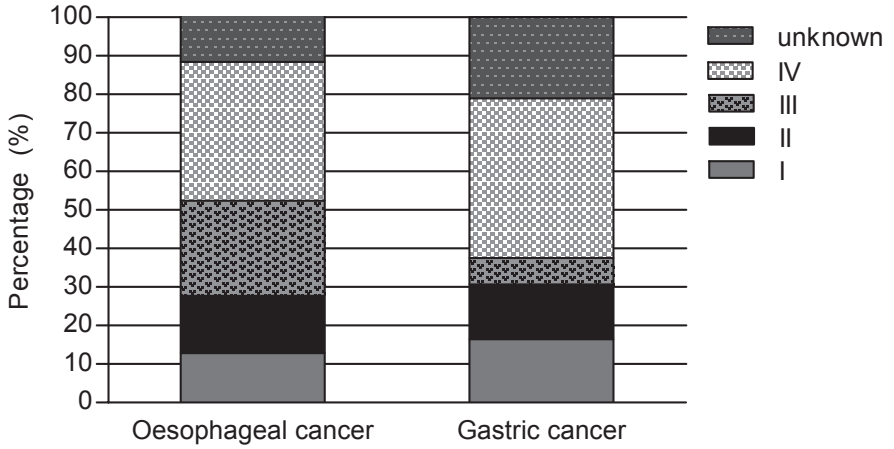

Figure 4 Clinical tumour stage distribution for patients with oesophageal and gastric cancer in the Netherlands in the period 2014-2015. Source: Netherlands Cancer Registry.

Treatment of oesophageal and gastric cancer

Oesophageal and gastric cancer are challenging diseases to treat. About 40% of the patients with oesophageal and gastric cancer has systemic disease at time of diagnosis (Figure 4), leaving palliative chemo(radio)therapy, stents and best supportive care as the main choice of treatment . According to the Dutch clinical practice guideline for gastric cancer, a palliative gastrectomy to improve quality of life and/or survival may be considered for metastatic gastric cancer patients younger than 70 years with one item of incurability- either distant metastasis or tumour infiltrating surrounding organs.[30] However, the effects of palliative gastrectomy on survival and quality of life remains unclear.[31,32]

Furthermore, most patients who are eligible for curative treatment have locally advanced, lymph node positive disease which requires a combination of surgery and chemo(radio)therapy. Moreover, patients may be unfit for surgery because of fragility, severe comorbidity or a poor nutritional status. Definitive chemoradiotherapy is increasingly considered as a well-tolerated alternative for surgery in inoperable oesophageal cancer patients and especially in irresectable cervical oesophageal cancer.[33] An endoscopic mucosal resection is the preferred treatment of early stage tumours without lymph node metastasis.[34]

Even after radical surgery, many patients suffered from recurrence with consequently a poor prognosis.[35,36] Therefore, several multimodality treatment approaches have been proposed and studied in the late 1990s and 2000s. As a result of these trials, preoperative chemoradiotherapy followed by surgery is currently the preferred treatment for locally advanced oesophageal cancer and perioperative chemotherapy is the preferred treatment for locally advanced gastric cancer in the Netherlands.[37-39] Both treatment regimes have been shown to improve radicality, reduce local recurrence and increase survival.

Over the last decade, more and more patients are treated by multimodality treatment approaches, including different combinations of endoscopic treatment, chemotherapy,

radiotherapy and surgery. However, the efficacy and tolerability of various treatment modalities varies from patient to patient in daily clinical practice. Therefore, it is highly desirable to move from a one-size-fits all approach to a more tailored treatment approach for the individual patient. Evaluating the results of treatment on outcome among subgroups of patients based on patients and tumour characteristics can identify patients who might benefit from a particular treatment approach. Moreover, it can avoid unnecessary mortality or morbidity in patients who have little or no benefit from that particular treatment. Several studies in this thesis focus on aspects of this multimodality approach in order to improve the quality of care for patients with oesophageal and gastric cancer, by investigating patterns of care and outcomes among specific patient groups.

Centralisation of surgery and hospital of diagnosis

Surgery is the cornerstone of curative treatment for oesophageal and gastric cancer. However, both oesophagectomy and gastrectomy are high-risk surgical procedures associated with high postoperative morbidity and mortality rates. Due to the relatively low incidence, procedures used to be mainly performed in multiple low-volume hospitals.[13,37,40] Over the last two decades, a large number of studies observed that increasing hospital volume is associated with lower postoperative mortality and higher survival rates in the Western world and Asia.[41-45] Therefore, centralisation has been initiated in several European countries including the Netherlands. As of 2006, hospitals should perform a minimum of 10 oesophageal resections per year, and since 2011 the minimal volume increased to 20 oesophageal resections per year in the Netherlands. Centralisation of gastric cancer surgery started somewhat later in the Netherlands. As of 2012 a yearly minimum of 10 gastric resections was implemented and since 2013 this minimal volume increased to 20 gastric resections per year. One study in this thesis investigates the impact of centralisation for gastric cancer surgery on patients outcomes.

Although surgery for oesophageal and gastric cancer is nowadays centralised, the initial decision which treatment modality to perform, including the decision whether or not to refer patients for potential curative treatment, is made in all Dutch hospitals. Therefore, two studies in this thesis focus on the impact of the hospital diagnosis on the probability to undergo curative treatment for oesophageal and gastric cancer. Furthermore, the impact of variation in curative treatment among these hospitals of diagnosis on survival was investigated.

Data source

Netherlands Cancer Registry

The research presented in this thesis was mainly based on the data from the Netherlands Cancer Registry. The registration of cancer in the Netherlands started in 1955 and comprised data of three hospitals located in Eindhoven. Data on all new cancer patients were collected directly from pathology reports and medical records. The area gradually expanded and from 1986 on it covers the entire province Noord-Brabant and the northern part of Limburg, an area of 2.4 million inhabitants with 10 community hospitals and two radiotherapy institutions served by six regional pathology laboratories.

Since 1989 the entire Dutch population was covered by nine regional registries, together establishing the Netherlands Cancer registry, managed by nine regional Comprehensive Cancer Centres. In the period 2011-2014 the regional centres merged into the Netherlands Comprehensive Cancer Organisation (IKNL), which now maintains the Netherlands Cancer Registry. The uptake of data in this database is performed by specially trained data managers of IKNL. The Netherlands Cancer Registry is based on notification of all newly diagnosed malignancies in the Netherlands by the national automated pathological archive, PALGA. Additional sources are the national registry hospital discharge and radiotherapy institutions. Information is registered about diagnosis, tumour stage and treatment from the medical records. Information on vital status is obtained through an annual linkage with the Municipal Administrative Database, in which all deceased and emigrated persons in the Netherlands are registered. The municipal registries provide virtually complete coverage of all deceased citizens of the Netherlands.

Outline of this thesis

The studies presented in this thesis focus on important changes and challenges in diagnosis and treatment of oesophageal and gastric cancer.

The main objectives of the studies described in this thesis were:

1. To investigate patterns of care for patients with a Barrett's oesophagus, with an emphasis on the quality of surveillance endoscopy.
2. The examine the influence of the hospital of diagnosis on the probability to receive curative treatment and its impact on survival among patients with oesophageal and gastric cancer.
3. To investigate the effects of centralisation of surgery on survival among patients with gastric cancer.
4. To study the patterns of care and its impact on survival for specific groups of patients with oesophageal and gastric cancer in a large population-based setting.

References

1. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012, 2015. Int J Cancer;136:E359-386.
2. Weir HK, Anderson RN, Coleman King SM, Soman A, Thompson TD, Hong Y, Moller B, Leadbetter S. Heart Disease and Cancer Deaths - Trends and Projections in the United States, 1969-2020, 2016. Prev Chronic Dis;13:E157.
3. Wilson L, Bhatnagar P, Townsend N. Comparing trends in mortality from cardiovascular disease and cancer in the United Kingdom, 1983-2013: joinpoint regression analysis, 2017. Popul Health Metr;15:23.
4. Pereira M, Peleteiro B, Capewell S, Bennett K, Azevedo A, Lunet N. Changing patterns of cardiovascular diseases and cancer mortality in Portugal, 1980-2010, 2012. BMC Public Health;12:1126.
5. Volksgezondheidenzorg.info, 2017. Sterfte naar doodsoorzaak in Nederland. RIVM, www.volksgezondheidenzorg.info. Accessed on: 24-10-2017.
6. Signaleringscomissie Kanker van KWF Kankerbestrijding. Kanker in Nederland tot 2020, Trends en prognoses, 2011ed. Oisterwijk: VBD Almedeon BV.
7. Cijfers over kanker., Netherlands Cancer Registry. www.cijfersoverkanker.nl. Accessed on: 1-3-2017.
8. Dassen AE, Dikken JL, Bosscha K, Wouters MW, Cats A, van de Velde CJ, Coebergh JW, Lemmens VE. Gastric cancer: decreasing incidence but stable survival in the Netherlands, 2014. Acta Oncol;53:138-142.
9. Dikken JL, Lemmens VE, Wouters MW, Wijnhoven BP, Siersema PD, Nieuwenhuijzen GA, van Sandick JW, Cats A, Verheij M, Coebergh JW, van de Velde CJ. Increased incidence and survival for oesophageal cancer but not for gastric cardia cancer in the Netherlands, 2012. Eur J Cancer;48:1624-1632.
10. Bernards N, Creemers GJ, Nieuwenhuijzen GA, Bosscha K, Pruijt JF, Lemmens VE. No improvement in median survival for patients with metastatic gastric cancer despite increased use of chemotherapy, 2013. Ann Oncol;24:3056-3060.
11. Bernards N, Haj Mohammad N, Creemers GJ, Rozema T, Roukema JA, Nieuwenhuijzen GA, van Laarhoven HW, van der Sangen M, Lemmens VE. Improvement in survival for patients with synchronous metastatic esophageal cancer in the south of the Netherlands from 1994 to 2013, 2016. Acta Oncol;55:1161-1167.
12. Koppert LB, Lemmens VE, Coebergh JW, Steyerberg EW, Wijnhoven BP, Tilanus HW, Janssen-Heijnen ML. Impact of age and co-morbidity on surgical resection rate and survival in patients with oesophageal and gastric cancer, 2012. Br J Surg;99:1693-1700.
13. van Gestel YR, Lemmens VE, de Hingh IH, Steevens J, Rutten HJ, Nieuwenhuijzen GA, van Dam RM, Siersema PD. Influence of comorbidity and age on 1-, 2-, and 3-month postoperative mortality rates in gastrointestinal cancer patients, 2013. Ann Surg Oncol;20:371-380.
14. Arnold M, Soerjomataram I, Ferlay J, Forman D. Global incidence of oesophageal cancer by histological subtype in 2012, 2015. Gut;64:381-387.
15. Pohl H, Sirovich B, Welch HG. Esophageal adenocarcinoma incidence: are we reaching the peak?, 2010. Cancer Epidemiol Biomarkers Prev;19:1468-1470.
16. Pennathur A, Gibson MK, Jobe BA, Luketich JD. Oesophageal carcinoma, 2013. Lancet;381:400-412.
17. Arnold M, Laversanne M, Brown LM, Devesa SS, Bray F. Predicting the Future Burden of Esophageal Cancer by Histological Subtype: International Trends in Incidence up to 2030, 2017. Am J Gastroenterol.
18. Splittgerber M, Velanovich V. Barrett esophagus, 2015. Surg Clin North Am;95:593-604.
19. Coleman HG, Bhat S, Murray LJ, McManus D, Gavin AT, Johnston BT. Increasing incidence of Barrett's oesophagus: a population-based study, 2011. Eur J Epidemiol;26:739-745.

20. Bhat S, Coleman HG, Yousef F, Johnston BT, McManus DT, Gavin AT, Murray LJ. Risk of malignant progression in Barrett's esophagus patients: results from a large population-based study, 2011. J Natl Cancer Inst;103:1049-1057.
21. Hvid-Jensen F, Pedersen L, Drewes AM, Sorensen HT, Funch-Jensen P. Incidence of adenocarcinoma among patients with Barrett's esophagus, 2011. N Engl J Med;365:1375-1383.
22. Fitzgerald RC, di Pietro M, Ragunath K, Ang Y, Kang JY, Watson P, Trudgill N, Patel P, Kaye PV, Sanders S, O'Donovan M, Bird-Lieberman E, Bhandari P, Jankowski JA, Attwood S, Parsons SL, Loft D, Lagergren J, Moayyedi P, Lyratzopoulos G, de Caestecker J. British Society of Gastroenterology guidelines on the diagnosis and management of Barrett's oesophagus, 2014. Gut;63:7-42.
23. Fock KM. Review article: the epidemiology and prevention of gastric cancer, 2014. Aliment Pharmacol Ther;40:250-260.
24. La Vecchia C, Negri E, D'Avanzo B, Franceschi S. Electric refrigerator use and gastric cancer risk, 1990. Br J Cancer;62:136-137.
25. Hohenberger P, Gretschel S. Gastric cancer, 2003. Lancet;362:305-315.
26. Tsugane S, Sasazuki S. Diet and the risk of gastric cancer: review of epidemiological evidence, 2007. Gastric Cancer;10:75-83.
27. Brown LM. Helicobacter pylori: epidemiology and routes of transmission, 2000. Epidemiol Rev;22:283-297.
28. Thrift AP, Pandeya N, Smith KJ, Green AC, Hayward NK, Webb PM, Whiteman DC. Helicobacter pylori infection and the risks of Barrett's oesophagus: a population-based case-control study, 2012. Int J Cancer;130:2407-2416.
29. Xie FJ, Zhang YP, Zheng QQ, Jin HC, Wang FL, Chen M, Shao L, Zou DH, Yu XM, Mao WM. Helicobacter pylori infection and esophageal cancer risk: an updated meta-analysis, 2013. World J Gastroenterol;19:6098-6107.
30. Oncoline. Cancer Clinical Practice Guidelines: Gastric Carcinoma 2017. Accessed on: 3 October 2017.
31. Bonenkamp JJ, Sasako M, Hermans J, van de Velde CJ. Tumor load and surgical palliation in gastric cancer, 2001. Hepatogastroenterology;48:1219-1221.
32. Hartgrink HH, Putter H, Klein Kranenbarg E, Bonenkamp JJ, van de Velde CJ. Value of palliative resection in gastric cancer, 2002. Br J Surg;89:1438-1443.
33. Crosby TD, Brewster AE, Borley A, Perschky L, Kehagioglou P, Court J, Maughan TS. Definitive chemoradiation in patients with inoperable oesophageal carcinoma, 2004. Br J Cancer;90:70-75.
34. Richtlijn oesophaguscarcinoom 3.1 en richtlijn maagcarcinoom 2.2, www.oncoline.nl. Accessed on: July 2017.
35. Gunderson LL. Gastric cancer--patterns of relapse after surgical resection, 2002. Semin Radiat Oncol;12:150-161.
36. Müller JM, Erasmi H, Stelzner M, Zieren U, Pichlmaier H. Surgical therapy of oesophageal carcinoma, 1990. British Journal of Surgery;77:845-857.
37. Cunningham D, Allum WH, Stenning SP, Thompson JN, Van de Velde CJ, Nicolson M, Scarffe JH, Lofts FJ, Falk SJ, Iveson TJ, Smith DB, Langley RE, Verma M, Weeden S, Chua YJ, Participants MT. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer, 2006. N Engl J Med;355:11-20.
38. van Hagen P, Hulshof MC, van Lanschot JJ, Steyerberg EW, van Berge Henegouwen MI, Wijnhoven BP, Richel DJ, Nieuwenhuijzen GA, Hospers GA, Bonenkamp JJ, Cuesta MA, Blaisse RJ, Busch OR, ten Kate FJ, Creemers GJ, Punt CJ, Plukker JT, Verheul HM, Spillenaar Bilgen EJ, van Dekken H, van der Sangen MJ, Rozema T, Biermann K, Beukema JC, Piet AH, van Rij CM, Reinders JG, Tilanus HW, van der Gaast A. Preoperative chemoradiotherapy for esophageal or junctional cancer, 2012. N Engl J Med;366:2074-2084.
39. Ychou M, Boige V, Pignon JP, Conroy T, Bouche O, Lebreton G, Ducourtieux M, Bedenne L, Fabre JM, Saint-Aubert B, Geneve J, Lasser P, Rougier P. Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCD multicenter phase III trial, 2011. J Clin Oncol;29:1715-1721.
40. Dikken JL, Dassen AE, Lemmens VE, Putter H, Krijnen P, van der Geest L, Bosscha K, Verheij M, van de Velde CJ, Wouters MW. Effect of hospital volume on postoperative mortality and survival after oesophageal and gastric cancer surgery in the Netherlands between 1989 and 2009, 2012. Eur J Cancer;48:1004-1013.

41. Luft HS, Bunker JP, Enthoven AC. Should operations be regionalized? The empirical relation between surgical volume and mortality, 1979. N Engl J Med;301:1364-1369.

42. van de Poll-Franse LV, Lemmens VE, Roukema JA, Coebergh JW, Nieuwenhuijzen GA. Impact of concentration of oesophageal and gastric cardia cancer surgery on long-term population-based survival, 2011. Br J Surg;98:956-963.

43. Wouters MW, Karim-Kos HE, le Cessie S, Wijnhoven BP, Stassen LP, Steup WH, Tilanus HW, Tollenaar RA. Centralization of esophageal cancer surgery: does it improve clinical outcome?, 2009. Ann Surg Oncol;16:1789-1798.

44. Birkmeyer JD, Siewers AE, Finlayson EV, Stukel TA, Lucas FL, Batista I, Welch HG, Wennberg DE. Hospital volume and surgical mortality in the United States, 2002. N Engl J Med;346:1128-1137.

45. Coupland VH, Lagergren J, Luchtenborg M, Jack RH, Allum W, Holmberg L, Hanna GB, Pearce N, Moller H. Hospital volume, proportion resected and mortality from oesophageal and gastric cancer: a population-based study in England, 2004-2008, 2013. Gut;62:961-966.

Chapter 2

'Missed' oesophageal adenocarcinoma and high-grade dysplasia in Barrett's oesophagus patients: a large population-based study

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Abstract

Background
A systematic review suggests that 25% of oesophageal adenocarcinomas (OAC) are 'missed' at index endoscopy for Barrett's oesophagus (BO); however this included few population-based studies and may be an overestimate.

Objective
The objective of this article is to quantify the 'missed' rates of high-grade dysplasia (HGD) and OAC at index BO endoscopy.

Methods
Patients from the Northern Ireland BO register diagnosed between 1993-2010 (n=13 159) were linked to the Northern Ireland Cancer Registry to identify patients who developed OAC or HGD. Logistic regression analysis compared characteristics of 'missed' versus 'incident' HGD/OAC, defined as diagnoses within 3-12 months versus >1 year after incident BO, respectively.

Results
A total of 267 patients were diagnosed with HGD/OAC ≥3 months after BO diagnosis, of which 34 (12.7%) were potentially 'missed'. The proportion of 'missed' HGD/OAC was 25% among BO patients with low-grade dysplasia (LGD) and 9% among non-dysplastic BO patients. Older age and BO-LGD carried a higher risk of 'missed' HGD/OAC. Non-dysplastic BO patients were more often diagnosed with a 'missed' OAC (rather than HGD; 89%), compared with BO-LGD patients (40%).

Conclusions
Approximately one in 10 HGD/OAC cases are 'missed' at incident BO diagnosis, which is significant but lower than previous reports. However 'missed' HGD/OAC cases represent only 0.26% of all BO patients.

Introduction

Barrett's oesophagus (BO) is currently the only known precursor for oesophageal adenocarcinoma (OAC), which has a poor prognosis with five year survival rates between 15% and 20%.[1] Although the incidence of BO and OAC are increasing in the Western world, only approximately 0.4% of BO patients will progress to OAC each year.[2-5] This raises issues for how to manage the increasing number of patients with BO and how to identify high-risk patients, without overburdening services.

Endoscopic surveillance is recommended in BO patients to reduce morbidity and mortality through early detection of dysplasia and cancer.[6, 7] The British Society of Gastroenterology (BSG) guidelines recommends repeated endoscopy at three- to five year intervals among BO patients with a Barrett's length of under 3 cm, and repeated endoscopy at two- to three year intervals is recommended for patients with longer Barrett's segments or specialised intestinal metaplasia (SIM).[6] Patients with low-grade dysplasia (LGD) should receive surveillance endoscopy at six monthly intervals. However, as of 2015, endoscopic ablation, preferably with radiofrequency ablation (RFA), has been recommended for high-grade dysplasia (HGD) or LGD diagnosed on two occasions in addition to repeat surveillance endoscopy at six months for patients with LGD.[6] In spite of relatively intensive surveillance, the impact of these programs on preventing deaths from OAC is equivocal.[8-10] A contributing problem for the optimal management of BO surveillance is the occurrence of 'interval' and 'missed' cancers.[11, 12]

'Missed' cancers can be defined as cancers that were already present at the index BO endoscopy, but were not detected, whereas it is hypothesised that truly incident cancers develop after the index BO endoscopy.[13, 14] A recent systematic review found that amongst BO patients, 25% of patients who later developed OAC, were diagnosed within one year after index BO endoscopy, and could therefore be considered 'missed' cancers.[14] However, this review included only a few population-based studies and included diagnoses within three months after the index BO endoscopy in their definition of a 'missed' cancer. Both of these considerations are likely to have resulted in an overestimate of the magnitude of 'missed' cancers. Therefore, this study aimed to quantify the 'missed' rates of HGD and OAC at index endoscopy among patients with a BO diagnosis utilising one of the largest population-based registers of BO worldwide. We further sought to identify risk factors which may contribute to these missed cases.

Methods

BO patients

The Northern Ireland Barrett's register (NIBR) includes 13 294 patients with BO aged ≥ 16 years diagnosed between 1993 and 2010 in Northern Ireland (NI) (population of 1.8 million). Descriptions of the NIBR have been previously reported.[4] Strict criteria for BO were used, which was defined as columnar-lined epithelium of the oesophagus. Trained staff extracted information on BO length, the presence of SIM and visible BO at endoscopy, using standardised guidelines, from all pathology reports relating to oesophageal biopsies carried out in NI over this time period. The date of the earliest (index) biopsy showing BO was taken as the date of entry into the register.

Outcomes

The NIBR was matched to the Northern Ireland Cancer Registry (NICR),[15] which was used to identify BO patients who progressed to oesophageal or gastric cardia adenocarcinoma (hereafter referred to as OAC) between January 1993 and 2013 in NI. Gastric cardia adenocarcinoma was also included as an outcome because it is likely that these tumours in BO patients are oesophageal in origin. This process has been described previously.[3] Histologically unspecified cancers were reviewed by a gastrointestinal pathologist. Oesophageal squamous cell carcinomas were excluded. Deaths were identified through matching to the NI Registrar General's Office. Matching of BO patients diagnosed after 2005 with the NICR was performed by using the unique Health and Social Care Number, which is available for over 90% of patients. The remaining patients and patients diagnosed before 2005 were matched using patients' forename, surname and date of birth.

BO patients who developed HGD were identified by examining all oesophageal pathology reports from NI for the period 1993-2013. Patients were considered to have HGD if diagnosed twice within one year or in two subsequent biopsies, even if the duration between them was more than one year, or if HGD was present in a single biopsy and the duration of available follow-up after the development of HGD was less than one year. HGD which occurred in squamous epithelium was not included as an outcome. According to the Central Committee on Research involving Human Subjects (CCMO), this type of study does not require approval from an ethics committee.

Statistical analysis

The primary outcome was 'missed' OAC and HGD after a BO diagnosis. Patients with HGD/OAC were divided in two categories: 'missed' and incident cases. In line with previous studies, 'missed' HGD/OAC was defined as diagnoses within 3-12 months after the index BO biopsy. An outcome less than three months after index BO could be part of the diagnostic work-up instead of 'missed' and therefore these patients were excluded from the analysis (n=187).[13, 16] Incident HGD/OAC was defined as being diagnosed at least one year after index BO biopsy. Follow-up was defined from the first BO diagnosis until first HGD or OAC diagnosis and was available until 31 December 2013.

Data were analysed for the combined outcome of HGD and OAC, and for OAC only. Chi-squared tests and analysis of variance (ANOVA) were used to compare categorical and continuous variables, respectively, between patients diagnosed 3-12 months, one to three year and more than three year following BO diagnosis. Univariable and multivariable logistic regression were used to examine factors associated with being diagnosed within 3-12 months after a BO diagnosis versus being diagnosed later than one year after BO diagnosis.

Two analyses were performed among a selected group of BO patients. First, restriction was applied to the analysis to examine differences in the proportion of 'missed' HGD/OAC cases in the period 1993-2001 and 2002-2010. Patients who progressed more than three years after BO diagnosis were excluded from this particular analysis as the maximum time of follow-up was three years for patients diagnosed with BO in 2010. Second, restriction was applied to the analysis to investigate tumour stage according to time between BO diagnosis and HGD/OAC diagnosis. As tumour stage was less accurately registered for BO patients who progressed

to OAC before 2002, only patients diagnosed with BO as of 2002 were included. A secondary analysis compared median survival time between all 'missed' and incident OAC patients for whom survival time was defined from OAC diagnosis until death or until 9 December 2016, whichever occurred earlier. Statistical analyses were conducted using Intercooled STATA V11.0.

Results

Proportion of 'missed' HGD/OAC cases

During the study period, n=267 patients developed HGD/OAC after three months of follow-up, of whom n=34 patients (12.7%) were diagnosed within 3-12 months after BO diagnosis (Table 1). The proportion of HGD/OAC classified as 'missed' was reduced in non-dysplastic BO (9%), whereas a higher proportion was observed in BO-LGD (25%). When restricting analysis to OAC progressors only, n=210 patients developed OAC after three months of follow-up, of whom n=26 patients (12%) were diagnosed within 3-12 months after BO diagnosis (Appendix 1). The distribution of HGD/OAC diagnoses over time is shown in Figures 1 and 2. Figure 1 shows that approximately half of HGD/OAC progressors were diagnosed more than 5 years after their first BO biopsy. Furthermore, the proportion of non-dysplastic BO patients increases, and the proportion of LGD-BO patients decreases with increasing follow-up years after first BO biopsy among patients who progressed in HGD/OAC (Figure 2).

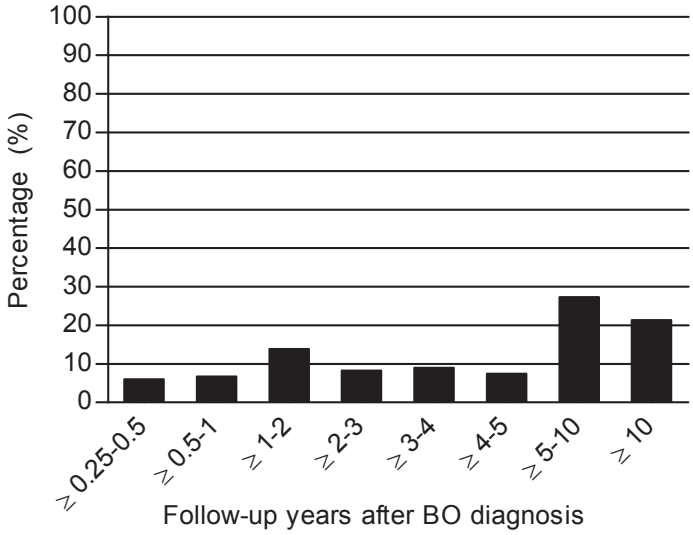

Figure 1 Distribution of time to HGD/OAC diagnosis among 267 detected cases of HGD/OAC.
BO: Barrett's oesophagus; HGD: high-grade dysplasia; OAC: oesophageal adenocarcinoma

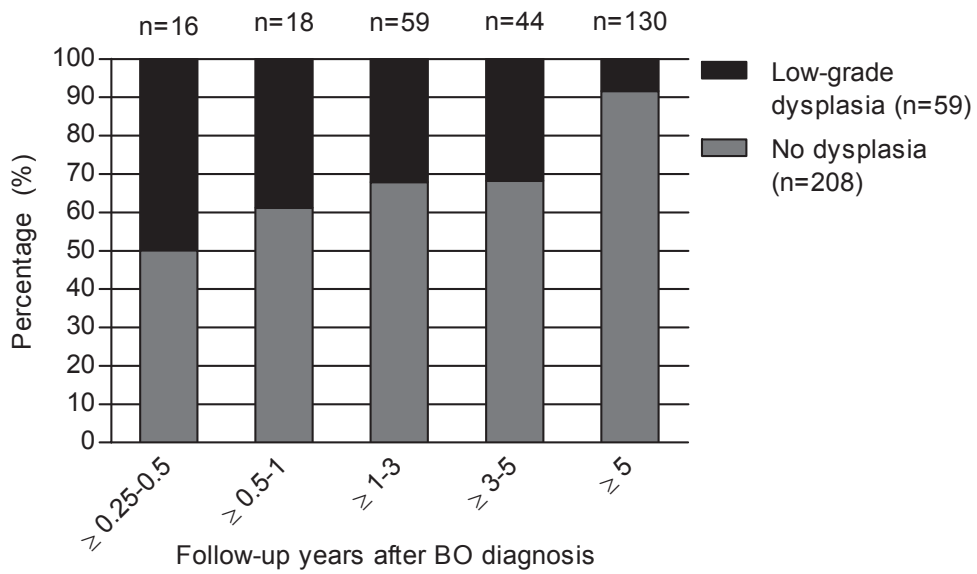

Figure 2 Dysplasia status at BO diagnosis by time to HGD/OAC diagnosis among 267 detected cases of HGD/OAC.
BO: Barrett's oesophagus; HGD: high-grade dysplasia; OAC: oesophageal adenocarcinoma

Clinical factors associated with risk of 'missed' versus incident HGD/OAC

Patients with a 'missed' HGD/OAC were significantly older compared to patients diagnosed after three years with HGD/OAC (median age of 66.9 vs 60.1 years; Table 1). Approximately a quarter of the patients who were 75 years or older and progressed to HGD/OAC progressed within 3-12 months after a BO diagnosis, whereas only 9% of progressors younger than 65 years did so (*P*=0.008; Table 1). In multivariable analysis, patients aged ≥75 v. <65 years still had higher odds of a 'missed' compared with incident HGD/OAC (odds ratio (OR)= 2.78 95% confidence interval (CI) 1.02-7.61). Overall, sex, SIM, length of Barrett's segment, visible segment seen at index endoscopy and socioeconomic status were not associated with risk of a 'missed' compared with incident HGD/OAC (Table 2). Similar findings were observed when restricted to OAC progressors only (data not shown).

Patients with LGD had 3.5-fold higher odds of being diagnosed within 3-12 months rather than incident HGD/OAC compared to non-dysplastic BO patients (OR=3.48 95%CI 1.56-7.76; Table 2). LGD or non-dysplastic status also influenced the severity of HGD/OAC detected within 'missed' cases. Among the BO-LGD patients, 40% developed HGD and 60% developed OAC. In contrast, within the non-dysplastic BO patients who developed a 'missed' HGD/OAC, only 11% had HGD detected and the majority (89%) had OAC detected (Figure 3).

Table 1 Characteristics of patients with a Barrett's oesophagus (BO) who progressed to HGD/ OAC after three months after a Barrett's diagnosis (n=267)

Features at index BO endoscopy [b]	HGD/OAC progressors ≥ 3-12 months n=34 (13%)		HGD/OAC progressors within ≥ 1-3 year n=59 (22%)		HGD/OAC progressors ≥ 3 years n=174 (65%)		
	n	%[c]	n	%[c]	n	%[c]	*P* value
Sex							0.601
Female	8	11.76	18	26.47	42	61.76	
Male	26	13.07	41	20.60	132	66.33	
Median age(IQR)	66.9	60.7-75.3	65.2	56.7-73.7	60.1	52.3-68.3	<0.001
Age group							0.008
<65	15	9.15	29	17.68	120	73.17	
65-74	10	15.38	20	30.77	35	53.85	
≥75	9	23.68	10	26.32	19	50.00	
Socio-economic status [a]							0.146
Most deprived	16	15.53	16	15.53	71	68.93	
Middle deprived	7	13.73	8	15.69	36	70.59	
Least deprived	9	9.68	29	31.18	55	59.14	
Unknown	2	10.00	6	30.00	12	60.00	
Specialised intestinal metaplasia							0.412
Absent / unknown	9	14.75	14	22.95	38	62.30	
Present	25	12.14	45	21.84	136	66.02	
Visible segment seen at endoscopy							0.843
Unknown/no	22	13.02	39	23.08	108	63.91	
Yes	12	12.24	20	20.41	66	67.17	
Dysplasia							<0.001
No dysplasia	19	9.13	40	19.23	149	71.63	
Low-grade dysplasia	15	25.42	19	32.20	25	42.37	

[a] Category 'most deprived quintile' and 'quintile 2' are merged into 'most deprived'. Category 'quintile 4' and 'Least deprived quintile' were merged into 'Least deprived'.

[b] Numbers for short, long and unknown Barrett's segment are not presented due to small cell counts (<3) and to avoid disclosure of potentially identifiable information.

[c] Percentages were calculated across the rows to emphasise the proportions of all missed or incident cancers over time, rather than calculating the percentages within the columns.

HGD: high-grade dysplasia; OAC: oesophageal adenocarcinoma; IQR: interquartile range

Proportion of missed HGD/OAC by period of BO diagnosis

We then sought to evaluate if proportions of 'missed' HGD/OAC diagnoses had changed over time. Similar proportions of HGD/OAC cases diagnosed within 3-12 months after their BO diagnosis were observed in the earlier 1993-2001 time period (36%) and the more recent 2002-2013 period (38%) (Table 3). Results indicate a higher proportion of 'missed' cases compared to main results in Table 1 due to exclusion of patients diagnosed more than three years after a BO diagnosis.

Tumour stage and survival among 'missed' versus incident OAC patients

Patients diagnosed with a 'missed' OAC were diagnosed with an earlier or unknown tumour stage compared with OAC patients diagnosed after 3 years (*P*=0·175). Among the patients with a 'missed' OAC, 33% had a stage I tumour, whereas 27% and 18% of the patients diagnosed within one to three year and after three years, respectively, had a stage I tumour (Appendix 2). Better overall survival outcomes were also observed amongst 'missed' compared with incident OAC cases (median (interquartile range (IQR) 3.96 (0.90-9.46) and 1.94 (0.44-6.12) years, respectively).

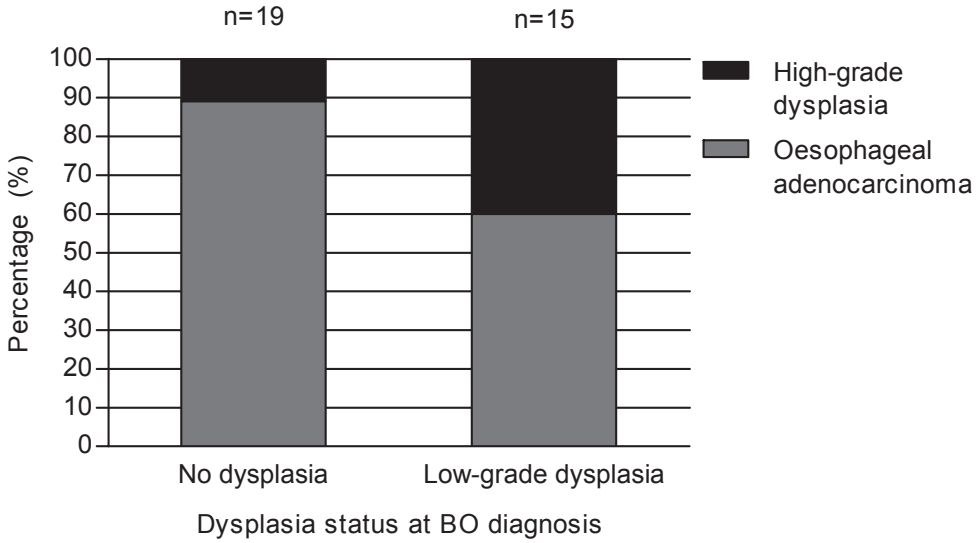

Figure 3 Progression in HGD/OAC according to dysplasia status among 34 'missed' cases of HGD/OAC.
BO: Barrett's oesophagus; HGD: high-grade dysplasia; OAC: oesophageal adenocarcinoma

Table 2 Univariable and multivariable logistic regression analysis to examine the likelihood of being diagnosed with HGD/ OAC after 3-12 months compared to ≥ 1 year after a Barrett's oesophagus diagnosis (n=267).

Features at index BO endoscopy	3-12 months	≥ 1 year	Univariable		Multivariable [b]	
	n=34	n=233	OR	95%CI	OR	95%CI
Sex						
Female	8	60	ref		ref	
Male	26	173	1.13	0.48-2.62	1.31	0.51-3.33
Age group						
<65	15	149	ref		ref	
65-74	10	55	1.81	0.77-4.26	1.90	0.77-4.67
≥75	9	29	3.08	1.23-7.71	2.78	1.02-7.61
Socio-economic status [a]						
Most deprived	16	87	ref		ref	
Middle deprived	7	44	0.87	0.33-2.26	1.10	0.39-3.06
Least deprived	9	84	0.58	0.24-1.39	0.62	0.25-1.54
Unknown	2	18	0.60	0.13-2.86	0.75	0.15-3.79
Specialised intestinal metaplasia						
Absent / unknown	9	52	ref		ref	
Present	25	181	0.80	0.35-1.82	0.76	0.31-1.83
Visible segment seen at endoscopy						
No / unknown	22	147	ref		ref	
Yes	12	86	0.93	0.44-1.98	0.97	0.42-2.27
Length of Barrett' s segment [c]						
Long ≥ 3 cm	NR	NR	0.54	0.09-3.03	0.53	0.08-3.29
Short < 3 cm	NR	NR	ref		ref	
Unknown	27	148	1.37	0.30-6.33	1.44	0.27-7.77
Dysplasia at index biopsy						
No dysplasia	19	189	ref		ref	
Low-grade dysplasia	15	44	3.39	1.60-7.20	3.48	1.56-7.76

[a] Category 'most deprived quintile' and 'quintile 2' are merged into 'most deprived'. Category 'quintile 4' and 'Least deprived quintile' were merged into 'Least deprived'. [b] Adjusted for all variables listed in table 2. [c] Numbers for short and long Barrett's segment are not presented due to small cell counts (<3) and to avoid disclosure of potentially identifiable information. HGD: high-grade dysplasia; OAC: oesophageal adenocarcinoma; NR= not reported; OR= adds ratio; CI: confidence interval

Table 3 Proportion of 'missed' HGD or OAC according to period of Barrett's (BO) diagnosis among patients who progressed in HGD or OAC within 3-36 months after their Barrett's diagnosis.[a]

	Diagnosed 3-12 months after BO diagnosis n=34	Diagnosed ≥1-3 year after BO diagnosis n=59	*P* value [b]
Period of BO diagnosis			0.835
1993-2001	20 (36%)	36 (64%)	
2002-2010	14 (38%)	23 (62%)	

[a] Patients diagnosed more than three year after a BO diagnosis were excluded from the analysis as the maximum follow-up is three year for BO patients diagnosed in 2010. [b] based on a chi-squared test. HGD: high-grade dysplasia; OAC: oesophageal adenocarcinoma

Discussion

This is one of the largest population-based studies to date to investigate the magnitude of 'missed' HGD or OAC in patients with BO. We defined a 'missed' case as being diagnosed with HGD/OAC within 3-12 months after index BO diagnosis. Results showed 'missed' rates of 13% and 9% among all BO patients and all non-dysplastic BO patients, respectively, who were subsequently diagnosed with HGD/OAC. The proportion of 'missed' cases remained stable during the study period.

The 'missed' rate reported in the present study is significant but lower than previously reported estimates. A systematic review of 24 studies reported a 'missed' rate of 25%.[14] Furthermore, three population-based studies, which were also included in the review, reported that 32-66% of the patients who progressed in OAC were diagnosed within one year after BO diagnosis.[2, 3, 17] In contrast with our study, these studies defined 'missed' as being diagnosed with HGD/OAC within one year after BO diagnosis. However, HGD/OAC patients diagnosed less than three months after BO may be part of the diagnostic work-up.[16] Chadwick et al also excluded patients diagnosed within three months after a BO diagnosis for the calculation of their 'missed' rate.[13] They found that 7.8% of the patients with OAC underwent a previous endoscopy three to 36 months preceding diagnosis of OAC, which is similar to the 'missed' rate of 9% detected in non-dysplastic BO patients in the present study. Furthermore, Holmberg et al also noted a high incidence of OAC within the first 100 days after BO diagnosis.[16] Still, it is worth noting that all of the above reported 'missed' rates after an oesophagogastroduodenoscopy are unfavourable compared with reported rates of missed colorectal cancers after a colonoscopy, which ranges from 0.5% to 6%.[18, 19]

There could be two overarching explanations for the 'missed' cancers. First, the missed cancers may be truly missed, which means that the cancer or premalignant lesions were already present at index endoscopy but not detected. A previous study has found that errors by the endoscopist account for the majority (73%) of 'missed' oesophageal or gastric cancers at endoscopy and the remaining 27% were related to errors by pathologists.[20] It is possible that HGD or OAC was not detected due to features that make them less likely to be seen by the endoscopist such as oesophagitis, oesophageal stricture and ulceration.[20] Methods to increase detection of HGD/OAC such as advanced endoscopic imaging techniques[6], greater time examining BO segments[21], greater number of targeted biopsies[20] and dedicated time slots for examination[22] may identify HGD or malignant lesions and decrease the burden of missed HGD/OAC through early detection of HGD/OAC which could increase cure and survival rates.[7, 23]

Cases may be truly missed if the second endoscopy was not part of routine surveillance. Based on a previous case note review (unpublished) among 60% of the HGD/OAC progressors, more than half of the 'missed' cases were not entered into routine surveillance and surveillance was probably performed due to new symptoms. These cases may be truly 'missed' cases. Moreover, taking into account the time interval between BO and OAC, one can suggest that the OAC cases were already present at index endoscopy. Nevertheless, the missed cases represents only 0.26% of all BO patients diagnosed in NI over this timeframe, and so the ever-important question of identifying the very small proportion of high-risk patients ('missed' or incident HGD/OAC) remains a considerable challenge.

Second, it is plausible that the missed cancers may be more aggressive cancers which have no visible evidence at index endoscopy but develop rapidly afterward. Therefore, biomarkers could assist in determining the risk of progression at BO diagnosis and guide the targeting of endoscopic surveillance.[24] Previous studies indicate that there are two main pathways of progression among BO patients: [25, 26] a more indolent pathway which moves through to dysplasia to OAC, acquiring a variety of mutations and a more aggressive pathway dominated by genomic doubling with more frequent oncogenic amplification and less frequent inactivation of tumour suppressors.[25] Results from the present study provide some support for these two pathways, as non-dysplastic BO patients were more often diagnosed with 'missed' OAC than 'missed' HGD compared to LGD patients. However, the present study has found that patients diagnosed within 3-12 months after BO diagnosis had more often a stage I or stage II tumour and a longer median survival compared to patients diagnosed more than three year after BO diagnosis. Patients with a missed OAC had a better median survival probably because they had more often an earlier tumour stage which can effectively be treated with endoscopic techniques such as endoscopic resection and RFA.

A higher 'missed' rate of 25% among LGD-BO patients likely reflects appropriate clinical management and planned surveillance after BO diagnosis. Results of the present study support the effectiveness of BSG guidelines, which recommend more frequent surveillance endoscopy among LGD-BO patients, as these patients had a higher likelihood to have HGD/OAC diagnosed within 3-12 months, compared to non-dysplastic BO patients. This conclusion is supported by the proportion of 'missed' HGD cases among all 'missed' HGD/OAC cases being higher among patients with LGD-BO compared with non-dysplastic BO (60% vs 11%). Our study timelines pre-date the recent changes to BSG guidelines[6] to allow endoscopic ablation, preferably with RFA, for LGD patients, instead of repeated endoscopy after six months of being treated with proton pump inhibitors (PPIs).[6, 27, 28]

We also explored if clinical or demographic features may differ between 'missed' or incident HGD/OAC cases. Having an older age was associated with a higher risk of a 'missed' HGD/OAC instead of an incident HGD/OAC. It is possible that simply the older you are the more likely you are to have cancer and therefore the more likely for it to be missed. However, higher rates of 'missed' cases among elderly patients may simply reflect shorter life expectancies and therefore a reduced likelihood of developing HGD/OAC three years after first BO biopsy. In addition, a previous study from Visrodia et al found that the presence of a long-segment BO could place patients at greater risk of 'missed' HGD or OAC.[29] In contrast, the length of Barrett's segment was not associated with a higher risk of a 'missed' HGD or OAC in the present study. However, information on Barrett's length was limited in our cohort.

This study has important strengths, in particular the completeness of identification of outcomes, large size and population-based analysis within a region with limited migration.[15] However, this study also has some limitations. The exclusion of patients diagnosed within three months for the definition of 'missed' cases is somewhat arbitrary. However, a previous study also excluded these patients as a diagnosis within three months after BO diagnosis could be part of the diagnostic work-up.[13] Furthermore, BO guidelines have been updated since conclusion of this study period. Within the updated BSG guidelines published in 2015, clinicians can now discharge patients from endoscopic surveillance who have a short Barrett's segment and

repeated confirmation that SIM is not present.[6] Therefore, future research may need to reassess these estimates to evaluate any impact on potential 'missed' diagnoses; however, the perceived low cancer risk in these patients is likely to have minimal influence. In addition, information about PPI use was not available. Finally, we acknowledge that the term 'missed' is somewhat controversial in the capacity of this, and similar, studies. We retained the term in this report primarily to ensure comparability with previous publications. However, we call on researchers to adopt a more appropriate term, such as underdiagnosed or short-term interval cancers, for future manuscripts.

In conclusion, based upon a large population-based study, we observed a 'missed' HGD/OAC rate of 13%, which is not negligible, but is substantially lower than rates suggested by a recent systematic review of this area.[14] Increased awareness, adequate biopsy sampling and identifying biomarkers may reduce the number of BO patients with a 'missed' oesophageal malignant or premalignant lesion. However, such efforts must be balanced in the context of 'missed' cases representing a small minority of the overall BO patient population.

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References

1. Pennathur A, Gibson MK, Jobe BA, Luketich JD. Oesophageal carcinoma, 2013. Lancet;381:400-412.
2. Hvid-Jensen F, Pedersen L, Drewes AM, Sorensen HT, Funch-Jensen P. Incidence of adenocarcinoma among patients with Barrett's esophagus, 2011. N Engl J Med;365:1375-1383.
3. Bhat S, Coleman HG, Yousef F, Johnston BT, McManus DT, Gavin AT, Murray LJ. Risk of malignant progression in Barrett's esophagus patients: results from a large population-based study, 2011. J Natl Cancer Inst;103:1049-1057.
4. Coleman HG, Bhat S, Murray LJ, McManus D, Gavin AT, Johnston BT. Increasing incidence of Barrett's oesophagus: a population-based study, 2011. Eur J Epidemiol;26:739-745.
5. Masclee GM, Coloma PM, de Wilde M, Kuipers EJ, Sturkenboom MC. The incidence of Barrett's oesophagus and oesophageal adenocarcinoma in the United Kingdom and The Netherlands is levelling off, 2014. Aliment Pharmacol Ther;39:1321-1330.
6. Fitzgerald RC, di Pietro M, Ragunath K, Ang Y, Kang JY, Watson P, Trudgill N, Patel P, Kaye PV, Sanders S, O'Donovan M, Bird-Lieberman E, Bhandari P, Jankowski JA, Attwood S, Parsons SL, Loft D, Lagergren J, Moayyedi P, Lyratzopoulos G, de Caestecker J. British Society of Gastroenterology guidelines on the diagnosis and management of Barrett's oesophagus, 2014. Gut;63:7-42.
7. Bhat SK, McManus DT, Coleman HG, Johnston BT, Cardwell CR, McMenamin U, Bannon F, Hicks B, Kennedy G, Gavin AT, Murray LJ. Oesophageal adenocarcinoma and prior diagnosis of Barrett's oesophagus: a population-based study, 2015. Gut;64:20-25.
8. Anderson LA, Murray LJ, Murphy SJ, Fitzpatrick DA, Johnston BT, Watson RG, McCarron P, Gavin AT. Mortality in Barrett's oesophagus: results from a population based study, 2003. Gut;52:1081-1084.
9. Sikkema M, de Jonge PJ, Steyerberg EW, Kuipers EJ. Risk of esophageal adenocarcinoma and mortality in patients with Barrett's esophagus: a systematic review and meta-analysis, 2010. Clin Gastroenterol Hepatol;8:235-244; quiz e232.
10. Hage M, Siersema PD, van Dekken H, Steyerberg EW, Dees J, Kuipers EJ. Oesophageal cancer incidence and mortality in patients with long-segment Barrett's oesophagus after a mean follow-up of 12.7 years, 2004. Scand J Gastroenterol;39:1175-1179.
11. Qiao Y, Hyder A, Bae SJ, Zarin W, O'Neill TJ, Marcon NE, Stein L, Thein HH. Surveillance in Patients With Barrett's Esophagus for Early Detection of Esophageal Adenocarcinoma: A Systematic Review and Meta-Analysis, 2015. Clin Transl Gastroenterol;6:e131.
12. Ramus JR, Gatenby PA, Caygill CP, Winslet MC, Watson A. Surveillance of Barrett's columnar-lined oesophagus in the UK: endoscopic intervals and frequency of detection of dysplasia, 2009. Eur J Gastroenterol Hepatol;21:636-641.
13. Chadwick G, Groene O, Hoare J, Hardwick RH, Riley S, Crosby TD, Hanna GB, Cromwell DA. A population-based, retrospective, cohort study of esophageal cancer missed at endoscopy, 2014. Endoscopy;46:553-560.
14. Visrodia K, Singh S, Krishnamoorthi R, Ahlquist DA, Wang KK, Iyer PG, Katzka DA. Magnitude of Missed Esophageal Adenocarcinoma After Barrett's Esophagus Diagnosis: A Systematic Review and Meta-analysis, 2016. Gastroenterology;150:599-607.e597.
15. Kearney TM, Donnelly C, Kelly JM, O'Callaghan EP, Fox CR, Gavin AT. Validation of the completeness and accuracy of the Northern Ireland Cancer Registry, 2015. Cancer Epidemiol;39:401-404.
16. Holmberg D, Ness-Jensen E, Mattsson F, El-Serag HB, Lagergren J. Risk of oesophageal adenocarcinoma in individuals with Barrett's oesophagus, 2017. Eur J Cancer;75:41-46.
17. de Jonge PJ, van Blankenstein M, Looman CW, Casparie MK, Meijer GA, Kuipers EJ. Risk of malignant progression in patients with Barrett's oesophagus: a Dutch nationwide cohort study, 2010. Gut;59:1030-1036.
18. Bressler B, Paszat LF, Chen Z, Rothwell DM, Vinden C, Rabeneck L. Rates of new or missed colorectal cancers after colonoscopy and their risk factors: a population-based analysis, 2007. Gastroenterology;132:96-102.
19. Ee HC, Semmens JB, Hoffman NE. Complete colonoscopy rarely misses cancer, 2002. Gastrointest Endosc;55:167-171.

20. Yalamarthi S, Witherspoon P, McCole D, Auld CD. Missed diagnoses in patients with upper gastrointestinal cancers, 2004. Endoscopy;36:874-879.

21. Gupta N, Gaddam S, Wani SB, Bansal A, Rastogi A, Sharma P. Longer inspection time is associated with increased detection of high-grade dysplasia and esophageal adenocarcinoma in Barrett's esophagus, 2012. Gastrointest Endosc;76:531-538.

22. Ooi J, Wilson P, Walker G, Blaker P, DeMartino S, O'Donohue J, Reffitt D, Lanaspre E, Chang F, Meenan J, Dunn JM. Dedicated Barrett's surveillance sessions managed by trained endoscopists improve dysplasia detection rate, 2017. Endoscopy;49:C1.

23. Beg S, Ragunath K, Wyman A, Banks M, Trudgill N, Mark Pritchard D, Riley S, Anderson J, Griffiths H, Bhandari P, Kaye P, Veitch A. Quality standards in upper gastrointestinal endoscopy: a position statement of the British Society of Gastroenterology (BSG) and Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland (AUGIS), 2017. Gut.

24. Bird-Lieberman EL, Dunn JM, Coleman HG, Lao-Sirieix P, Oukrif D, Moore CE, Varghese S, Johnston BT, Arthur K, McManus DT, Novelli MR, O'Donovan M, Cardwell CR, Lovat LB, Murray LJ, Fitzgerald RC. Population-based study reveals new risk-stratification biomarker panel for Barrett's esophagus, 2012. Gastroenterology;143:927-935.e923.

25. Stachler MD, Taylor-Weiner A, Peng S, McKenna A, Agoston AT, Odze RD, Davison JM, Nason KS, Loda M, Leshchiner I, Stewart C, Stojanov P, Seepo S, Lawrence MS, Ferrer-Torres D, Lin J, Chang AC, Gabriel SB, Lander ES, Beer DG. Paired exome analysis of Barrett's esophagus and adenocarcinoma, 2015;47:1047-1055.

26. Martinez P, Timmer MR, Lau CT, Calpe S, Sancho-Serra Mdel C, Straub D, Baker AM, Meijer SL, Kate FJ, Mallant-Hent RC, Naber AH, van Oijen AH, Baak LC, Scholten P, Bohmer CJ, Fockens P, Bergman JJ, Maley CC, Graham TA, Krishnadath KK. Dynamic clonal equilibrium and predetermined cancer risk in Barrett's oesophagus, 2016. Nat Commun;7:12158.

27. Phoa KN, van Vilsteren FG, Weusten BL, Bisschops R, Schoon EJ, Ragunath K, Fullarton G, Di Pietro M, Ravi N, Visser M, Offerhaus GJ, Seldenrijk CA, Meijer SL, ten Kate FJ, Tijssen JG, Bergman JJ. Radiofrequency ablation vs endoscopic surveillance for patients with Barrett esophagus and low-grade dysplasia: a randomized clinical trial, 2014. Jama;311:1209-1217.

28. Haidry RJ, Lipman G, Banks MR, Butt MA, Sehgal V, Graham D, Dunn JM, Gupta A, Sweis R, Miah H, Morris D, Smart HL, Bhandari P, Willert R, Fullarton G, Morris J, Di Pietro M, Gordon C, Penman I, Barr H, Patel P, Boger P, Kapoor N, Mahon B, Hoare J, Narayanasamy R, O'Toole D, Cheong E, Direkze NC, Ang Y, Veitch A, Dhar A, Nyalender D, Ragunath K, Leahy A, Fullard M, Rodriguez-Justo M, Novelli M, Lovat LB. Comparing outcome of radiofrequency ablation in Barrett's with high grade dysplasia and intramucosal carcinoma: a prospective multicenter UK registry, 2015. Endoscopy;47:980-987.

29. Visrodia K, Iyer PG, Schleck CD, Zinsmeister AR, Katzka DA. Yield of Repeat Endoscopy in Barrett's Esophagus with No Dysplasia and Low-Grade Dysplasia: A Population-Based Study, 2016. Dig Dis Sci;61:158-167.

Appendix 1 Characteristics of patients with a Barrett's oesophagus who progressed to OAC 3 months after a Barrett's diagnosis (n=210)

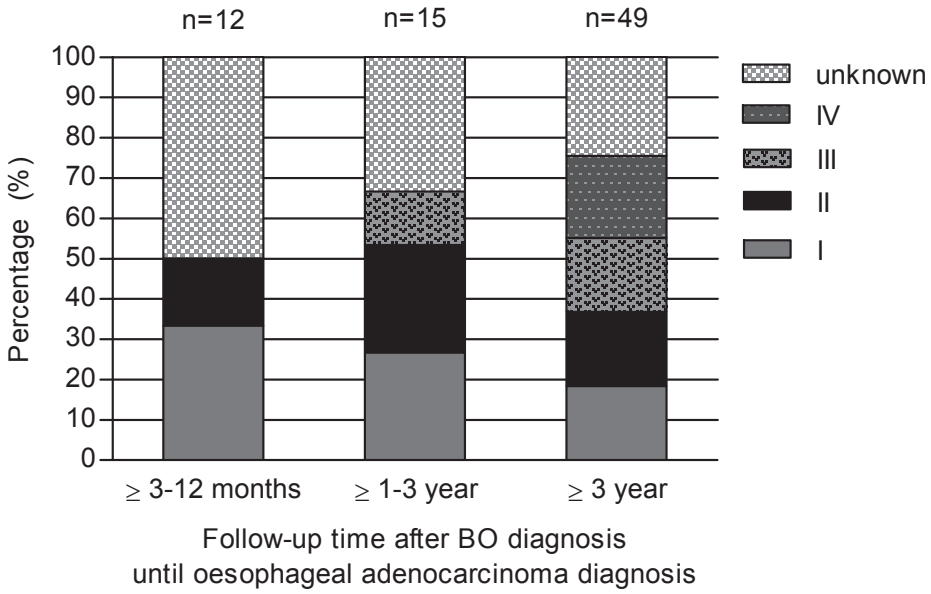
Features at index BO endoscopy *	Patients diagnosed ≥ 3-12 months n=26 (12%)		Patients diagnosed ≥ 1-3 year n=39 (19%)		Patients diagnosed ≥ 3 years n=145 (69%)		
	n	% **	n	% **	n	% **	*P* value
Sex							0.424
Female	5	9.09	13	23.64	37	67.27	
Male	21	13.55	26	16.77	108	69.68	
Median age(IQR)	68.2	60.7-79.1	68.4	58.4-74.5	60.7	52.5-69.2	0.007
Age group							0.012
<65	11	13.11	16	13.11	95	77.87	
65-74	7	12.96	15	27.78	32	59.26	
≥75	8	23.53	8	23.53	18	52.94	
Socio-economic status [a]							0.065
Most deprived	14	16.67	11	13.10	59	70.24	
Middle deprived	6	14.29	4	9.52	32	76.19	
Least deprived	5	7.04	21	29.58	45	63.38	
Unknown	1	7.69	3	23.08	9	69.23	
Specialised intestinal metaplasia							0.723
Absent/ unknown	6	12.24	11	22.45	32	65.31	
Present	20	12.42	28	17.39	113	70.19	
Visible segment seen at endoscopy							0.576
Unknown/no	17	12.50	28	20.59	91	66.91	
Yes	9	12.16	11	14.86	54	72.97	
Dysplasia							0.001
No dysplasia	17	10.24	24	14.46	125	75.30	
Low-grade dysplasia	9	20.45	15	34.09	20	45.45	

NR= not reported

[a] Category 'most deprived quintile' and 'quintile 2' are merged into 'most deprived'. Category 'quintile 4' and 'Least deprived quintile' were merged into 'Least deprived'.

* Numbers for short, long and unknown Barrett's segment are not presented due to small cell counts (<3) and to avoid disclosure of potentially identifiable information.

** Percentages were calculated across the rows as it rather suits the aim of this study than calculating the percentages within the columns.



Appendix 2 Tumour stage and time until oesophageal adenocarcinoma (OAC) diagnosis for patients with a Barrett's oesophagus diagnosed between 2002 and 2010 that progressed in OAC (n=76).
Patients diagnosed with a BO before 2002 and progressed in OAC were excluded from the analysis as their tumour stage was less accurately reported.

Chapter 3

Hospital of diagnosis influences the probability of receiving curative treatment for oesophageal cancer

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Abstract

Objective
The aim of this article was to study the influence of hospital of diagnosis on the probability of receiving curative treatment and its impact on survival among patients with oesophageal cancer.

Background
Although oesophageal cancer surgery is centralised in the Netherlands, the disease is often diagnosed in hospitals which do not perform this procedure.

Methods
Patients with potentially curable oesophageal or gastro-oesophageal junction tumours diagnosed between 2005 and 2013 who were potentially curable (cT1-3,X, any N, M0,X) were selected from the Netherlands Cancer Registry. Multilevel logistic regression was performed to examine the probability to undergo curative treatment (resection with or without neoadjuvant treatment, definitive chemoradiotherapy or local tumour excision) according to hospital of diagnosis. Effects of variation in probability of undergoing curative treatment among these hospitals on survival were investigated by Cox regression.

Results
All 13,017 patients with potentially curable oesophageal cancer, diagnosed in 91 hospitals, were included. The proportion of patients receiving curative treatment ranged from 37% to 83% and from 45% to 86% in the periods 2005-2009 and 2010-2013, respectively, depending on hospital of diagnosis. After adjustment for patient- and hospital-related characteristics these proportions ranged from 41% to 77% and from 50% to 82%, respectively (both $P<0.001$). Multivariable survival analyses showed that patients diagnosed in hospitals with a low probability of undergoing curative treatment had a worse overall survival (hazard ratio=1.13 95% confidence interval 1.06-1.20; hazard ratio=1.15; 95% confidence interval 1.07-1.24).

Conclusions
The variation in probability of undergoing potentially curative treatment for oesophageal cancer between hospitals of diagnosis and its impact on survival indicates that treatment decision-making in oesophageal cancer may be improved.

Background

Oesophageal cancer is the eighth most common cancer and the sixth leading cause of cancer-related mortality worldwide.[1] The incidence of oesophageal cancer in the Western world has risen over the past four decades and is still rising but at a slower rate than previously observed.[2,3] Although survival rates have improved during the past decade, they still remain poor with a 5-year relative survival ranging from 19%-25% for patients with M0 oesophageal cancer and a 2-year relative survival of 9% for M1oesophageal cancer.[4, 5]

Oesophagectomy with neo-adjuvant chemoradiotherapy is the most commonly used curative treatment modality for patients with locally advanced oesophageal cancer.[6, 7] Other curative treatment options include definitive chemoradiotherapy (dCRT) for non-metastasised patients with irrresectable tumours or patients who are too frail to undergo surgery [8-10], whereas endoscopic mucosal resection (EMR) is indicated for early stage oesophageal cancer (T1a-lesions).[11, 12] For oesophageal cancer patients with distant metastasis at diagnosis (40%), treatment with curative intent is no longer an option.[12] Similarly, curative treatment should be withheld when patients are too frail, have severe comorbidities or a reduced performance status.[13]

Previous nationwide studies have shown that the probability of undergoing curative treatment for gastric or pancreatic cancer is associated with hospital of diagnosis.[14, 15] Referring physicians may have several reasons to consider the patient to be unsuitable for surgery and withhold possible curative options. Furthermore, a regional Dutch study showed that among potentially curable oesophageal cancer patients the percentage of patients undergoing surgical treatment varied between 33% and 67% according to hospital of diagnosis.[16] These results were however based on data from eleven general hospitals in the South of the Netherlands, with only 2 of them being centres for oesophageal cancer surgery.

Both surgical treatment of oesophageal cancer and EMR for early cancer are nowadays centralised, but the initial decision which treatment modality to perform, including the decision whether or not to refer patients for a curative treatment option is made in all Dutch hospitals. Therefore, it is important to evaluate the impact of hospital of diagnosis on the referral pattern for curative treatment and ultimately survival. The aim of this study was to examine the influence of the hospital of diagnosis on the probability to undergo a curative treatment option for oesophageal cancer in the Netherlands. Furthermore, the association between the variation in curative treatment probability among hospitals of diagnosis and overall survival was assessed.

Methods

Netherlands Cancer Registry

Data were obtained from the Netherlands Cancer Registry (NCR). This registry serves the total Dutch population of 16.9 million inhabitants. The NCR is based on notification of all newly diagnosed malignancies in the Netherlands by the national automated pathological archive (PALGA). Additional sources are the national registry of hospital discharge, radiotherapy institutions and diagnosis therapy combinations (specific codes for reimbursement purposes). Specially trained data managers of the NCR routinely extracted information on diagnosis,

tumour stage and treatment from the medical records. Information on vital status was obtained through an annual linkage with the Municipal Administrative Database, in which all deceased and emigrated persons in the Netherlands are registered.

Topography and morphology were coded according to the International Classification of Diseases for Oncology (ICD-O-3),[17] in which subsite distribution is divided as: proximal (C15.0, C15.3), mid (C15.4), distal (C15.5), overlapping or not otherwise specified (C15.8, C15.9) and gastro-oesophageal junction (GOJ) (C16.0). Tumour staging was performed according to the International Union Against Cancer (UICC) TNM classification that was valid at the time of diagnosis. Patients diagnosed between 2005 and 2009 were staged according to TNM-6 and patients diagnosed between 2010 and 2013 were staged according to TNM-7.[18,19] Patients with GOJ cancer diagnosed between 2005 and 2009 were staged according to the TNM-6 classification for gastric and after 2010 according to the TNM-7 classification for oesophageal cancer. Clinical tumour stage was assessed for the inclusion of patients and used in the multilevel logistic regression analyses. For survival analyses, the pathologic reports of the resection specimen were assessed, or, if not available, clinical tumour stage was noted.

Patients with a potentially curable oesophageal and GOJ cancer (cT1-3,X, any N, M0,X) were eligible for this study (Figure 1). Patients were considered to be potentially curable in this study if they had no clinically distant metastasis (cM0 and cM1a according to TNM-6 and cM0 according to TNM-7) and no tumour infiltrating into surrounding organs (no cT4 according to TNM-6 and no cT4A or cT4b according to TNM-7). For the analyses, patients with a cM1a tumour according to TNM-6 were categorised as having cN+ as most patients with a cM1a tumour had a distal tumour with coeliac lymph nodes which can be considered as having cN+ according to TNM-7. Furthermore, patients with unknown clinical distant metastases (cMX) were included. It should be noted that as of 2010 coding regulations to register a cM0 or cM1 status into the NCR were less strict than prior to 2010, and therefore as of 2010 relatively more patients were registered with a cM0 rather than a cMX into the NCR. To account for this, we decided to include all patients with cMX.

Curative treatment

Curative treatment was defined as surgical resection, dCRT or a local tumour excision in potentially curable patients with cT1-3,X, any N, M0,X disease. A surgical resection could be combined with or without (neo)adjuvant therapy. dCRT was defined as undergoing chemotherapy combined with radiotherapy without a surgical resection. A local tumour excision was defined as having a local tumour excision or an EMR.

Hospital of diagnosis

As the focus of this study was the decision-making process, the hospital of diagnosis was investigated rather than the hospital of resection. Hospital of diagnosis was defined as the hospital of histological confirmation for patients with a histological confirmation of the tumour (98%). If patients only had a clinical diagnosis, the hospital of diagnosis was defined as the hospital of clinical diagnosis. Patients were excluded from the study if oesophageal cancer was diagnosed abroad.

In the Netherlands, patients are diagnosed with oesophageal cancer in any of the 91 hospitals, usually the one closest to the patient's place of residence. If the hospital of diagnosis does not perform oesophageal cancer surgery or EMR, patients should be referred to an expert centre when these treatments are indicated.

The experience of the hospital in performing oesophageal cancer surgery was divided in two categories: Those that performed at least 20 resections per year and those with a lower annual volume, according to the year of diagnosis. For example, if a patient was diagnosed in 2011 in a hospital that performed 20 or more resections in 2011, the patient was included in the group of hospitals with an annual resection volume of at least 20 procedures.

Outcome measures

Curative treatment probability and overall survival were the primary outcomes investigated in this study. The curative treatment probability was defined as the proportion of patients diagnosed in a hospital who eventually underwent surgical resection, dCRT or local tumour excision, regardless of the hospital in which those treatments were undertaken. Survival time was defined as time from diagnosis to death or until February 1st 2016 for patients who were still alive.

Statistical analysis

Multilevel logistic regression analyses were used to analyse the hierarchically structured data as patients were nested within hospitals. These analyses provide more accurate estimates when dealing with hierarchically structured data than traditional logistic regression analyses since it accounts for dependency of patients within hospitals. [20,21] The outcome variable was curative treatment probability. Multilevel logistic regression models were performed for the periods 2005-2009 and 2010-2013 as the entire study period included centralisation of oesophageal cancer surgery and two new treatment paradigms: the introduction of neoadjuvant chemoradiotherapy and the introduction of EMR. The multivariate multilevel regression models were generated, and patient-, tumour-, and hospital-related variables were added. The effect of a variable on the likelihood of curative treatment was expressed as an odds ratio (OR) with 95% confidence intervals (CIs).

Each patient's adjusted likelihood of undergoing curative treatment was given by the following formula: $P = e^{L}/(1+e^{L})$ where L is the calculated value from the logistic regression for that particular patient. The mean adjusted curative treatment probability for each hospital of diagnosis was obtained by calculating the mean adjusted curative treatment probability of all patients diagnosed within a hospital adjusted for differences in patient- and tumour characteristics between hospitals. Differences between probabilities for hospitals were tested for statistical significance by means of analysis of variance (ANOVA) with Bonferroni correction. Information on comorbidity and socioeconomic status was not routinely collected by the NCR but only in a subcohort, that is, the Eindhoven Cancer Registry, which is also part of the NCR. Therefore, a similar analysis was performed in the group of patients within the Eindhoven Cancer Registry to examine the influence of comorbidity and socioeconomic status on the probabilities to undergo curative treatment depending on the hospital of diagnosis.

Multivariable Cox regression analyses were performed to investigate the impact of the variation in curative treatment probability among the hospitals of diagnosis on the overall survival of the patients, after adjustment for patient-, tumour- and hospital-related characteristics. The hospitals of diagnosis, including the patients, were clustered into three groups with a similar number of patients according to the adjusted probability to undergo curative treatment within a hospital. Two multivariable Cox regression analyses were performed to investigate the prognostic impact of the variation separately for the periods 2005-2009 and 2010-2013. Calculation of the curative treatment probabilities of the hospitals in the entire study period would not provide an accurate estimate and so hospitals, and thus patients, could be categorised erroneous. Results from survival analyses using Cox regression analyses were reported as hazard ratios (HRs) and 95% CI. All analyses were conducted using SAS version 9.4 (SAS Institute, Cary, North Caroline, USA) and reported *P* values of <0.050 were considered statistically significant.

Results

Patients

Between January 2005 and December 2013, 21 621 patients were diagnosed with oesophageal or GOJ cancer. Exclusion of patients (Figure 1) resulted ultimately in a study population of 13 017 patients with potentially curable oesophageal or GOJ cancer (cT1-3,X, any N, M0,X). General characteristics of the patients are shown in table 1. The median age was 69 (interquartile range 61-78) years and the majority (73%) of the patients were male.

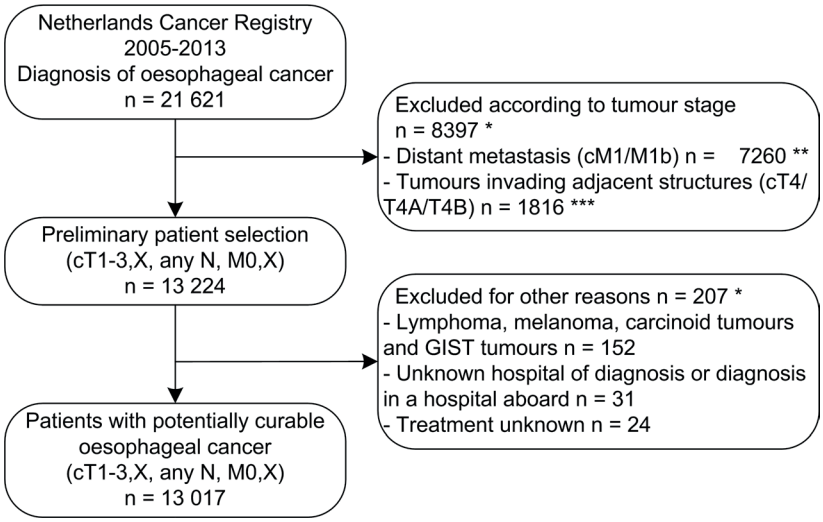


Figure 1 Study flowchart

*The sum of the excluded patients per exclusion criteria is larger than the total number of excluded patients because some patients met two exclusion criteria. ** cM1B according to TNM-6 and cM1 according to TNM-7. Patients with a cM1A tumour were categorised as having a cN+ tumour. *** cT4 according to TNM-6 and cT4A and cT4B according to TNM-7.

Curative treatment

The curative treatment rate was 57% (n=3950) in the period 2005-2009, of which 44% underwent surgery, 9% received dCRT and 4% underwent a local tumour excision. In the period 2011-2013, the curative treatment rate was higher; 68% (n=4162), of which 46% undergoing surgery, 16% received dCRT and 6% underwent a local tumour excision (Table 1).

Patients were diagnosed with oesophageal cancer in 91 hospitals. Twenty of these hospitals performed at least 20 oesophageal cancer resections in 2013, whereas in 2005 only 2 hospitals had a volume of 20 or more resections. The hospitals that performed in 2013 at least 20 resections comprised both academic and teaching hospitals. Surgery was not performed in 33 hospitals in 2005, which increased to 66 hospitals in 2013. Furthermore, 42% of the patients (n=224) diagnosed in 2005 and who underwent a resection was referred to another hospital for surgery, whereas 67% of the patients (n=464) diagnosed in 2013 and who underwent a resection were referred to another hospital for surgery in 2013.

Hospital of diagnosis and probability of curative treatment

The unadjusted percentage of patients who underwent a curative treatment differed significantly between hospitals of diagnosis in the period 2005-2009, varying from 37% to 83% (Figure 2a; P <0.001), and in the period 2010-2013 from 45% to 86% (Figure. 2b; P <0.001). In the most recent period, the proportion of patients who underwent surgery varied from 21% to 71%, while the percentage of patients receiving dCRT or local tumour resection varied from 0% to 38% and 0% to 31%, respectively.

Multivariate multilevel analysis confirmed the effect of hospital of diagnosis on the probability to undergo curative treatment. After adjustment for patient-, tumour- and hospital-related factors, curative treatment rates ranged from 41% to 77% in the period 2005-2009 and from 50% to 82% in the period 2010-2013 depending on the hospital of diagnosis (both P <0.001; Figure 3a and 3b). Subgroup analysis of patients within the Eindhoven Cancer Registry showed that, after adjustment for comorbidity and socioeconomic status, the mean probability to undergo curative treatment per hospital of diagnosis only changed by 0.1% to 1.5% compared with results from analyses without comorbidity and socioeconomic status.

Additional analyses based on outcomes of the multilevel analyses showed that patients diagnosed in 9 hospitals had a significant higher probability to undergo curative treatment than the average probability of all hospitals in the period 2010-2013, whereas patients diagnosed in 6 other hospitals had a significant lower probability than the average probability of all hospitals (Appendix 1).

Results of the multivariate multilevel analysis showed that being diagnosed in a hospital that performed 20 or more resections per year was associated with a higher probability of undergoing curative treatment compared to being diagnosed in hospitals with less than 20 resections in the earlier period (OR 1.54; 95%CI 1.19-1.98) (Table 2). However, in the recent period this association was no longer found. In figure 3a and 3b, hospitals which performed 20 or more resections in 2009 and 2013 respectively, were highlighted.

Table 1 Characteristics and differences in curative treatment among patients with potentially curable oesophageal cancer (cT1-3,X,any N, M0,X), diagnosed between 2005 and 2013 in the Netherlands (N=13017)

	Number of patients	%*	Surgical treatment rate (%)**	dCRT rate (%)**	Local tumour-excision (%)**	Curative treatment rate (%)**	*P* ***
All patients	13017	100%	45%	12%	5%	62%	
Gender							<0.001
Male	9486	73%	48%	12%	5%	66%	
Female	3531	27%	37%	12%	4%	53%	
Age (years.)							<0.001
< 60	2820	22%	66%	12%	5%	83%	
60-74	5751	44%	56%	14%	5%	76%	
≥ 75	4446	34%	17%	9%	5%	31%	
Interval of diagnosis							<0.001
2005-2009	6915	53%	44%	9%	4%	57%	
2010-2013	6102	47%	46%	16%	6%	68%	
Tumour location							<0.001
Proximal	659	5%	9%	42%	2%	53%	
Mid	1608	12%	34%	18%	4%	55%	
Distal	7639	59%	48%	11%	6%	66%	
GEJ	2550	20%	55%	5%	2%	62%	
Overlapping, unknown	561	4%	28%	14%	5%	47%	
Morphology							<0.001
Squamous cell carcinoma	3185	24%	32%	23%	2%	57%	
Adenocarcinoma	9211	71%	52%	8%	6%	66%	
Other	621	5%	15%	13%	2%	31%	
cT classification							<0.001
T1	844	6%	37%	5%	36%	78%	
T2	2378	18%	59%	14%	<1%	73%	
T3	5243	40%	61%	17%	<1%	79%	
TX	4552	35%	21%	7%	7%	35%	
cN classification							<0.001
N0	4492	35%	52%	11%	8%	71%	
N+	6165	47%	51%	17%	<1%	68%	
NX	2360	18%	15%	3%	13%	31%	
cM classification							<0.001
M0	11550	89%	49%	13%	5%	67%	
MX	1467	11%	16%	5%	8%	28%	
Number of oesophageal cancer resections in hospital of diagnosis							<0.001
<20	10520	81%	45%	12%	4%	61%	
≥20	2497	19%	45%	14%	11%	70%	

dCRT= definitive chemoradiotherapy, GOJ= gastro-oesophageal junction, *column percentage **row percentage. *** chi^2 test based on curative treatment rate.

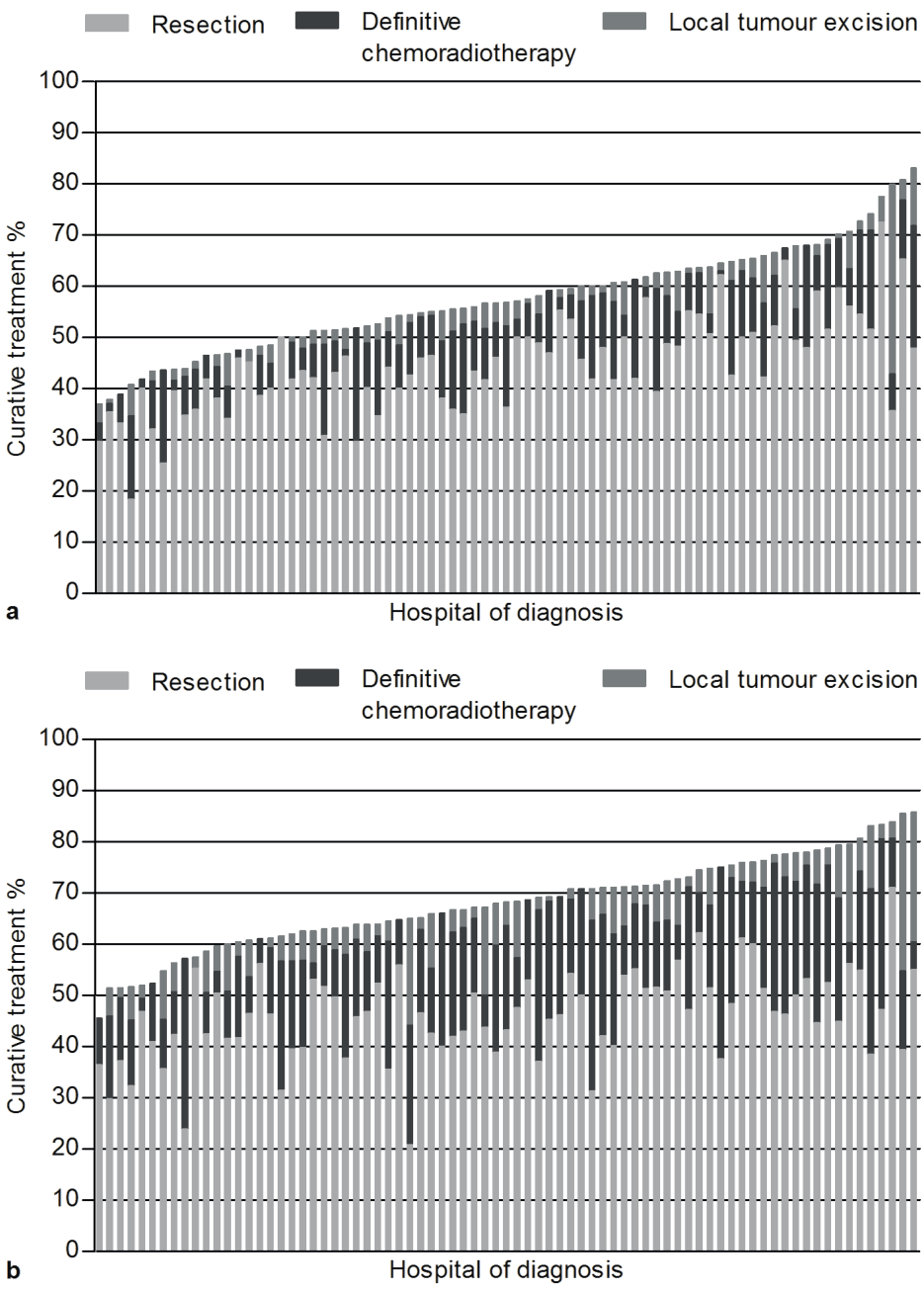


Figure 2 Observed variation in the proportion of patients with potentially curable oesophageal cancer (cT1-3,X,any N, M0,X) who underwent a curative treatment (resection, definitive chemoradiotherapy or local tumour excision). a) period 2005-2009 (n=6915, *P*<0.01). b) period 2010-2013 (n=6102, *P*<0.01).
Each bar represents one hospital.

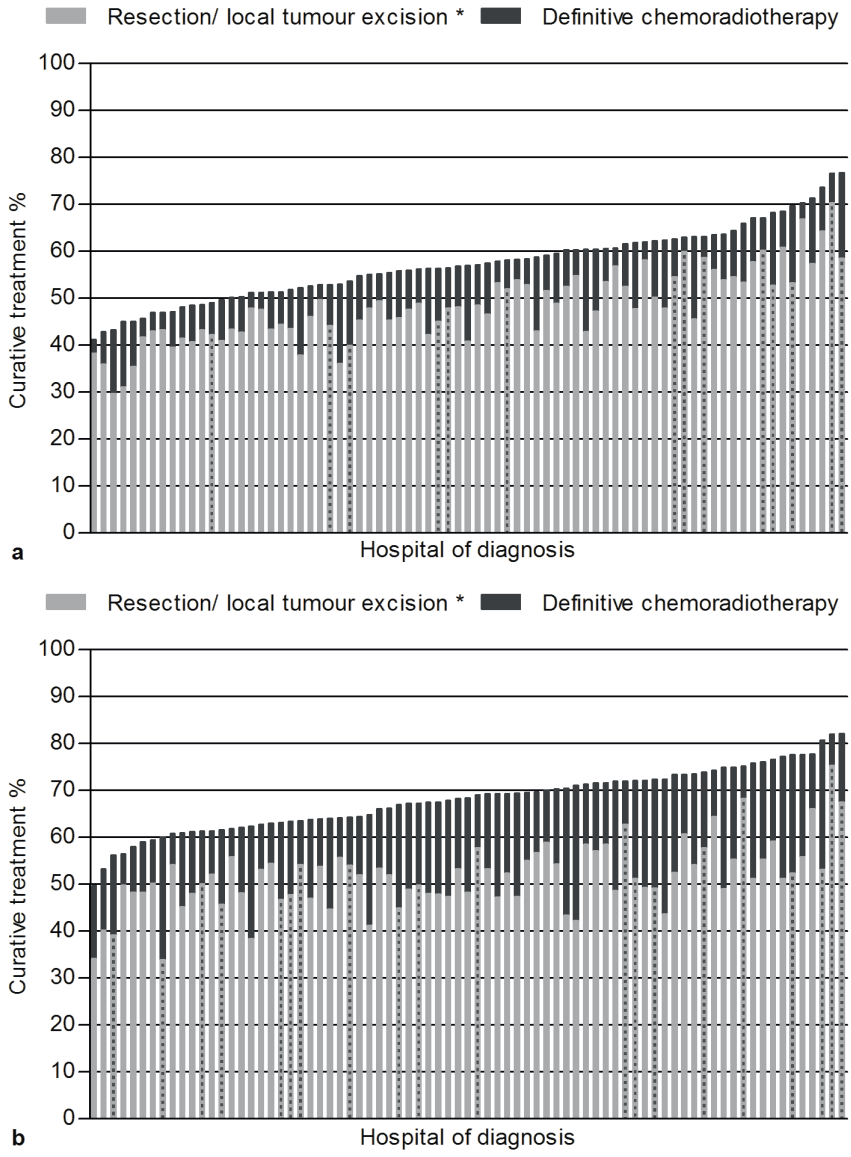


Figure 3 Case-mix adjusted variation in the proportion of patients with potentially curable oesophageal cancer (cT1-3,X,any N, M0,X) who underwent a curative treatment (resection, definitive chemoradiotherapy or local tumour excision) after adjustment for gender, age, cT classification, cN classification, tumour location, morphology, period of diagnosis and number of esophageal resections in the hospital of diagnosis. a) period 2005-2009 (n=6915, *P*<0.01). b) period 2010-2013 (n=6102, *P*<0.01).

Each bar represents one hospital and hospitals which performed 20 or more resections in 2009 and 2013 were highlighted in respectively figure 3a and 3b.

*Patients who underwent a surgical resection or local tumour excision were combined as the multilevel logistic model provided inaccurate results as the number of patients who underwent a local tumour excision per hospital of diagnosis was too small.

Table 2 Multivariate multilevel logistic regression analyses to examine predictors of curative treatment in patients diagnosed with potentially curable oesophageal cancer in the Netherlands.

	Period 2005-2009 n=6915				Period 2010-2013 n=6102			
	Curative treatment				Curative treatment			
	Yes	No	OR*	95%CI	Yes	No	OR*	95%CI
Gender								
Male	3043	1965	1.0		3210	1268	1.0	
Female	907	1000	0.87	0.75-0.99	952	672	0.80	0.68-0.94
Age (yrs.)								
< 60	1250	324	1.0		1097	149	1.0	
60- 74	2075	835	0.64	0.57-0.78	2303	538	0.62	0.50-0.76
≥ 75	625	1806	0.10	0.08-0.12	762	1253	0.10	0.08-0.13
cT classification								
T1	301	109	1.05	0.77-1.42	356	78	1.43	1.04-1.97
T2	802	318	1.0		936	322	1.0	
T3	1855	638	1.17	0.97-1.41	2266	484	1.57	1.30-1.89
TX	992	1900	0.28	0.23-0.33	604	1056	0.29	0.24-0.35
cN classification								
N0	1583	710	1.0		1606	593	1.0	
N+	1934	1192	0.38	0.33-0.45	2253	786	0.64	0.55-0.76
NX	433	1063	0.31	0.26-0.37	303	561	0.38	0.30-0.47
Tumour location								
Proximal	169	183	0.98	0.73-1.30	179	128	0.73	0.53-0.99
Mid	414	423	0.91	0.74-1.11	476	295	0.89	0.70-1.12
Distal	2389	1612	1.0		2638	1000	1.0	
GEJ	870	565	1.47	1.25-1.73	716	399	0.67	0.56-0.80
Overlapping, unknown	108	182	0.62	0.45-0.85	153	118	0.65	0.47-0.89
Morphology								
Squamous cell	882	788	0.67	0.56-0.79	944	571	0.57	0.47-0.70
Adenocarcinoma	2972	1897	1.0		3123	1219	1.0	
Other	96	280	0.34	0.25-0.46	95	150	0.37	0.26-0.53
Number of oesophageal cancer resections in hospital of diagnosis								
<20 resections	3334	2671	1.0.		3031	1484	1.0	
≥20 resections	616	294	1.54	1.19-1.98	1131	456	1.08	0.82-1.42

*Adjusted for all variables listed in table 2 and hospital of diagnosis by using multilevel analysis. GOJ= gastro-oesophageal junction.

Hospital of diagnosis and overall survival

Multivariable Cox regression analyses showed that patients diagnosed in hospitals with a lower probability of undergoing curative treatment had a worse overall survival than those diagnosed in hospitals with a higher probability. In the recent time period, patients diagnosed in hospitals with a probability to undergo curative treatment ranging from 72% to 82% had a significant favourable overall survival compared with patients diagnosed in hospitals with a lower probability ranging from 50% to 64% (HR=1.15 95%CI 1.07-1.24; Table 3). A similar association was also found in the earlier time period (HR=1.13 95%CI 1.06-1.20). Furthermore, the same multivariable Cox regression analyses demonstrated that patients diagnosed in high-volume surgery hospitals had a favourable survival compared to patients diagnosed in low-volume surgery hospitals (HR=0.90 95%CI 0.83-0.98). However, this association was not found in the recent time period (HR=0.99 95%CI 0.93-1.08).

Table 3 Multivariable Cox proportional hazards analyses of overall survival for patients with potentially curable oesophageal cancer in the Netherlands for two separated periods of diagnosis.

	Number of patients	Crude 2-year OS	Univariable		Multivariable	
			HR	95%CI	HR*	95%CI
2005-2009 (n=6915)						
Curative treatment probability **						
41%-53%	2261	32%	1.28	1.20-1.36	1.13	1.06-1.20
54%-59%	2128	33%	1.18	1.11-1.26	1.10	1.03-1.17
60%-77%	2526	42%	1.0		1.0	
2010-2013 (n=6102)						
Curative treatment probability **						
50%-64%	2308	40%	1.26	1.18-1.36	1.15	1.07-1.24
65%-71%	1711	47%	1.13	1.04-1.22	1.05	0.96-1.14
72%-82%	2083	50%	1.0		1.0	

OS= overall survival.

* Adjusted for gender, age, tumour stage, tumour location, morphology, tumour differentiation and number of oesophageal cancer resections in hospital of diagnosis.

** Patients were divided in three groups with a similar number of patients according to the adjusted probability to undergo curative treatment of the hospital in which they were diagnosed.

Discussion

In this population-based nationwide study the proportion of oesophageal cancer patients who underwent curative treatment (surgery, dCRT or local tumour excision) varied between 37% and 83% in the period 2005-2009 and between 45% and 86% in the period 2010-2013. Multivariate multilevel regression analysis confirmed the effect of hospital of diagnosis on the likelihood to undergo curative treatment. Patients with oesophageal cancer who had been diagnosed in hospitals with a low probability to undergo curative treatment had a worse overall survival than those diagnosed in hospitals with a high probability.

Hospital variation and treatment probability

Our results show that the differences between hospitals in the proportion of patients that underwent dCRT were larger than the differences in the proportion of patients that underwent surgery. An explanation may be that dCRT has only recently been introduced. Therefore, increased awareness of the possibilities of chemoradiation combined with favourable results reported by previous studies might have played a role in the implementation of dCRT as a potential curative option.[22,23] Furthermore, this variation might also be explained by the fact that the indications for dCRT are less well defined compared to the indications for surgery.

In previous studies it has been suggested that comorbidity and socioeconomic status play a role in the probability of undergoing curative treatment.[13, 24] However, subgroup analysis of patients diagnosed in the Eindhoven Cancer Registry, in which comorbidity is registered, revealed only small changes in the probability of curative treatment after adjustment for comorbidity and socioeconomic status. These findings suggest that comorbidity and socioeconomic status only minimally contributed to the observed variation in curative treatment probability between the hospitals of diagnosis.

Centralisation, specialisation, and multidisciplinary team meetings

In the Netherlands, oesophageal cancer surgery is currently performed in high volume hospitals. Since 2006, a yearly minimum of 10 oesophageal resections per hospital was enforced by the Dutch Health Care Inspectorate, which was increased to a yearly minimum of 20 oesophageal resections per hospital in 2011. Centralisation of surgical treatment for oesophageal cancer patients has shown to improve long-term outcome in the Netherlands.[24-27] Results from the present study showed that the number of patient that are referred by the hospital of diagnosis for surgery increased during the study period, which is likely related to the centralisation of surgical treatment for oesophageal cancer patients. These changes due to centralisation emphasise the important role of the hospital of diagnosis on the likelihood to undergo a curative treatment.

The probability to undergo curative treatment may be influenced by various factors, such as type of hospital and its facilities, for example, the availability of radiotherapy, endoscopy, regional agreements, and treatment protocols that are used. In general, all hospitals in the Netherlands have at least an endoscopy unit and radiology department, including computed tomography (CT) scan for optimal staging. The probability of receiving curative treatment may also be affected by the available specialisation of the hospital and medical specialists. Two previous studies have reported that patients treated by medical specialists with higher

caseload were more likely to undergo surgery or other treatments compared to patients treated by medical specialists with a limited caseload.[28,29] Higher-volume medical specialists also used a wider range of diagnostic investigations, which was not only explained by a better access to these facilities.[28] Possibly, patients with potentially curable disease managed by low-volume medical specialists regarded incurable, could be regarded still curable by a more experienced physician because this physician may be more aware of the curative treatment possibilities.[29] The present study also shows that patients diagnosed in high-volume surgery hospitals had a greater likelihood of undergoing surgery and a better overall survival than those diagnosed in low-volume surgery hospitals. However, these associations were only found in the earlier period in which centralisation of surgery was initiated.

All oesophageal cancer patients should be discussed in a multidisciplinary team (MDT) meeting for a consensus-based treatment decision in the Netherlands. Regional expert MDT meetings have been shown to alter initial treatment plans frequently in patients with oesophageal, gastric, colorectal and breast cancer.[30-34] However, no information is available as to whether a medical specialist with experience in curative treatment of oesophageal cancer is always present in this MDT. Regional MDT meetings become even more important when treatment decisions are complex as in oesophageal cancer and it might be hypothesised that the presence of experienced specialists in these MDT meetings might explain differences between hospitals in the proportion of patients undergoing curative treatment.

Survival

The variation in the probability of curative treatment among hospitals of diagnosis was found to be associated with survival in both time periods. A similar study performed by the same lead author among patients with gastric cancer has also found that variation in the likelihood to undergo surgery was associated with survival.[15] However, this study has only found an association in the more recent time period. An explanation for the differences in findings of these studies could be that centralisation of gastric cancer surgery has only been implemented since 2012, which is 6 years later than the implementation of centralisation of oesophageal cancer surgery. Centralisation of surgery could have led to a decrease in the number of medical specialists with experience in curative treatment options for oesophageal and gastric cancer patients in hospitals of diagnosis, which have no longer a program for these curative treatment options. This negative consequence of centralisation may have influenced the selection of patients who are eligible for curative treatment and subsequently the referral and survival of these patients among hospitals of diagnosis.

Strengths and limitations

This study has some limitations. First, some factors influencing treatment, such as performance status of the patient and information about MDT meetings decisions, were not registered and could therefore not be included in the analyses. Second, possible incompleteness of registration of local tumour excision in the earlier period could have led to more variation in curative treatment probability between hospitals in the earlier period compared with the recent period. Third, information about the intention of the chemoradiotherapy was not available. However, as

only potentially curable oesophageal cancer patients were included it was assumed that these patients underwent chemoradiotherapy with curative intention.

Finally, patients with distant metastasis (cM1) and cT4 tumours were excluded from the study. However, the accuracy of the diagnostic and staging methods used is unknown. Because endoscopic ultrasonography is not always performed in patients with oesophageal cancer, clinical stage was unknown in a relatively high percentage of patients (Table 1). Nevertheless, the variation in cT, cN status and cM status between hospitals was much smaller than the interhospital variation in curative treatment probabilities and is therefore unlikely to have influenced the results substantially. Moreover, clinical decision-making in oesophageal cancer treatment is more often based on cN and cM rather than on cT status [35] and it is assumed that most of the patients with a cMX prior to 2010 had in fact a cM0 as the percentage of patients with a cM0 increased after 2010 when fewer diagnostic procedures were required to register a cM0 or cM1 according to the coding regulations of the NCR.

This study has also several strengths, such as its population-based design resulting in a large and representative study population. This nationwide study enabled the evaluation of the influence of the hospital of diagnosis on the probability to undergo curative treatment and its impact on survival among patients with oesophageal cancer.

Conclusions

This study revealed a large variation in the probability to undergo curative treatment for oesophageal cancer depending on the hospitals of diagnosis, which also affected the survival of these patients. Regional expert MDT meetings with involvement of experienced specialists in this field should be initiated for all patients with oesophageal cancer. The decisions made by these panels may improve the selection of patients with oesophageal cancer who are eligible for a curative treatment option leading to an overall improvement of survival on the long term.

References

1. Pennathur A, Gibson MK, Jobe BA, Luketich JD. Oesophageal carcinoma, 2013. Lancet;381:400-412.
2. Cijfers over kanker., Netherlands Cancer Registry. www.cijfersoverkanker.nl. Accessed on: 30-9-2016.
3. Pohl H, Sirovich B, Welch HG. Esophageal adenocarcinoma incidence: are we reaching the peak?, 2010. Cancer Epidemiol Biomarkers Prev;19:1468-1470.
4. Dikken JL, Lemmens VE, Wouters MW, Wijnhoven BP, Siersema PD, Nieuwenhuijzen GA, van Sandick JW, Cats A, Verheij M, Coebergh JW, van de Velde CJ. Increased incidence and survival for oesophageal cancer but not for gastric cardia cancer in the Netherlands, 2012. Eur J Cancer;48:1624-1632.
5. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012, 2012. CA Cancer J Clin;62:10-29.
6. van Hagen P, Hulshof MC, van Lanschot JJ, Steyerberg EW, van Berge Henegouwen MI, Wijnhoven BP, Richel DJ, Nieuwenhuijzen GA, Hospers GA, Bonenkamp JJ, Cuesta MA, Blaisse RJ, Busch OR, ten Kate FJ, Creemers GJ, Punt CJ, Plukker JT, Verheul HM, Spillenaar Bilgen EJ, van Dekken H, van der Sangen MJ, Rozema T, Biermann K, Beukema JC, Piet AH, van Rij CM, Reinders JG, Tilanus HW, van der Gaast A. Preoperative chemoradiotherapy for esophageal or junctional cancer, 2012. N Engl J Med;366:2074-2084.
7. Shapiro J, van Lanschot JJ, Hulshof MC, van Hagen P, van Berge Henegouwen MI, Wijnhoven BP, van Laarhoven HW, Nieuwenhuijzen GA, Hospers GA, Bonenkamp JJ, Cuesta MA, Blaisse RJ, Busch OR, Ten Kate FJ, Creemers GJ, Punt CJ, Plukker JT, Verheul HM, Bilgen EJ, van Dekken H, van der Sangen MJ, Rozema T, Biermann K, Beukema JC, Piet AH, van Rij CM, Reinders JG, Tilanus HW, Steyerberg EW, van der Gaast A. Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): long-term results of a randomised controlled trial, 2015. Lancet Oncol;16:1090-1098.
8. Gwynne S, Hurt C, Evans M, Holden C, Vout L, Crosby T. Definitive chemoradiation for oesophageal cancer--a standard of care in patients with non-metastatic oesophageal cancer, 2011. Clin Oncol (R Coll Radiol);23:182-188.
9. Morgan MA, Lewis WG, Casbard A, Roberts SA, Adams R, Clark GW, Havard TJ, Crosby TD. Stage-for-stage comparison of definitive chemoradiotherapy, surgery alone and neoadjuvant chemotherapy for oesophageal carcinoma, 2009. Br J Surg;96:1300-1307.
10. Crosby TD, Brewster AE, Borley A, Perschky L, Kehagioglou P, Court J, Maughan TS. Definitive chemoradiation in patients with inoperable oesophageal carcinoma, 2004. Br J Cancer;90:70-75.
11. Ngamruengphong S, Wolfsen HC, Wallace MB. Survival of patients with superficial esophageal adenocarcinoma after endoscopic treatment vs surgery, 2013. Clin Gastroenterol Hepatol;11:1424-1429.e1422; quiz e1481.
12. Rustgi AK, El-Serag HB. Esophageal carcinoma, 2014. N Engl J Med;371:2499-2509.
13. Koppert LB, Lemmens VE, Coebergh JW, Steyerberg EW, Wijnhoven BP, Tilanus HW, Janssen-Heijnen ML. Impact of age and co-morbidity on surgical resection rate and survival in patients with oesophageal and gastric cancer, 2012. Br J Surg;99:1693-1700.
14. Bakens MJ, van Gestel YR, Bongers M, Besselink MG, Dejong CH, Molenaar IQ, Busch OR, Lemmens VE, de Hingh IH, Dutch Pancreatic Cancer G. Hospital of diagnosis and likelihood of surgical treatment for pancreatic cancer, 2015. Br J Surg;102:1670-1675.
15. van Putten M, Verhoeven RH, van Sandick JW, Plukker JT, Lemmens VE, Wijnhoven BP, Nieuwenhuijzen GA. Hospital of diagnosis and probability of having surgical treatment for resectable gastric cancer, 2016. Br J Surg;103:233-241.
16. Koeter M, van Steenbergen LN, Lemmens VE, Rutten HJ, Roukema JA, Wijnhoven BP, Nieuwenhuijzen GA. Hospital of diagnosis and probability to receive a curative treatment for oesophageal cancer, 2014. Eur J Surg Oncol;40:1338-1345.

17. Fritz A, Percy C, Jack A, Shanmugaratnam K, Sobin L, Parkin DM, Whelan S, editors. International Classification of Diseases for Oncology, third edition., 2000ed. Geneva: World Health Organization.

18. Sobin L, Wittekind C. TNM classification of malignant tumours, 2002, 6th ed. New York: Wiley-Liss.

19. Sobin L, Gospodarowicz M, Wittekind C. TNM classification of malignant tumours, 2009, 7th ed. New York: Wiley-Liss.

20. Austin PC, Tu JV, Alter DA. Comparing hierarchical modeling with traditional logistic regression analysis among patients hospitalized with acute myocardial infarction: should we be analyzing cardiovascular outcomes data differently?, 2003. Am Heart J;145:27-35.

21. Twisk JW. Applied multilevel analysis: a practical guide, 2006ed. Cambridge, United Kingdom: Cambridge University Press.

22. Stahl M, Stuschke M, Lehmann N, Meyer HJ, Walz MK, Seeber S, Klump B, Budach W, Teichmann R, Schmitt M, Schmitt G, Franke C, Wilke H. Chemoradiation with and without surgery in patients with locally advanced squamous cell carcinoma of the esophagus, 2005. J Clin Oncol;23:2310-2317.

23. Wong R, Malthaner R. Combined chemotherapy and radiotherapy (without surgery) compared with radiotherapy alone in localized carcinoma of the esophagus, 2006. Cochrane Database Syst Rev:Cd002092.

24. Dikken JL, Dassen AE, Lemmens VE, Putter H, Krijnen P, van der Geest L, Bosscha K, Verheij M, van de Velde CJ, Wouters MW. Effect of hospital volume on postoperative mortality and survival after oesophageal and gastric cancer surgery in the Netherlands between 1989 and 2009, 2012. Eur J Cancer;48:1004-1013.

25. Lemmens VE, Bosscha K, van der Schelling G, Brenninkmeijer S, Coebergh JW, de Hingh IH. Improving outcome for patients with pancreatic cancer through centralization, 2011. Br J Surg;98:1455-1462.

26. van de Poll-Franse LV, Lemmens VE, Roukema JA, Coebergh JW, Nieuwenhuijzen GA. Impact of concentration of oesophageal and gastric cardia cancer surgery on long-term population-based survival, 2011. Br J Surg;98:956-963.

27. Wouters MW, Karim-Kos HE, le Cessie S, Wijnhoven BP, Stassen LP, Steup WH, Tilanus HW, Tollenaar RA. Centralization of esophageal cancer surgery: does it improve clinical outcome?, 2009. Ann Surg Oncol;16:1789-1798.

28. Bachmann MO, Alderson D, Edwards D, Wotton S, Bedford C, Peters TJ, Harvey IM. Cohort study in South and West England of the influence of specialization on the management and outcome of patients with oesophageal and gastric cancers, 2002. Br J Surg;89:914-922.

29. Bachmann MO, Alderson D, Peters TJ, Bedford C, Edwards D, Wotton S, Harvey IM. Influence of specialization on the management and outcome of patients with pancreatic cancer, 2003. Br J Surg;90:171-177.

30. Davies AR, Deans DA, Penman I, Plevris JN, Fletcher J, Wall L, Phillips H, Gilmour H, Patel D, de Beaux A, Paterson-Brown S. The multidisciplinary team meeting improves staging accuracy and treatment selection for gastro-esophageal cancer, 2006. Dis Esophagus;19:496-503.

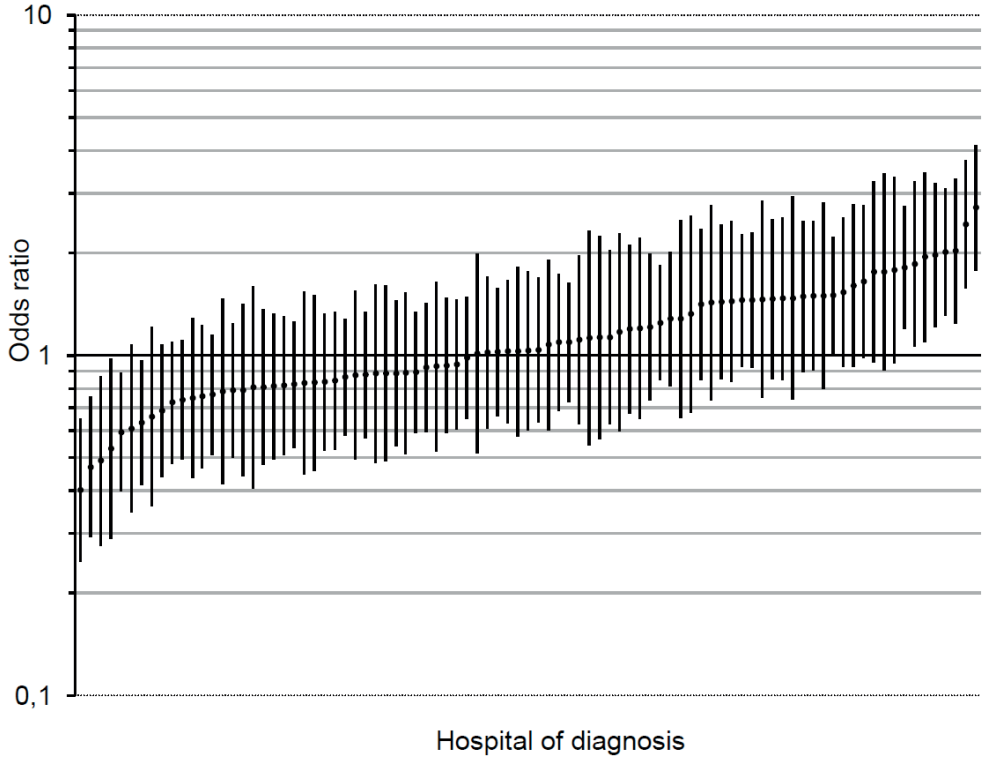
31. Du CZ, Li J, Cai Y, Sun YS, Xue WC, Gu J. Effect of multidisciplinary team treatment on outcomes of patients with gastrointestinal malignancy, 2011. World J Gastroenterol;17:2013-2018.

32. MacDermid E, Hooton G, MacDonald M, McKay G, Grose D, Mohammed N, Porteous C. Improving patient survival with the colorectal cancer multi-disciplinary team, 2009. Colorectal Dis;11:291-295.

33. Newman EA, Guest AB, Helvie MA, Roubidoux MA, Chang AE, Kleer CG, Diehl KM, Cimmino VM, Pierce L, Hayes D, Newman LA, Sabel MS. Changes in surgical management resulting from case review at a breast cancer multidisciplinary tumor board, 2006. Cancer;107:2346-2351.

34. van Hagen P, Spaander MC, van der Gaast A, van Rij CM, Tilanus HW, van Lanschot JJ, Wijnhoven BP. Impact of a multidisciplinary tumour board meeting for upper-GI malignancies on clinical decision making: a prospective cohort study, 2013. Int J Clin Oncol;18:214-219.

35. Berry MF. Esophageal cancer: staging system and guidelines for staging and treatment, 2014. J Thorac Dis;6 Suppl 3:S289-297.



Appendix 1 Case-mix adjusted variation in the proportion of patients with potentially curable oesophageal cancer (cT1-3,X,any N, M0,X) who underwent a curative treatment (resection, definitive chemoradiotherapy or local tumour excision) in the period 2010-2013 on a log scale with an odds ratio for every hospital of diagnosis presented as a dot with 95% confidence interval.
The 1-line represents the average probability of all hospitals. Patients diagnosed in hospitals with an odds ratio less than 1 had a lower likelihood to undergo curative treatment. Adjustment was made for gender, age, cT classification, cN classification, tumour location, morphology, period of diagnosis and number of esophageal resections in the hospital of diagnosis (n=6102).

Chapter 4

Hospital of diagnosis and probability of having surgical treatment for resectable gastric cancer

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Abstract

Background
Gastric cancer surgery is increasingly being centralised in the Netherlands, whereas the diagnosis is often made in hospitals where gastric cancer surgery is not performed. The aim of this study was to assess whether hospital of diagnosis affects the probability of undergoing surgery and its impact on overall survival.

Methods
All patients with potentially curable gastric cancer according to stage (cT1/1b–4a, cN0–2, cM0) diagnosed between 2005 and 2013 were selected from the Netherlands Cancer Registry. Multilevel logistic regression was used to examine the probability of undergoing surgery according to hospital of diagnosis. The effect of variation in probability of undergoing surgery among hospitals of diagnosis on overall survival during the intervals 2005–2009 and 2010–2013 was examined by using Cox regression analysis.

Results
A total of 5620 patients with potentially curable gastric cancer, diagnosed in 91 hospitals, were included. The proportion of patients who underwent surgery ranged from 53.1 to 83.9 per cent according to hospital of diagnosis ($P < 0.001$); after multivariable adjustment for patient and tumour characteristics it ranged from 57.0 to 78.2 per cent ($P < 0.001$). Multivariable Cox regression showed that patients diagnosed between 2010 and 2013 in hospitals with a low probability of patients undergoing curative treatment had worse overall survival (hazard ratio 1.21; $P < 0.001$)

Conclusion
The large variation in probability of receiving surgery for gastric cancer between hospitals of diagnosis and its impact on overall survival indicates that gastric cancer decision-making is suboptimal.

Introduction

Gastric cancer is the fifth most common cancer and the third leading cause of cancer death worldwide.[1] Although the incidence has decreased in recent decades in the Netherlands, prognosis is still poor. The 5-year overall survival rate for patients with stage I–III disease is 31 per cent and the median survival time for stage IV is only 6 months.[2,3]

Surgery is the only potential curative treatment for gastric cancer.[4] Gastric surgery is associated with high morbidity and mortality rates, and performed mainly in low-volume hospitals.[5,6] Therefore, centralisation by defining minimum volumes per centre has been initiated in the Netherlands. From 2012 onwards, hospitals should have performed a minimum of ten resections per year, increasing to a minimum of 20 resections annually from 2013. The probability of undergoing surgical treatment is influenced by several factors. Surgery with curative intent is generally not of benefit in patients with distant metastasis.[2] Patients can otherwise be regarded as less suitable for gastric cancer surgery because of advanced age, severe comorbidity or decreased performance status.

Previous studies[7,8] have shown that the probability of receiving curative treatment for oesophageal and pancreatic cancer is associated with the hospital of diagnosis. Referring physicians may consider the patient too frail and unsuitable for surgery, and withhold possible curative options. In the study of patients with potentially curable oesophageal cancer[8], the proportion who underwent oesophagectomy varied between 33 and 67 per cent according to hospital of diagnosis.

It is of importance to evaluate the influence of hospital of diagnosis on referral for surgical treatment and, ultimately, survival, especially when surgical treatment for gastric cancer is being centralised within specialised centres. The aim of this study was, therefore, to examine the influence of hospital of diagnosis on the probability of undergoing surgery for gastric cancer in the Netherlands. The association between the variation in surgical treatment probability among hospitals of diagnosis and overall survival was also assessed.

Methods

Data were obtained from the Netherlands Cancer Registry (NCR). This registry serves the total Dutch population of 16.6 million inhabitants. The NCR is based on notification of all newly diagnosed malignancies in the Netherlands by the national automated pathological archive (PALGA). Additional sources are the national registry of hospital discharge and radiotherapy institutions. Information on diagnosis, staging and treatment is extracted routinely from the medical records by specially trained data managers of the cancer registry.

Patients with a potentially curable non-cardia gastric cancer were eligible for this study. The gastro-oesophageal junction could be involved, but the bulk of the tumour had to be in the stomach. Patients were considered potentially curable if they had no clinical distant metastasis, no tumour infiltrating surrounding organs, and no non-regional or unresectable conglomeration of suspicious nodes.

Topography and morphology were coded according to the International Classification of Diseases for Oncology (ICD-O-3).[9] Distribution of the location in the stomach is divided as follows:

proximal/middle (fundus, corpus, and lesser and greater curvature (C16.1, C16.2, C16.5, C16.6), pyloric and antrum (C16.3, C16.4), and overlapping or not otherwise specified (C16.8, C16.9).

Tumours were staged according to the International Union Against Cancer (UICC) TNM classification that was valid at the time of diagnosis. Patients diagnosed between 2005 and 2009 were staged using the sixth edition[10], and those diagnosed between 2010 and 2013 according to the seventh edition.[11] For this, the pathological stage of the resection specimen was used, or, if not available, clinical tumour stage was noted. Information on vital status was obtained from hospital records and by annual linkage with the Municipal Administrative Databases, which register all deceased and emigrated persons in the Netherlands.

Surgery

Surgery for gastric cancer was classified according to the NCR as subtotal gastrectomy, total gastrectomy and multiple organ resection, which was defined as a gastrectomy and surgical removal of other organs. Laparoscopy as a staging method was not regarded as surgery.

Hospital of diagnosis, hospital status, and volume

The hospital of diagnosis was defined as the hospital in which the histological diagnosis of gastric cancer was made. Patients were excluded from the study if the diagnosis was made in a hospital abroad. As the focus of this study was the decision-making process, the hospital of diagnosis was investigated rather than the hospital of resection.

In the Netherlands, patients can be diagnosed in any of the 91 hospitals, usually the one closest to their place of residence. If the hospital of diagnosis does not perform gastrectomies, patients are referred when gastrectomy is indicated. Type of hospital of diagnosis was classified as university (academic) hospital, teaching non-university hospital or non-teaching hospital.

Hospital of diagnosis was divided into two categories according to the number of gastric cancer resections: those that performed at least 10 resections per year and those with a lower annual volume, according to the year of diagnosis. For example, if a patient was diagnosed in 2008 in a hospital that carried out 10 or more resections in that year, the patient was included in the group of hospitals with an annual resection volume of at least 10.

Outcome measures

Surgical treatment probability and survival were the outcomes investigated in this study. The surgical treatment probability of a hospital of diagnosis was defined as the proportion of patients diagnosed in a certain hospital who eventually underwent surgery, regardless of the hospital in which the surgery was performed. Survival time was defined as time from diagnosis to death, or until 1 January 2015 for patients who were still alive.

Statistical analysis

All analyses were conducted using SAS® version 9.4 (SAS Institute, Cary, North Carolina, USA). A multilevel logistic regression analysis was used to analyse the hierarchically structured data as patients were nested within hospitals. Multilevel regression analyses provide more accurate estimates when dealing with hierarchically structured data than traditional regression analyses as they accounts for dependency of patients within hospitals.[12,13] The outcome variable was surgery (0, no; 1, yes). A multivariable multilevel logistic regression model was generated, and

patient- and tumour-related variables and type of hospital were added. The effect of a variable on the likelihood of surgical treatment was expressed as an odds ratio (OR) with 95 per cent c.i.

Each patient's adjusted chance of undergoing surgery was given by the following formula: $P = e^L/(1+e^L)$, where L is the calculated value from the logistic regression for that particular patient. The mean adjusted surgical probability for each hospital of diagnosis was defined as the mean adjusted surgical probability of the patients diagnosed within that hospital. This resulted in a range of surgical probabilities adjusted for differences in patient characteristics between hospitals. The variation in surgical probabilities between hospitals of diagnosis was tested for statistical significance by means of ANOVA with Bonferroni correction. Information on comorbidity and socioeconomic status was not routinely collected by the NCR but solely by the Eindhoven Cancer Registry (ECR), which is representative of the NCR. Therefore, a similar analysis was performed in the subgroup of patients within the ECR to examine the influence of comorbidity and socioeconomic status on changes in surgical probabilities among hospitals of diagnosis.

Multivariable Cox regression analyses were undertaken to investigate the prognostic impact of the variation in surgical treatment probability among hospitals of diagnosis on overall survival, after adjustment for patient characteristics. The hospitals of diagnosis, and thereby the patients, were clustered within four groups with a comparable number of patients according to the adjusted surgical probabilities of the hospitals. Two multivariable Cox regression analyses were performed to investigate the prognostic impact of the variation separately in the intervals 2005–2009 and 2010–2013. These two intervals were defined because from 2010 an increasing effect of centralisation of gastric cancer surgery in the data set might influence the surgical probabilities of hospitals of diagnosis. Furthermore, the interval 2005–2013 included a new treatment paradigm: the introduction of perioperative chemotherapy in the earlier time period. Therefore, calculation of the surgical probabilities of hospitals in the entire study interval (2005–2013) would not provide an accurate estimate. Patients without histological confirmation were classified as having an adenocarcinoma in multivariable analyses, as approximately 99 per cent of the patients with histological confirmation of gastric cancer had an adenocarcinoma. Results from survival analyses using Cox regression analyses were reported as hazard ratios (HRs) with 95 per cent c.i. $P < 0.050$ was considered statistically significant.

Results

Between January 2005 and December 2013, 12 877 patients were diagnosed with non-cardia gastric cancer. Exclusion of patients for several reasons (Figure 1) resulted in a study population of 5620 patients with potentially curable gastric cancer (cT1/T1b–4a, cN0–2, cM0).

General characteristics of the patients are shown in Table 1. The median age was 73 (i.q.r. 64–73) years. The overall surgical resection rate was 69.1 per cent (3881 patients); 59.5 per cent of these patients underwent resection without neoadjuvant or adjuvant treatment, 16.3 per cent received only neoadjuvant chemotherapy, 20.9 per cent received neoadjuvant chemotherapy as well as adjuvant chemotherapy or chemoradiotherapy and 3.3 per cent received adjuvant treatment alone. The most commonly performed operation was subtotal gastrectomy (64.3 per cent). Some 36.3 per cent of the patients were diagnosed in a non-teaching hospital and 69.7

per cent of these underwent surgery, either in the hospital of diagnosis or in a referral hospital (Table 1).

Surgical treatment

Surgical treatment rates were 74.0, 72.5 and 59 per cent for cT2, cT3 and cT4a tumours respectively ($P < 0.001$) (Table 1). Surgical treatment decreased with age. In addition, a small decline was noted in the use of surgery during the study; 73.4 per cent of the patients underwent surgical treatment in 2005–2009 compared with 64.6 per cent in 2010–2013 ($P < 0.001$).

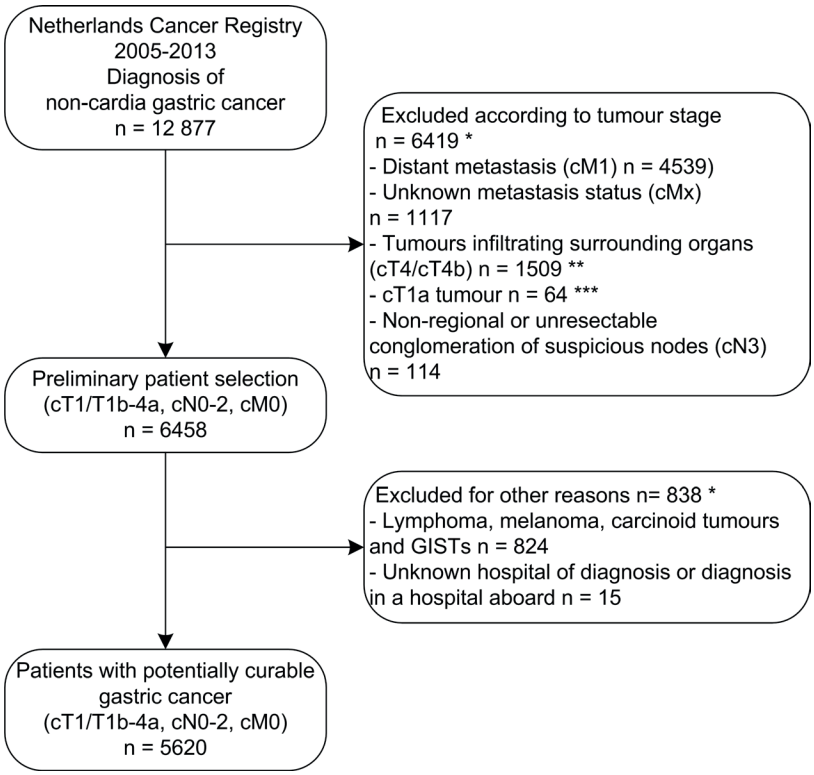

Figure 1 Study flowchart

*Some patients met two exclusion criteria.

** cT4 according to sixth edition of TNM classification and cT4b according to seventh edition.

*** Eligible for endoscopic mucosal resection instead of an operation.

GIST, gastrointestinal stromal tumour

Patients were diagnosed with gastric cancer in 91 hospitals. Seven hospitals performed at least 20 gastric cancer resections in 2013, whereas no hospital reached a volume of 20 resections in 2005. Surgery was not performed in six hospitals in which the diagnosis of gastric cancer was made in 2005; this increased to 47 hospitals in 2013. Furthermore, 6.0 per cent of the patients were referred to another hospital for surgery in 2005, whereas 57.6 per cent of the patients were referred from a hospital that did not perform gastrectomies in 2013.

Table 1 Characteristics of patients with potentially curable gastric cancer (cT1/1b–4a, cN0–2, cM0), diagnosed between 2005 and 2013 in the Netherlands

	No. of patients (n = 5620)	Surgical treatment rate (%)	*P*†
Age (years)			< 0.001
< 60	883 (15.7)	86.6	
60–74	2119 (37.7)	81.2	
≥ 75	2618 (46.6)	53.3	
Sex			< 0.001
M	3345 (59.5)	71.0	
F	2275 (40.5)	66.2	
Interval of diagnosis			< 0.001
2005–2009	2853 (50.8)	73.4	
2010–2013	2767 (49.2)	64.6	
Morphology			< 0.001
Adenocarcinoma	5474 (97.4)	69.3	
Other	56 (1.0)	50.0	
No histological confirmation	90 (1.6)	0	
Clinical tumour classification			< 0.001
cT1/1b*	248 (4.4)	68.2	
cT2	1038 (18.5)	74.0	
cT3	619 (11.0)	72.5	
cT4a	68 (1.2)	58.8	
cTx/missing	3647 (64.9)	67.3	
Clinical node classification			< 0.001
cN0	2861 (50.9)	80.3	
cN1	1065 (19.0)	71.6	
cN2	258 (4.6)	61.6	
cNx/unknown	1436 (25.6)	46.2	
Type of hospital of diagnosis			0.694
Academic	370 (6.6)	68.1	
Teaching	3212 (57.2)	68.7	
Non-teaching	2038 (36.3)	69.7	
No. of gastric cancer resections in hospital of diagnosis			
≥ 10	1890 (33.6)	73.7	< 0.001
< 10	3730 (66.4)	68.0	

Values in parentheses are percentages. *T1 according to sixth edition of TNM classification (2005–2009) and cT4b according to seventh edition (2010–2013). †chi^2 test.

Hospital of diagnosis and probability of surgical treatment

The proportion of patients who underwent surgical treatment differed significantly between hospitals of diagnosis, varying from 53.1 to 83.9 per cent ($P < 0.001$). Multivariable multilevel analysis confirmed the effect of hospital of diagnosis on the probability of undergoing surgery. After adjustment for patient-related factors and type of hospital, surgical treatment rates ranged from 57.0 to 78.2 per cent according to hospital of diagnosis ($P < 0.001$) (Figure 2a). Comparing 2005–2009 with 2010–2013, the adjusted variation in surgical treatment probability between hospitals of diagnosis was comparable (54.3–84.8 per cent in 2005–2009 versus 47.8–78.4 per cent in 2010–2013) (Figure 2b,c). Subgroup analysis of patients within the ECR showed that, after adjustment for comorbidity and socioeconomic status, the mean probability of surgical treatment changed by 0.2 –2.3 per cent in the hospitals of diagnosis.

Table 2 Multivariable multilevel logistic regression analysis to examine predictors of surgery in patients diagnosed with potentially curable gastric cancer.

	Odds ratio
Age (years)	
< 60	1.00 (reference)
60–74	0.61 (0.48, 0.78)
≥ 75	0.16 (0.13, 0.21)
Sex	
M	1.00 (reference)
F	0.83 (0.73, 0.95)
Interval of diagnosis	
2005–2009	1.00 (reference)
2010–2013	0.47 (0.41, 0.55)
Clinical tumour classification	
cT1/1b	0.60 (0.41-0.88)
cT2	0.92 (0.71-1.19)
cT3	1.00 (reference)
cT4a	0.59 (0.33-1.05)
cTx/missing	0.86 (0.68-1.07)
Clinical node classification	
cN0	2.50 (1.85, 3.38)
cN1	1.16 (0.85, 1.60)
cN2	1.00 (reference)
cNx/unknown	0.45 (0.32, 0.61)
Type of hospital of diagnosis	
Academic	1.00 (reference)
Teaching	1.19 (0.85, 1.67)
Non-teaching	1.34 (0.95, 1.90)
No. of gastric cancer resections in hospital of diagnosis	
≥10	1.55 (1.27, 1.89)
<10	1.00 (reference)

Values in parentheses are 95 per cent c.i. Analyses adjusted for morphology, tumour location and all variables listed in this table.

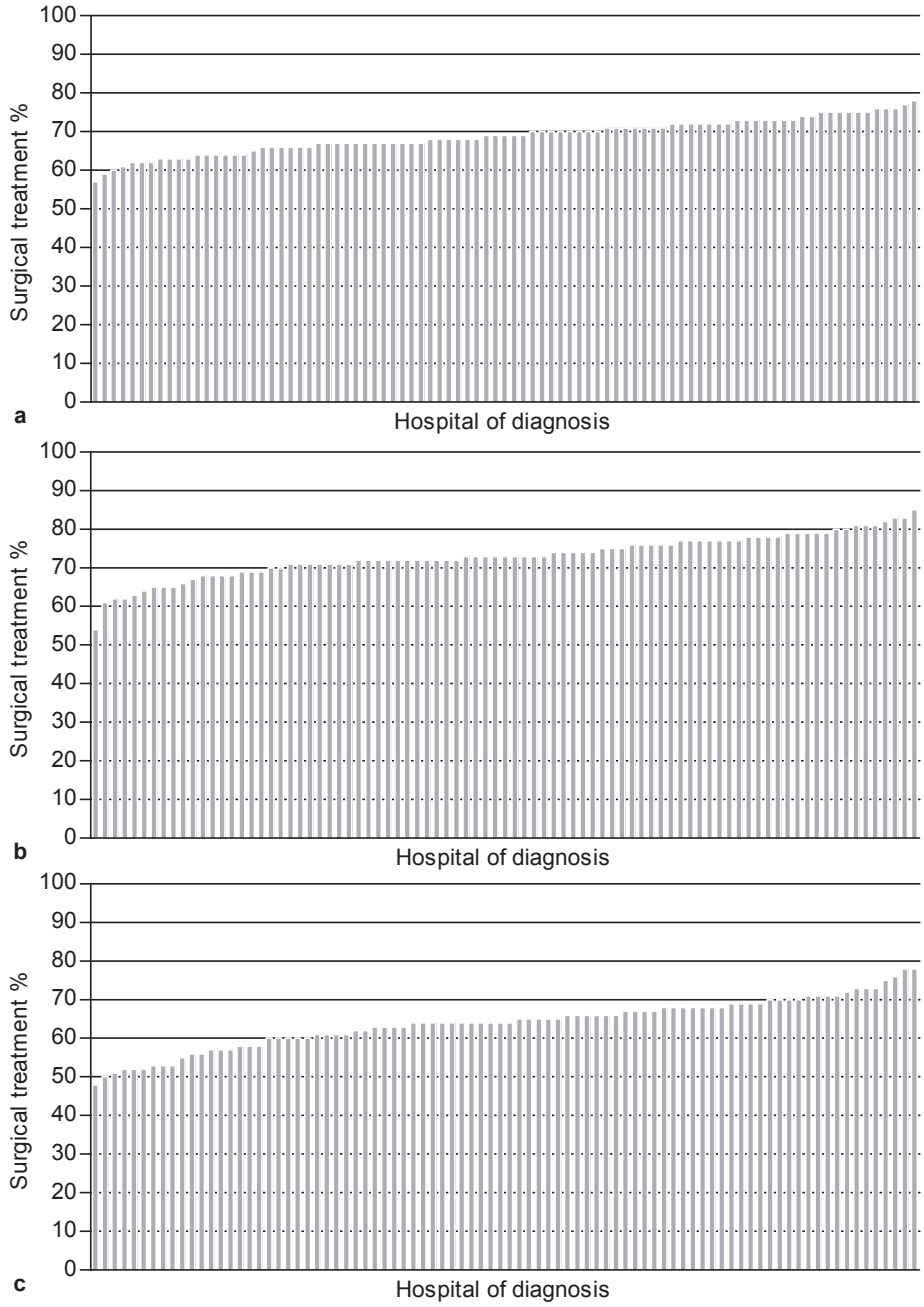

Figure 2 Multilevel adjusted variation in the proportion of patients with potentially curable gastric carcinoma who received a gastrectomy in the interval a 2005–2013 (5620 patients), b 2005–2009 (2821 patients) and c 2010–2013 (2739 patients).

Adjustment was made for age, sex, cT classification, cN classification, tumour location, morphology, interval of diagnosis, type of hospital of diagnosis, and annual number of resections in hospital of diagnosis. Each bar represents one hospital. Three hospitals were excluded from b and c because each had ten or fewer diagnoses in that interval.

Results of the multivariable multilevel analysis showed that, in addition to hospital of diagnosis, the following factors were associated with a lower probability of undergoing surgical treatment: older age, female sex, a cT1 tumour and clinically lymph node-positive disease. Being diagnosed in a hospital that performed ten or more resections per year was associated with a higher probability of having surgery (OR 1.55; $P < 0.001$) (Table 2). However, there was no association with type of hospital of diagnosis either in 2005–2009 or 2010–2013.

Hospital of diagnosis and overall survival

Multivariable Cox regression analysis showed that patients diagnosed between 2010 and 2013 in hospitals with a lower probability of undergoing surgical treatment (48–59 per cent) had worse overall survival than those diagnosed in hospitals with a higher probability (69–78 per cent) (adjusted HR 1.21; $P < 0.001$ (Table 3). However, in 2005–2009 no such association was found (Table 4).

Table 3 Univariable and multivariable Cox proportional hazards analyses of overall survival for patients with potentially curable gastric cancer in the Netherlands, 2010–2013

			Hazard ratio	
Surgical treatment probability (%)*	No. of patients (n = 2739)	Crude 2-year overall survival (%)	Univariable analysis	Multivariable analysis †
48–59	473	37.5	1.45 (1.25, 1.68)	1.21 (1.04, 1.41)
60–64	841	45.1	1.17 (1.03, 1.34)	1.04 (0.91, 1.19)
65–68	722	44.6	1.20 (1.04, 1.37)	1.10 (0.95, 1.26)
69–78	703	50.3	1.00 (reference)	1.00 (reference)

Values in parentheses are 95 per cent c.i. *Patients are included in one of the four groups according to the adjusted mean surgical treatment probability of the hospital where they were diagnosed in the interval 2010–2013. Twenty-eight patients were excluded from the analysis because they were diagnosed in a hospital that diagnosed ten or fewer patients in this interval. †Adjusted for age, sex, tumour stage, tumour location, morphology, tumour differentiation, type of hospital of diagnosis, and annual number of resections in hospital of diagnosis.

Table 4 Univariable and multivariable Cox proportional hazards analyses of overall survival for patients with potentially curable gastric cancer in the Netherlands, 2005–2009

			Hazard ratio	
Surgical treatment probability (%)*	No. of patients (n = 2821)	Crude 2-year overall survival (%)	Univariable analysis	Multivariable analysis†
54–69	594	50.0	1.11 (0.98, 1.25)	1.00 (0.88, 1.13)
70–72	604	48.2	1.15 (1.02, 1.30)	1.04 (0.91, 1.18)
73–75	766	48.8	1.13 (1.01, 1.27)	1.03 (0.91, 1.16)
76–85	857	52.0	1.00 (reference)	1.00 (reference)

Values in parentheses are 95 per cent c.i. *Patients are included in one of the four groups according to the adjusted mean surgical treatment probability of the hospital where they were diagnosed in the interval 2005–2009. Thirty-two patients were excluded from the analysis because they were diagnosed in a hospital that diagnosed ten or fewer patients in this interval. †Adjusted for age, sex, tumour stage, tumour location, morphology, tumour differentiation, type of hospital of diagnosis, and annual number of resections in hospital of diagnosis.

Discussion

In this population-based nationwide study the proportion of patients who underwent surgery varied between 53.1 and 83.9 per cent according to hospital of diagnosis. Multivariable multilevel logistic regression analysis confirmed the effect of hospital of diagnosis on the probability of undergoing surgical treatment. Patients with gastric cancer who had been diagnosed more recently in hospitals with a low probability of surgical treatment had worse overall survival than those diagnosed in hospitals with a high probability.

Variation in the probability of surgical treatment between hospitals of diagnosis remained after adjustment for differences in patient characteristics and type of hospital of diagnosis. In a previous study[14], it was suggested that comorbidity and socioeconomic status could also have influenced the probability of undergoing surgery.[14] Subgroup analysis of data from the ECR in the present study revealed only slight changes in probability of surgery after adjustment for comorbidity and socioeconomic status, indicating a minimal contribution of these factors to the variation in probabilities between hospitals of diagnosis. The present study has confirmed the variation in treatment probability among patients with gastric cancer, as shown previously for numerous other types of cancer, including bladder, breast and colonic cancer.[15–17]

Factors associated with a lower probability of surgery were older age and female sex. In concordance with this, previous Dutch studies[18,19] found that older age was associated with a lower probability of having surgery. There are no published reports on the relationship between sex and likelihood of gastric cancer surgery. However, four Dutch studies[8,18–20] noted that sex did not affect the probability of surgery for oesophageal cancer, whereas a North American study[21] found a significantly lower probability of oesophagectomy among women. Furthermore, patients with cT1 tumour were less likely to undergo surgical treatment. This was probably a result of the introduction of endoscopic mucosal resection in recent years.

In the present study, patients diagnosed between 2005 and 2009 had a higher probability of having surgery than those diagnosed between 2010 and 2013. These findings may be explained by developments in more sensitive diagnostic modalities that have led to more accurate tumour staging.[22] The decrease in resection rates could also be related to the introduction and extensive use of perioperative chemotherapy more recently, with some patients progressing to incurable disease during preoperative chemotherapy.

The type of hospital of diagnosis was not associated with the probability of surgery for gastric cancer in either time interval. This means that patients diagnosed in non-teaching hospitals do not have a lower chance of having surgery than those diagnosed in a teaching or academic hospital. Referral of patients diagnosed in non-teaching hospitals results in their likelihood of undergoing surgery being comparable to that of patients diagnosed in teaching and academic hospitals. However, there is still a large variation in probability of resection across hospitals of diagnosis that could probably be explained by factors other than institution type, such as patient frailty, patient preference, specialisation of the hospital and multidisciplinary team (MDT) meetings.[23]

In the Netherlands, gastric cancer surgery is increasingly being performed in higher-volume hospitals[24], the minimum volume having been increased to 20 gastrectomies per year from 2013. In Denmark, centralisation of gastric cancer has been associated with better surgical quality and a significant decline in mortality.[25] Similarly, centralisation of surgical treatment for

oesophageal and pancreatic cancer in the Netherlands has also been associated with improved outcomes.[24,26,27] Because centralisation of gastric cancer surgery has been introduced in the Netherlands more recently, the effect on mortality and survival could not be examined here.

The probability of surgical treatment could be influenced by organisational structures within a hospital or department, radiotherapy and endoscopic facilities, established clinical pathways or regional agreements, and protocols between one or multiple hospitals. In general, all hospitals in the Netherlands have an endoscopy unit and CT available at least. The probability of having surgical treatment could also be affected by the grade of specialisation of the hospital and medical specialists. The present study has shown that patients diagnosed in high-volume hospitals had a greater likelihood of receiving surgery than those diagnosed in low-volume hospitals. Two previous studies[22,28] reported that patients treated by medical specialists with higher caseloads were more likely to undergo surgery and other treatments than patients treated by lower-volume medical specialists. Higher-volume specialists used a wider range of investigations, which could not be explained by better access to these facilities.[22]

In the Netherlands, all patients with gastric cancer should be discussed in a MDT meeting for proper treatment decisions to be made. A MDT meeting could improve the adequacy and uniformity of treatment decisions, which may increase the probability of curative surgical treatment. Regional expert MDT meetings have shown to alter initial treatment plans frequently in patients with gastric, oesophageal, colorectal and breast cancer.[29] However, it is unknown whether a surgeon with experience in gastrectomies is always present. Implementation of regional expert MDT meetings with involvement of experienced surgeons may increase the overall survival of patients with gastric cancer through better selection for curative treatment or optimal palliative treatment.

Centralisation could have led to a greater influence of hospitals of diagnosis in the recent time interval. Centralisation would have led to an overall decrease in the number of gastric cancer specialists in the hospitals of diagnosis with sufficient experience in clinical decision-making, possibly resulting in fewer referrals to a specialised centre for curative treatment. However, in the earlier interval the introduction of perioperative chemotherapy, and thereby variation in quality of care, could have influenced survival more than hospital of diagnosis.

A limitation of the present study was that some factors influencing treatment decisions, such as frailty of the patient and performance status, were not registered adequately and could not therefore be included in the analyses. Furthermore, patients with distant metastasis (M1) and T4b tumours were excluded. However, the accuracy of the clinical staging and diagnostic methods used are unknown. Because endoscopic ultrasonography is not always performed in patients with gastric cancer, clinical stage was unknown in a relatively high percentage of patients (Table 1). The variation in missing data on cT and cN status between hospitals was much smaller than the interhospital variation in resection probabilities and is unlikely to have influenced the results substantially. In addition, clinical decision-making in gastric cancer is more often based on cN and cM than cT status; the exact cT category is often unknown because endoscopic ultrasonography is not performed and so the cT status is estimated by CT.

This study also has several strengths, such as its observational nature resulting in a representative population. This nationwide population-based study, including a large number of patients with potentially curable gastric cancer, has enabled evaluation of the probability of undergoing surgical treatment and its impact on survival.

References

1. Fock KM. Review article: the epidemiology and prevention of gastric cancer, 2014. Aliment Pharmacol Ther;40:250-260.
2. Dassen AE, Dikken JL, Bosscha K, Wouters MW, Cats A, van de Velde CJ, Coebergh JW, Lemmens VE. Gastric cancer: decreasing incidence but stable survival in the Netherlands, 2014. Acta Oncol;53:138-142.
3. Dassen AE, Lemmens VE, van de Poll-Franse LV, Creemers GJ, Brenninkmeijer SJ, Lips DJ, Vd Wurff AA, Bosscha K, Coebergh JW. Trends in incidence, treatment and survival of gastric adenocarcinoma between 1990 and 2007: a population-based study in the Netherlands, 2010. Eur J Cancer;46:1101-1110.
4. Tegels JJ, De Maat MF, Hulsewe KW, Hoofwijk AG, Stoot JH. Improving the outcomes in gastric cancer surgery, 2014. World J Gastroenterol;20:13692-13704.
5. Yasuda K, Shiraishi N, Adachi Y, Inomata M, Sato K, Kitano S. Risk factors for complications following resection of large gastric cancer, 2001. Br J Surg;88:873-877.
6. Dikken JL, van Sandick JW, Allum WH, Johansson J, Jensen LS, Putter H, Coupland VH, Wouters MW, Lemmens VE, van de Velde CJ, van der Geest LG, Larsson HJ, Cats A, Verheij M. Differences in outcomes of oesophageal and gastric cancer surgery across Europe, 2013. Br J Surg;100:83-94.
7. Bakens MJ, van Gestel YR, Bongers M, Besselink MG, Dejong CH, Molenaar IQ, Busch OR, Lemmens VE, de Hingh IH. Hospital of diagnosis and likelihood of surgical treatment for pancreatic cancer, 2015. Br J Surg.
8. Koeter M, van Steenbergen LN, Lemmens VE, Rutten HJ, Roukema JA, Wijnhoven BP, Nieuwenhuijzen GA. Hospital of diagnosis and probability to receive a curative treatment for oesophageal cancer, 2014. Eur J Surg Oncol;40:1338-1345.
9. Fritz AG. International classification of diseases for oncology: ICD-O 2000, 3rd ed. Geneva: World Health Organization.
10. UICC. TNM classification of malignant tumours, 2002, 6th ed. New York: Wiley-Liss.
11. UICC. TNM classification of malignant tumours, 2009, 7th ed. New York: Wiley-Liss.
12. Twisk JW. Applied multilevel analysis: a practical guide, 2006ed.: Cambridge University Press.
13. Austin PC, Tu JV, Alter DA. Comparing hierarchical modeling with traditional logistic regression analysis among patients hospitalized with acute myocardial infarction: should we be analyzing cardiovascular outcomes data differently?, 2003. Am Heart J;145:27-35.
14. Koppert LB, Lemmens VE, Coebergh JW, Steyerberg EW, Wijnhoven BP, Tilanus HW, Janssen-Heijnen ML. Impact of age and co-morbidity on surgical resection rate and survival in patients with oesophageal and gastric cancer, 2012. Br J Surg;99:1693-1700.
15. Goossens-Laan CA, Visser O, Wouters MW, Jansen-Landheer ML, Coebergh JW, van de Velde CJ, Hulshof MC, Kil PJ. Variations in treatment policies and outcome for bladder cancer in the Netherlands, 2010. Eur J Surg Oncol;36 Suppl 1:S100-107.
16. Gort M, Broekhuis M, Otter R, Klazinga NS. Improvement of best practice in early breast cancer: actionable surgeon and hospital factors, 2007. Breast Cancer Res Treat;102:219-226.
17. Lemmens VE, van Halteren AH, Janssen-Heijnen ML, Vreugdenhil G, Repelaer van Driel OJ, Coebergh JW. Adjuvant treatment for elderly patients with stage III colon cancer in the southern Netherlands is affected by socioeconomic status, gender, and comorbidity, 2005. Ann Oncol;16:767-772.
18. Trip AK, Stiekema J, Visser O, Dikken JL, Cats A, Boot H, van Sandick JW, Jansen EP, Verheij M. Recent trends and predictors of multimodality treatment for oesophageal, oesophagogastric junction, and gastric cancer: A Dutch cohort-study, 2015. Acta Oncol:1-9.
19. Dassen AE, Dikken JL, van de Velde CJ, Wouters MW, Bosscha K, Lemmens VE. Changes in treatment patterns and their influence on long-term survival in patients with stages I-III gastric cancer in The Netherlands, 2013. Int J Cancer;133:1859-1866.
20. Bus P, Aarts MJ, Lemmens VE, van Oijen MG, Creemers GJ, Nieuwenhuijzen GA, van Baal JW, Siersema PD. The effect of socioeconomic status on staging and treatment decisions in esophageal cancer, 2012. J Clin Gastroenterol;46:833-839.

21. Paulson EC, Ra J, Armstrong K, Wirtalla C, Spitz F, Kelz RR. Underuse of esophagectomy as treatment for resectable esophageal cancer, 2008. Arch Surg;143:1198-1203; discussion 1203.

22. Bachmann MO, Alderson D, Edwards D, Wotton S, Bedford C, Peters TJ, Harvey IM. Cohort study in South and West England of the influence of specialization on the management and outcome of patients with oesophageal and gastric cancers, 2002. Br J Surg;89:914-922.

23. Hamaker ME, Bastiaannet E, Evers D, Water W, Smorenburg CH, Maartense E, Zeilemaker AM, Liefers GJ, Geest L, de Rooij SE, van Munster BC, Portielje JE. Omission of surgery in elderly patients with early stage breast cancer, 2013. Eur J Cancer;49:545-552.

24. Dikken JL, Dassen AE, Lemmens VE, Putter H, Krijnen P, van der Geest L, Bosscha K, Verheij M, van de Velde CJ, Wouters MW. Effect of hospital volume on postoperative mortality and survival after oesophageal and gastric cancer surgery in the Netherlands between 1989 and 2009, 2012. Eur J Cancer;48:1004-1013.

25. Jensen LS, Nielsen H, Mortensen PB, Pilegaard HK, Johnsen SP. Enforcing centralization for gastric cancer in Denmark, 2010. Eur J Surg Oncol;36 Suppl 1:S50-54.

26. Lemmens VE, Bosscha K, van der Schelling G, Brenninkmeijer S, Coebergh JW, de Hingh IH. Improving outcome for patients with pancreatic cancer through centralization, 2011. Br J Surg;98:1455-1462.

27. van de Poll-Franse LV, Lemmens VE, Roukema JA, Coebergh JW, Nieuwenhuijzen GA. Impact of concentration of oesophageal and gastric cardia cancer surgery on long-term population-based survival, 2011. Br J Surg;98:956-963.

28. Bachmann MO, Alderson D, Peters TJ, Bedford C, Edwards D, Wotton S, Harvey IM. Influence of specialization on the management and outcome of patients with pancreatic cancer, 2003. Br J Surg;90:171-177.

29. Davies AR, Deans DA, Penman I, Plevris JN, Fletcher J, Wall L, Phillips H, Gilmour H, Patel D, de Beaux A, Paterson-Brown S. The multidisciplinary team meeting improves staging accuracy and treatment selection for gastro-esophageal cancer, 2006. Dis Esophagus;19:496-503.

Chapter 5

Improved survival after centralisation of gastric cancer surgery in the Netherlands

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Abstract

Background
Centralisation of surgery has been shown to improve outcomes for oesophageal and pancreatic cancer and has been imposed for gastric cancer since 2012 in the Netherlands. This study evaluates the impact of centralising gastric cancer surgery on outcome for all patients with gastric cancer.

Methods
Patients diagnosed between 2009-2011 and 2013-2015 with non-cardia gastric adenocarcinoma were selected from the Netherlands Cancer Registry. Results were compared for the period before centralisation (2009-2011) and after centralisation (2013-2015). Cox regression analyses were used to assess differences in overall survival between periods.

Results
A total of 7204 patients were included. Resection rates slightly increased from 38.0% pre-centralisation to 40.6% post-centralisation (*P*=0.026). Pre-centralisation, 50.1% of the surgically treated patients underwent a gastrectomy in hospitals that annually performed <10 procedures, whereas post-centralisation 9.2% of the patients underwent a gastrectomy in these low-volume hospitals. Patients who underwent a gastrectomy in the second period were younger and underwent more often a total gastrectomy (29.3% pre-centralisation vs. 41.2% post-centralisation). Postoperative 30- and 90-day mortality rates dropped from 6.5 to 4.1% and from 10.6 to 7.2%, respectively (*P*=0.004 and *P*=0.002). Two-year overall survival rates increased from 55.4 to 58.5% for patients who had gastrectomy (*P*=0.031) and from 27.1 to 29.6% for all patients (*P*=0.003). Improvements remained after adjustment for case-mix however, adjustment for hospital volume attenuated this association for surgically treated patients.

Conclusions
Centralisation of gastric cancer surgery was related with a reduced postoperative mortality for surgically treated patients and an improved survival for gastric cancer patients, irrespective of treatment.

Introduction

Gastric cancer is the fifth most common cancer and the third leading cause of cancer death worldwide.[1] Although the incidence has decreased over the last decades in the Netherlands, prognosis remains poor. The 5-year overall survival rate for patients with gastric cancer is approximately 25% in Western countries.[2-4] Although survival remained dismal during the last two decades, only a minor improvement was observed in recent years in the Netherlands.[3, 5]

Surgery is the cornerstone of curative treatment for gastric cancer, however due to the rather low incidence of gastric cancer in the Netherlands most hospitals in the Netherlands previously performed only a limited annual number of gastrectomies.[6] Moreover, gastric cancer surgery is considered to be surgery with relative high morbidity and mortality rates.[7-9]

Numerous studies have shown a strong and consistent inverse relationship between the hospital volume of high-risk surgical procedures and postoperative mortality.[10-14] In order to improve survival and decrease morbidity for gastric cancer patients, centralisation has been initiated in the Netherlands. Since 2012, hospitals should perform a minimum of 10 gastrectomies per year, and since 2013 the minimal annual hospital volume of gastrectomies for cancer was increased to 20.

Results from previous studies investigating the effects of centralisation of gastric cancer surgery on patient outcome are ambiguous.[12,14,15] On the one hand, studies from Denmark and the United Kingdom showed that patients who underwent a gastrectomy in the period after centralisation had a lower postoperative mortality and better overall survival compared to patients in the period before centralisation.[12,14] Also other studies have shown that increased volumes were associated with a lower postoperative mortality and improved survival after gastric cancer surgery.[11,13] On the other hand, a previous Dutch study including surgically treated patients in the Eastern part of the country, has found no improvement in overall survival for surgically treated patients after centralisation probably related to a small number of patients.[15] Furthermore, a study from Thompson et al found no relationship between hospital volume and long-term survival after gastric cancer surgery.[16]

The abovementioned studies only included patients who underwent a gastrectomy. The improvement in survival after a gastrectomy found by several studies may be explained by patient selection rather than better care. Medical specialists may perform a more critical pre-operative selection withholding the less fit patients from surgical treatment. As a result, overall survival may only be improved for the selected group of patients and may be worse for all patients.[17] Tor avoid the possible confounding effect of selective patient referral, this study evaluates the impact of centralisation of gastric cancer surgery for all gastric cancer patients in a population-based setting.

Methods

Data source

Data were obtained from the population-based Netherlands Cancer Registry (NCR). This registry serves the total Dutch population of 16.9 million inhabitants. The NCR is based on notification of all newly diagnosed malignancies in the Netherlands by the national automated

pathological archive (PALGA). Additional sources are the national registry of hospital discharge and radiotherapy institutions. Specially trained data managers of the NCR routinely extract information on diagnosis, tumour stage, and treatment from the medical records. Information on vital status was obtained through an annual linkage with the Municipal Administration Database, in which all deceased and emigrated persons in the Netherlands are registered. This study was approved by the Privacy Review Board of the Netherlands Cancer Registry and does not require approval from an ethics committee in the Netherlands.

Patient selection criteria

The reporting of this study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[18] For this study we selected patients diagnosed with non-cardia gastric adenocarcinoma between 2009-2011 and 2013-2015 in the Netherlands from the NCR. This study compared overall survival for all patients between the period preceding centralisation (2009-2011) and the period after centralisation (2013-2015) and those treated surgically in the same intervals. We considered 2012 as a transition year, as the first initiatives to centralize gastric cancer surgery started in the first months of 2012 and the current minimum hospital volume of 20 resections per year was imposed as of 2013. Survival of all patients with gastric cancer, regardless of treatment, was evaluated to rule out the possible confounding effect of patient selection.

Tumour location and stage

Topography and morphology were coded according to the International Classification of Diseases for Oncology (ICD-O-3).[19] Tumour staging was performed according to the International Union Against Cancer (UICC) TNM classification that was valid at the time of diagnosis. Patients diagnosed in 2009 were staged according to TNM-6 and patients diagnosed between 2010 and 2015 were staged according to TNM-7.[20,21] For analyses among all patients, regardless of treatment, the pathologic stage of the resection specimen was used, or, if not available, clinical tumour stage was noted. For analyses among patients who underwent a gastrectomy the pathological tumour stage was used. TNM-7 tumour staging was recoded according to TNM-6, which means that patients with a cT4A tumour according to TNM-7 were recoded as having a cT3 tumour according to TNM-6. Furthermore, patients with a cN1 or cN2 according to TNM-7 were recoded as having a cN1 tumour according to TNM-6.

Surgery

Surgery for gastric cancer was classified according to the NCR as subtotal gastrectomy, total gastrectomy or multi-organ resection, which was defined as a gastrectomy and surgical removal of other organs. The experience of hospitals performing gastrectomies was defined in categories. For example, if a patients underwent a gastrectomy in 2015 in a hospital that performed 20 or more gastrectomies in 2015, the patient was included in the group of hospitals with an annual volume of at least 20 procedures. As gastrectomies could also be performed for tumours of the cardia, we included both cardia and non-cardia gastric cancer in our calculations for defining the annual number of gastrectomies per hospital. Data of cardia tumours were only used to define the annual number of gastrectomies per hospital and were not used for other purposes.

Statistical analysis

Descriptive statistics were used to characterize the patients before and after centralisation of surgery. Differences in characteristics were analysed by means of chi-squared tests for nominal data and ANOVA for continuous data.

Kaplan-Meier curves were generated to examine overall survival before and after centralisation for all patients and for surgically treated patients. Survival curves were compared with the log-rank test. Cox proportional hazard regression analyses were performed to investigate the effect of period on overall survival for all patients and surgically treated patients after adjustment for potential confounding factors. For survival analyses based on patients who underwent a gastrectomy survival time was defined as time from gastrectomy to death or until February 1st 2017 for patients who were still alive. For survival analyses based on all patients, irrespective of treatment, survival time was defined as time from diagnosis to death or until February 1st 2017 for patients who were still alive. Hazard ratios (HRs) were calculated with 95 percent confidence intervals. All analyses were conducted using SAS version 9.4 (Statistical Analysis System). All reported *p* values of <0.05 were considered statistically significant.

Results

Between 2009-2011 and 2013-2015, 7204 patients were diagnosed with gastric cancer. 3777 patients were diagnosed between 2009-2011 and 3427 patients between 2013-2015. No clinically relevant differences were observed for patients in the period before centralisation and after centralisation of surgery (Table 1). Patients diagnosed in the period before centralisation had more often an unknown tumour stage compared to the period thereafter. The proportion of patients who underwent a gastrectomy slightly increased over time as 38.0 per cent of the patients underwent a gastrectomy in the period before centralisation and 40.6 per cent of the patients underwent a gastrectomy in the later period (*P*=0.026).

In the first period, 50.1 per cent of the surgically treated patients underwent a gastrectomy in hospitals that performed less than 10 procedures each year, whereas in the second period only 9.2 per cent of the patients underwent a gastrectomy in these low-volume hospitals (Figure 1). After centralisation, 54.3 per cent of the patients underwent a gastrectomy in a high-volume hospital (performing 20 or more procedures each year). The percentage of patients who underwent a gastrectomy in high-volume hospitals increased in the second period from 39.2 per cent in 2013 to 61.0 per cent in 2015. Furthermore, the percentage of patients referred by the hospital of diagnosis to another hospital for preoperative chemotherapy slightly increased from 16.7 per cent in the period before centralisation to 24.7 per cent in the period thereafter.

Compared with those who had a gastrectomy in the first period, patient who underwent a gastrectomy in the second period were younger, more often had a proximal tumour, a stage III tumour, and underwent more often pre- and/or postoperative chemotherapy (Table 2). The proportion of patients who underwent chemotherapy prior to surgery increased from 45.3 per cent pre-centralisation to 55.5 per cent post-centralisation. Furthermore, the proportion of patients who underwent a total gastrectomy increased from 29.3 percent pre-centralisation to 41.2 percent post-centralisation. Patients who underwent a gastrectomy in the second period had a lower postoperative mortality. The postoperative 30- and 90-day mortality decreased

significantly from respectively 6.5 and 10.6 per cent before centralisation to 4.1 and 7.2 per cent in the period after centralisation. Furthermore, the proportion of patients with a radical resection increased from 76.8 per cent in the first period to 80.6 per cent in the second period and the proportion of patients with more than 15 resected lymph nodes retrieved increased as well, from 38.4 to 68.6 per cent during these time periods.

Table 1 Characteristics of patients with non-cardia gastric cancer by period of diagnosis in the Netherlands, 2009-2011 and 2013-2015 (n=7204).

	2009-2011 n=3777		2013-2015 n=3427		
	n	%	n	%	*P* value
Gender					0.404
Male	2256	59.7	2080	60.7	
Female	1521	40.4	1347	39.3	
Age (yrs.)					0.149
< 60	646	17.1	619	18.1	
60- 74	1440	38.1	1351	39.4	
≥ 75	1691	44.8	1457	42.5	
Tumour location					0.176
Proximal/ middle [a]	1101	29.2	1057	30.8	
Antrum	1102	29.2	949	27.7	
Pyloric	269	7.1	217	6.3	
Overlapping, unknown	1305	34.6	1204	35.1	
Pathological, or if not available clinical tumour stage					<0.001
Complete response	49	1.3	79	2.3	
I	496	13.1	431	12.6	
II	549	14.5	509	14.9	
III	595	15.8	617	18.0	
IV	1576	41.7	1389	40.5	
Unknown	513	13.6	402	11.7	
Tumour grade					0.286
Moderate/ well differentiated	546	14.5	538	15.7	
Poorly differentiated or anaplastic	1608	42.6	1459	42.6	
Unknown	1623	43.0	1430	41.7	
Treatment					0.001
Perioperative CT/CRT	375	9.9	447	13.0	
Preoperative CT – surgery	310	8.2	303	8.8	
Surgery alone	736	19.5	608	17.7	
Chemotherapy alone	699	18.5	619	18.1	
Other	350	9.3	304	8.9	
None	1307	34.6	1146	33.4	

[a] Proximal / middle = Fundus, corpus and greater and lesser curvature.
CT= chemotherapy, CRT=chemoradiotherapy

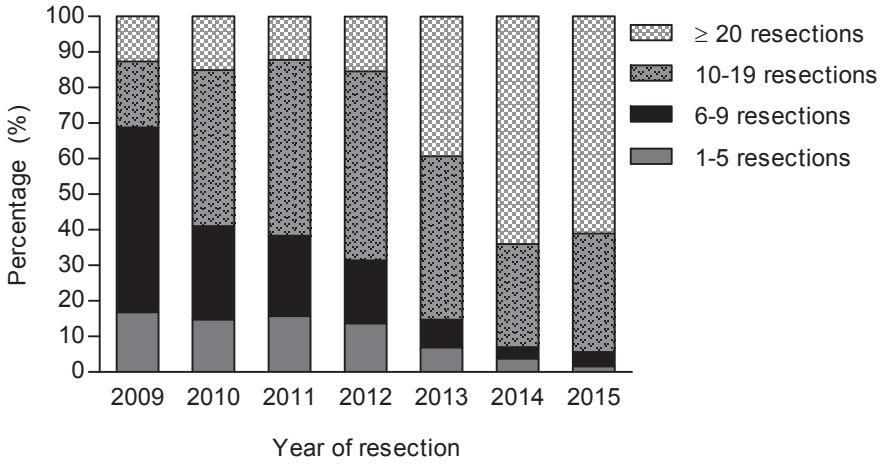

Figure 1 Percentage of patients treated with a gastrectomy for cancer per hospital volume category.

5

Table 2 Characteristics of patients with non-cardia gastric cancer who underwent a gastrectomy by period of surgery in the Netherlands, 2009-2011 and 2013-2015 (n=2819).

	2009-2011 n=1418		2013-2015 n=1401		
	n	%	n	%	*P* value
Gender					0.220
Male	867	61.1	888	63.4	
Female	551	38.9	513	36.6	
Age (years)					<0.001
< 60	290	20.5	304	21.7	
60- 74	580	40.9	654	46.7	
≥ 75	548	38.6	443	31.6	
Tumour location					0.012
Proximal/ middle [a]	419	29.5	492	35.1	
Antrum	506	35.7	468	33.4	
Pyloric	147	10.4	119	8.5	
Overlapping, unknown	346	24.4	322	23.0	
Pathological tumour stage					<0.001
Complete response	44	3.1	67	4.8	
I	429	30.3	338	24.1	
II	410	28.9	396	28.3	
III	397	28.0	496	35.5	
IV	137	9.7	96	6.9	
Unknown	1	<1.0	8	<1.0	

Table 2 continues on next page.

Tumour grade					0.896
Moderate/ well differentiated	287	20.2	285	20.3	
Poorly differentiated or anaplastic	713	50.3	693	49.5	
Unknown	418	29.5	423	30.2	
Preoperative chemotherapy					<0.001
No	776	54.7	623	44.5	
Yes	642	45.3	778	55.5	
Postoperative treatment					<0.001
No	1015	71.6	906	64.7	
Yes	403	28.4	495	35.3	
Type of gastrectomy					<0.001
Total	415	29.3	577	41.2	
Subtotal	962	67.8	792	56.5	
Multi-organ /unknown	41	2.9	32	2.3	
Hospital volume					<0.001
1-9	711	50.1	129	9.2	
10-19	523	36.9	511	36.5	
≥ 20	184	13.0	761	54.3	
Outcomes					
Radicality					0.009
R0	1089	76.8	1129	80.6	
R+	274	19.3	210	15.0	
Unknown	55	3.9	62	4.4	
Number of investigated lymph nodes					<0.001
< 15	868	61.2	425	30.3	
≥ 15	544	38.4	961	68.6	
Unknown	6	<1.0	15	1.1	
Hospital stay in days (Median (IQR))	10	8-15	9	7-13	<0.001[b]
Postoperative 30-day mortality	92	6.5	57	4.1	0.004
Postoperative 60-day mortality	124	8.7	81	5.8	0.003
Postoperative 90-day mortality	150	10.6	101	7.2	0.002

[a] Proximal / middle = Fundus, corpus and greater and lesser curvature. [b] ANOVA, unknown category excluded.

Kaplan Meier survival curves showed that patients who underwent a gastrectomy in the period after centralisation had a better 2-year overall survival compared to patients who underwent a gastrectomy in the period before centralisation (58.5 per cent and 55.4 per cent respectively, *P*=0.031; Figure 2). Multivariable Cox regression analysis confirmed that survival was better in the later period (HR=0.88 95%CI 0.79-0.98) after adjustment for age, gender, tumour location, tumour stage, neoadjuvant chemotherapy and type of gastrectomy (Table 3). However, additional adjustment for annual hospital volume attenuated this association (HR=0.91, 95%CI 0.80-1.03) suggesting that increasing volume through centralisation contributed to the improved survival over time. Hospital volume itself was however not significant in the model, but results showed a hazard ratio smaller than 1 suggesting a better overall survival for patients who underwent surgery in a high- volume hospital.

The 2-year overall survival for non-surgically treated patients did not change significantly and was 7.8 per cent in the period before centralisation and 7.4 per cent in the period after centralisation. Median survival for non-surgically treated patients remained stable with 17 weeks in the period before centralisation and 18 weeks in the period after centralisation (*P*=0.463).

Figure 3 showed an improvement over time among all patients, irrespective of treatment, from a 2-year overall survival rate of 27.1 per cent in the period before centralisation to 29.6 per cent in the period after centralisation (*P*=0.003). Multivariable Cox regression analysis confirmed that survival was better in the period after centralisation even after adjustment for age, gender, tumour stage, tumour location and tumour grade (HR=0.95 95%CI 0.90-0.99; Table 4).

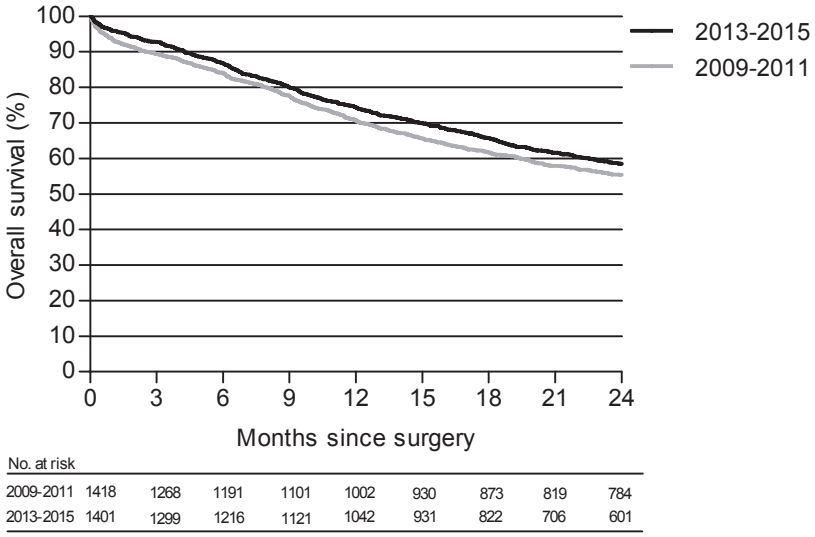

Figure 2 Overall survival among patients who underwent gastrectomy for gastric cancer in the period 2009-2011 and 2013-2015 (n=2819; *P*=0.031).
Survival time was defined as time from gastrectomy to death or until February 1st 2017 for patients who were still alive.

Table 3 Univariable and multivariable Cox regression analyses of gastric cancer patients who underwent a gastrectomy in the period 2009-2011 and 2013-2015 (n=2819).

	Univariable analysis	Multivariable analysis	Multivariable analysis**
	HR (95%CI)	HR (95%CI)	HR (95%CI)
Period of resection			
2009-2011	ref	ref	ref
2013-2015	0.89 (0.80-0.99)	0.88 (0.79-0.98)	0.91 (0.80-1.03)
Gender			
Male	ref	ref	ref
Female	0.96 (0.87-1.06)	0.98 (0.89-1.08)	0.98 (0.89-1.09)
Age (yrs.)			
< 60	ref	ref	ref
60- 74	1.11 (0.97-1.27)	1.11 (0.96-1.28)	1.11 (0.96-1.27)
≥ 75	1.57 (1.36-1.80)	1.38 (1.18-1.61)	1.38 (1.18-1.62)
Tumour location			
Proximal/ middle	ref	ref	ref
Antrum	1.04 (0.92-1.18)	1.10 (0.96-1.26)	1.10 (0.96-1.26)
Pyloric	1.20 (0.99-1.43)	1.18 (0.98-1.43)	1.18 (0.97-1.42)
Overlapping, unknown	1.47 (1.29-1.67)	1.32 (1.16-1.50)	1.31 (1.15-1.50)
Pathological tumour stage			
Complete response	0.31 (0.20-0.48)	0.36 (0.23-0.57)	0.36 (0.23-0.57)
I	0.48 (0.41-0.56)	0.47 (0.40-0.56)	0.47 (0.40-0.55)
II *	ref	ref	ref
III	2.48 (2.19-2.81)	2.41 (2.13-2.72)	2.40 (2.12-2.71)
IV	4.55 (3.82-5.38)	4.49 (3.79-5.32)	4.47 (3.77-5.29)
Preoperative chemotherapy***			
No	ref	ref	ref
Yes	0.66 (0.60-0.73)	0.74 (0.66-0.84)	0.74 (0.66-0.84)
Type of gastrectomy			
Total	ref	ref	ref
Subtotal	0.75 (0.68-0.84)	0.77 (0.69-0.87)	0.77 (0.68-0.86)
Multi-organ /unknown	1.11 (0.82-1.51)	0.86 (0.63-1.17)	0.86 (0.63-1.17)
Hospital volume			
1-9	ref		ref
10-19	0.95 (0.84-1.07)		0.96 (0.85-1.08)
≥ 20	0.89 (0.79-1.01)		0.92 (0.79-1.06)

Survival time was defined as time from gastrectomy to death or until February 1st 2017 for patients who were still alive.
* including 9 patients with an unknown pathological tumour stage
** Additionally adjusted for hospital volume
*** No adjustment was made for receiving postoperative chemotherapy as adjustment for postoperative chemotherapy would result in immortal time bias for patients who underwent postoperative chemotherapy

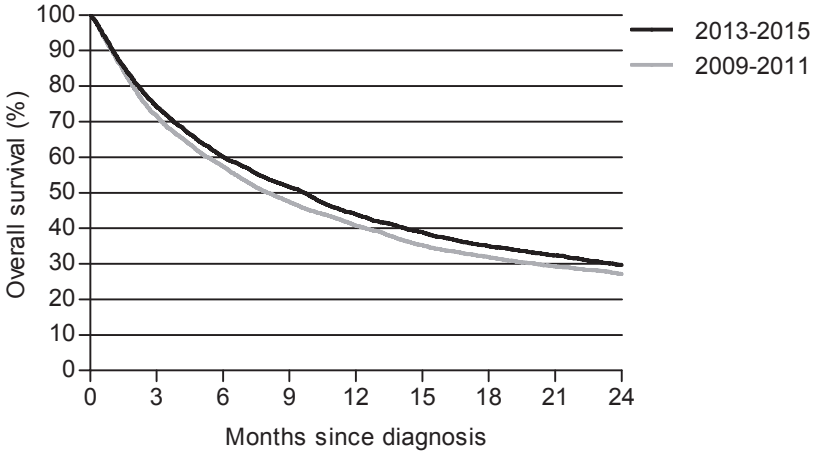

Figure 3 Overall survival among all patients with gastric cancer in the period 2009-2011 and 2013-2015 (n=7204; *P*=0.003).
Survival time was defined as time from diagnosis to death or until February 1st 2017 for patients who were still alive.

Discussion

This population-based study on the effect of centralisation of surgery for gastric cancer demonstrated an improvement of surgical quality (i.e. lymph node retrieval and radical resection rate), a reduction of postoperative mortality and an improvement in overall survival for all patients in the period after centralisation. Although other mechanisms may play a role, the fact that survival improved for both surgically treated patients and for all patients irrespective of treatment, but not among patients who did not undergo a gastrectomy, suggests that advances in (peri-)operative treatment and factors closely related to surgical treatment have made an important contribution to these improvements. Moreover, the variable 'period' was correlated with hospital volume for patients who underwent surgery.

Although centralisation of oesophageal and pancreatic cancer surgery has been shown to be beneficial in terms of overall survival, the benefits of centralising gastric cancer surgery seemed ambiguous according to previous studies.[11,16,22] Some studies found a reduced postoperative mortality and better overall survival for patients who underwent a gastrectomy in the period after centralisation, while others found no improvement in overall survival after centralisation, probably related to the small number of patients included.[12,14,15] These previous studies included only patients who underwent surgical treatment. To the best of our knowledge, the effect of centralisation of surgery for surgically as well as non-surgically treated patients with gastric cancer was not shown previously. Therefore, this study investigated the effect of centralisation of surgery for all patients with gastric cancer irrespective of treatment to rule out the possible confounding effect of selective referral. Results showed an improvement in overall survival for all gastric cancer patients which is in concordance with results from previous studies which

Table 4 Multivariable Cox regression analysis of all gastric cancer patients diagnosed in the period 2009-2011 and 2013-2015 (n=7204)

	Univariable analysis	Multivariable analysis
	HR (95%CI)	HR (95%CI)
Period of diagnosis		
2009-2011	ref	ref
2013-2015	0.92 (0.87-0.97)	0.95 (0.90-0.99)
Gender		
Male	ref	ref
Female	1.05 (0.99-1.11)	1.03 (0.97-1.08)
Age (yrs.)		
< 60	ref	ref
60- 74	1.14 (1.06-1.24)	1.27 (1.17-1.37)
≥ 75	1.65 (1.53-1.78)	2.04 (1.89-2.21)
Tumour location		
Proximal/ middle	ref	ref
Antrum	0.97 (0.90-1.04)	1.05 (0.97-1.12)
Pyloric	0.97 (0.87-1.09)	1.02 (0.91-1.15)
Overlapping, unknown	1.54 (1.45-1.64)	1.26 (1.18-1.34)
Pathological, or if not available clinical tumour stage		
I *	0.65 (0.58-0.74)	0.65 (0.57-0.74)
II	ref	ref
III	2.12 (1.91-2.35)	2.09 (1.89-2.32)
IV	5.76 (5.25-6.32)	5.73 (5.22-6.30)
Unknown	4.98 (4.47-5.55)	4.05 (3.62-4.52)
Tumour grade		
Moderate/ well differentiated	ref	ref
Poorly differentiated or anaplastic	1.48 (1.36-1.60)	1.28 (1.18-1.40)
Unknown	1.57 (1.45-1.70)	1.25 (1.15-1.36)

Survival time was defined as time from diagnosis to death or until February 1st 2017 for patients who were still alive.
*Including patients with a complete response as only a few patients of all patients with gastric cancer have a complete response.

investigated the impact of centralisation of surgery for all oesophageal and pancreatic cancer patients.[10,23]

An explanation for improved survival after centralisation could be 'practice makes perfect'. This suggests that more experience gained in hospitals that treat a greater number of patients could lead to improvements in the management of patients across the whole treatment pathway.[17] For example, specialisation of a surgeon should increase their experience including a better or more radical resection with extensive lymph node dissection in a higher proportion.[24,25] It is conceivable that the greater exposure of other medical specialists and nurses to patients after gastric cancer surgery increases their ability to timely recognize and treat complications at an earlier stage and by doing so decrease the failure to rescue rate and subsequently postoperative mortality.[26,27] Moreover, better patient selection by appropriate preoperative staging using endoscopic ultrasound and PET performed by experienced radiation oncologists and gastroenterologists is likely to play a significant role in improving survival.[28,29]

'Practice makes perfect' may also be reflected by another trend found by the present study. Results demonstrated a 11.9 per cent increase in the number of total gastrectomies and a decrease of 11.3 per cent in the number of subtotal gastrectomies after centralisation. Interestingly, even though a total gastrectomy, which is associated with more postoperative complications, is more commonly performed, postoperative mortality and survival still improved for surgically treated patients in the present study.[30,31] Furthermore, surgically treated patients had more often a stage III tumour in the period after centralisation compared to the period before which may be explained by stage migration due a more extensive lymph node dissection.

The improvement in survival after centralisation of gastric cancer surgery may also be supported by developments other than those affecting surgical volume. The increased use of perioperative chemotherapy since 2006 may have improved overall survival for patients who underwent a gastrectomy.[7] Medical oncologists may be more aware of the possibilities of perioperative chemotherapy when treating more patients with gastric cancer. In addition, postoperative complications are the main reason for not starting with chemotherapy after a gastrectomy.[7] The use of postoperative chemotherapy probably increased due to less complications after a gastrectomy. Even though we adjusted for preoperative chemotherapy in the multivariable analysis, survival was still better after centralisation for surgically treated patients. However, no adjustment was made for receiving postoperative chemotherapy as adjustment for postoperative chemotherapy would result in immortal time bias for patients who underwent postoperative chemotherapy. A landmark approach, assessing survival after four months after a gastrectomy, would have decreased the immortal time bias, however it excludes the patients who died within four months after a gastrectomy and obscures the effect of a reduced postoperative mortality on overall survival.

A reduction in postoperative mortality and improved overall survival for surgical patients with gastric cancer is sometimes challenged due to selection of patients that already have a higher chance on superior outcomes.[17] This phenomena can be accompanied by a decreased resection rate. In the present study however, the resection rate increased. On the other hand, patients were slightly younger in the period after centralisation. Nevertheless, overall survival improved for all patients in the period after centralisation. So, selective referral of patients may slightly have influenced the improved results found for surgically treated patients, but can certainly not be the only cause for improvement in survival.

During the study period the use of laparoscopic gastrectomy increased. It is suggested that laparoscopic gastrectomy causes less perioperative blood loss, fewer post-operative complications, shorter hospital stay, but have equal surgical oncological results (i.e. radicality and lymph nodes harvest) and post-operative mortality.[32,33] Furthermore, a previous Dutch study from Brenkman et al, also based on the NCR, found a comparable 1-year overall survival for patients who underwent an open versus laparoscopic gastrectomy in the period 2010-2014.[34] Therefore, improved survival for surgically treated patients after centralisation cannot be explained by the increased use of laparoscopic gastrectomy.

This study has some limitations. First, the impact of centralisation on other important outcomes was not examined, such as postoperative complications, health care cost or quality of life. Second, it was not possible to adjust for performance status and comorbidity as this information was lacking nationwide. A major strength of the present study is its population

based nature, which enables us to capture all patients with gastric cancer in the Netherlands and compare the outcomes for the entire group of patients before and after the period of centralisation.

In conclusion, the present study found an improved overall survival for all patients in the period after centralisation of gastric cancer surgery. The impact on survival is likely to be both due to individual surgical experience and collective team expertise.

References

1. Fock KM. Review article: the epidemiology and prevention of gastric cancer, 2014. Aliment Pharmacol Ther;40:250-260.
2. Anderson LA, Tavilla A, Brenner H, Luttmann S, Navarro C, Gavin AT, Holleczek B, Johnston BT, Cook MB, Bannon F, Sant M, Group E-W. Survival for oesophageal, stomach and small intestine cancers in Europe 1999-2007: Results from EUROCARE-5, 2015. Eur J Cancer;51:2144-2157.
3. Dassen AE, Dikken JL, Bosscha K, Wouters MW, Cats A, van de Velde CJ, Coebergh JW, Lemmens VE. Gastric cancer: decreasing incidence but stable survival in the Netherlands, 2014. Acta Oncol;53:138-142.
4. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016, 2016. CA Cancer J Clin;66:7-30.
5. Nelen SD, Verhoeven RH, Lemmens VE, de Wilt JH, Bosscha K. Increasing survival gap between young and elderly gastric cancer patients, 2017. Gastric Cancer.
6. Tegels JJ, De Maat MF, Hulsewe KW, Hoofwijk AG, Stoot JH. Improving the outcomes in gastric cancer surgery, 2014. World J Gastroenterol;20:13692-13704.
7. Cunningham D, Allum WH, Stenning SP, Thompson JN, Van de Velde CJ, Nicolson M, Scarffe JH, Lofts FJ, Falk SJ, Iveson TJ, Smith DB, Langley RE, Verma M, Weeden S, Chua YJ, Participants MT. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer, 2006. N Engl J Med;355:11-20.
8. Dikken JL, Dassen AE, Lemmens VE, Putter H, Krijnen P, van der Geest L, Bosscha K, Verheij M, van de Velde CJ, Wouters MW. Effect of hospital volume on postoperative mortality and survival after oesophageal and gastric cancer surgery in the Netherlands between 1989 and 2009, 2012. Eur J Cancer;48:1004-1013.
9. van Gestel YR, Lemmens VE, de Hingh IH, Steevens J, Rutten HJ, Nieuwenhuijzen GA, van Dam RM, Siersema PD. Influence of comorbidity and age on 1-, 2-, and 3-month postoperative mortality rates in gastrointestinal cancer patients, 2013. Ann Surg Oncol;20:371-380.
10. van de Poll-Franse LV, Lemmens VE, Roukema JA, Coebergh JW, Nieuwenhuijzen GA. Impact of concentration of oesophageal and gastric cardia cancer surgery on long-term population-based survival, 2011. Br J Surg;98:956-963.
11. Wouters MW, Karim-Kos HE, le Cessie S, Wijnhoven BP, Stassen LP, Steup WH, Tilanus HW, Tollenaar RA. Centralization of esophageal cancer surgery: does it improve clinical outcome?, 2009. Ann Surg Oncol;16:1789-1798.
12. Anderson O, Ni Z, Moller H, Coupland VH, Davies EA, Allum WH, Hanna GB. Hospital volume and survival in oesophagectomy and gastrectomy for cancer, 2011. Eur J Cancer;47:2408-2414.
13. Coupland VH, Lagergren J, Luchtenborg M, Jack RH, Allum W, Holmberg L, Hanna GB, Pearce N, Moller H. Hospital volume, proportion resected and mortality from oesophageal and gastric cancer: a population-based study in England, 2004-2008, 2013. Gut;62:961-966.
14. Jensen LS, Nielsen H, Mortensen PB, Pilegaard HK, Johnsen SP. Enforcing centralization for gastric cancer in Denmark, 2010. Eur J Surg Oncol;36 Suppl 1:S50-54.
15. Nelen SD, Heuthorst L, Verhoeven RHA, Polat F, Kruyt PM, Reijnders K, Ferenschild FTJ, Bonenkamp JJ, Rutter JE, de Wilt JHW, Spillenaar Bilgen EJ. Impact of Centralizing Gastric Cancer Surgery on Treatment, Morbidity, and Mortality, 2017. J Gastrointest Surg.
16. Thompson AM, Rapson T, Gilbert FJ, Park KG, Scottish Audit of G, Oesophageal C. Hospital volume does not influence long-term survival of patients undergoing surgery for oesophageal or gastric cancer, 2007. Br J Surg;94:578-584.
17. Luft HS, Hunt SS, Maerki SC. The volume-outcome relationship: practice-makes-perfect or selective-referral patterns?, 1987. Health Serv Res;22:157-182.
18. von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP, Initiative S. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies, 2007. Lancet;370:1453-1457.

19. Fritz A, Percy C, Jack A, Shanmugaratnam K, Sobin L, Parkin DM, Whelan S, editors. International Classification of Diseases for Oncology, third edition., 2000ed. Geneva: World Health Organization.

20. UICC. TNM classification of malignant tumours, 2002, 6th ed. New York: Wiley-Liss.

21. UICC. TNM classification of malignant tumours, 2009, 7th ed. New York: Wiley-Liss.

22. Pasquer A, Renaud F, Hec F, Gandon A, Vanderbeken M, Drubay V, Caranhac G, Piessen G, Mariette C, GroupFRENCH FW. Is Centralization Needed for Esophageal and Gastric Cancer Patients With Low Operative Risk?: A Nationwide Study, 2016. Ann Surg;264:823-830.

23. Lemmens VE, Bosscha K, van der Schelling G, Brenninkmeijer S, Coebergh JW, de Hingh IH. Improving outcome for patients with pancreatic cancer through centralization, 2011. Br J Surg;98:1455-1462.

24. Ghaferi AA, Birkmeyer JD, Dimick JB. Variation in hospital mortality associated with inpatient surgery, 2009. N Engl J Med;361:1368-1375.

25. Damhuis RA, Meurs CJ, Dijkhuis CM, Stassen LP, Wiggers T. Hospital volume and post-operative mortality after resection for gastric cancer, 2002. Eur J Surg Oncol;28:401-405.

26. Ghaferi AA, Birkmeyer JD, Dimick JB. Hospital volume and failure to rescue with high-risk surgery, 2011. Med Care;49:1076-1081.

27. Needleman J, Buerhaus P, Mattke S, Stewart M, Zelevinsky K. Nurse-staffing levels and the quality of care in hospitals, 2002. N Engl J Med;346:1715-1722.

28. Birkmeyer JD, Sun Y, Goldfaden A, Birkmeyer NJ, Stukel TA. Volume and process of care in high-risk cancer surgery, 2006. Cancer;106:2476-2481.

29. van Vliet EP, Hermans JJ, De Wever W, Eijkemans MJ, Steyerberg EW, Faasse C, van Helmond EP, de Leeuw AM, Sikkenk AC, de Vries AR, de Vries EH, Kuipers EJ, Siersema PD. Radiologist experience and CT examination quality determine metastasis detection in patients with esophageal or gastric cardia cancer, 2008. Eur Radiol;18:2475-2484.

30. Qi J, Zhang P, Wang Y, Chen H, Li Y. Does Total Gastrectomy Provide Better Outcomes than Distal Subtotal Gastrectomy for Distal Gastric Cancer? A Systematic Review and Meta-Analysis, 2016. PLoS One;11:e0165179.

31. Lepage C, Sant M, Verdecchia A, Forman D, Esteve J, Faivre J, group Ew. Operative mortality after gastric cancer resection and long-term survival differences across Europe, 2010. Br J Surg;97:235-239.

32. Haverkamp L, Weijs TJ, van der Sluis PC, van der Tweel I, Ruurda JP, van Hillegersberg R. Laparoscopic total gastrectomy versus open total gastrectomy for cancer: a systematic review and meta-analysis, 2013. Surg Endosc;27:1509-1520.

33. Chen K, Xu XW, Zhang RC, Pan Y, Wu D, Mou YP. Systematic review and meta-analysis of laparoscopy-assisted and open total gastrectomy for gastric cancer, 2013. World J Gastroenterol;19:5365-5376.

34. Brenkman HJ, Ruurda JP, Verhoeven RH, van Hillegersberg R. Safety and feasibility of minimally invasive gastrectomy during the early introduction in the Netherlands: short-term oncological outcomes comparable to open gastrectomy, 2017. Gastric Cancer.

Chapter 6

Poor compliance with perioperative treatment in patients with resectable gastric cancer

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Submitted

Abstract

Background
In several European countries it is recommended to treat gastric cancer patients with perioperative chemotherapy if they are eligible for surgery. However, little is known about its use in daily clinical practice. This study examines the use of perioperative treatment and its impact on survival in the Netherlands.

Methods
Patients diagnosed with potentially resectable gastric cancer (cT1N+/cT2-T3,X any cN, cM0,X) between 2006 and 2014 were selected from the Netherlands Cancer Registry (n=5824). Treatment trends were examined. Propensity score matching was used to create a subsample to reduce selection bias. Cox regression analysis was used to assess differences in overall survival.

Results
The percentage of patients treated with perioperative treatment increased from 3% in 2006 to 26% in 2014 and the use of only surgery decreased from 60% to 26%. 35% of all patients did not undergo surgery. Of the patients who underwent preoperative chemotherapy and surgery, 43% did not commence postoperative treatment. Cox regression analysis showed a better overall survival for patients who underwent perioperative treatment compared to patients who underwent preoperative treatment only (HR=0.80 95%CI 0.70-0.93; propensity matched sample: HR=0.84 95%CI 0.71-0.99), whereas survival was comparable for patients who underwent preoperative chemotherapy versus surgery alone (HR=0.89 95%CI 0.77-1.02, propensity matched sample: HR=0.85 95%CI 0.72-1.01).

Conclusion
This population-based study highlights that a significant proportion of the patients did not receive perioperative treatment. More research is necessary to elucidate the importance of the individual components of perioperative treatment.

Introduction

Gastric cancer is one of the leading cancers in incidence and mortality throughout the world. Survival rates are dismal with a 5-year relative survival of 18-33% in Europe.[1] Therefore, during the past decade several randomised trials have been conducted to improve survival of patients with gastric cancer. These studies showed a benefit of multimodality treatment in patients with resectable gastric cancer.[2-4] However, an international consensus on the best multimodality treatment has not been reached. In Northern America perioperative chemotherapy or postoperative chemoradiotherapy is the preferred treatment for patients with resectable gastric cancer whereas in Japan postoperative chemotherapy is the preferred treatment. [2,5,6]

In several European countries perioperative chemotherapy is recommended based on the results of the UK MAGIC trial.[7] Results of the this trial demonstrated that patients with resectable gastric or lower oesophageal adenocarcinoma randomised for perioperative chemotherapy had a 13% improved overall survival compared to surgery alone (35% vs. 23%).[2] According to the results of this trial perioperative chemotherapy consisting of epirubicine, cisplatin and 5-FU (ECF) or a similar regime is the recommended treatment as of May 2009 in the Dutch guidelines for patients with resectable gastric cancer unless patients are too frail or have severe comorbidities.[2,3,8]

Although perioperative chemotherapy is recommended for resectable gastric cancer in several European countries, the actual use seems limited in patients with gastric cancer as only 66% of the gastric cancer patients included in the MAGIC trial allocated to perioperative chemotherapy were able to start postoperative treatment.[2,9,10] However, to our knowledge, no data are available on the utilisation and impact of perioperative treatment on survival in daily clinical practice. Therefore, the aim of this nationwide observational study was to analyse trends in administration of perioperative treatment and its impact on survival among potentially resectable gastric cancer patients in the Netherlands.

Methods

Netherlands Cancer Registry

Data were obtained from the Netherlands Cancer Registry (NCR). This registry serves the total Dutch population of 16.9 million inhabitants. The NCR is based on notification of all newly diagnosed malignancies by the national automated pathological archive (PALGA). Additional sources are the national registry of hospital discharge and radiotherapy institutions. Specifically trained data managers of the NCR extract information on diagnosis, staging and treatment from the medical records. Information on vital status was obtained through an annual linkage with the Municipal Administrative Database, in which all deceased and emigrated persons in the Netherlands are registered. This study was approved by the Privacy Review Board of the Netherlands Cancer Registry and does not require approval from an ethics committee in the Netherlands.

Patients with a potentially resectable non-cardia gastric adenocarcinoma diagnosed in the period 2006-2014 eligible for perioperative treatment (cT1 cN+ / cT2-3,X, any cN, cM0,X (TNM-6)) were included in the study. The gastro-oesophageal junction could be involved, but the

bulk of the tumour had to be in the stomach. The study period 2006-2014 was chosen as the results of the MAGIC trial were published in 2006 which favoured perioperative chemotherapy for resectable gastric cancer patients instead of surgery alone[2]. Topography and morphology were coded according to the International Classification of Diseases for Oncology (ICD-O-3).[11]

Tumour staging was performed according to the International Union Against Cancer TNM classification that was valid at the time of diagnosis.[12, 13] TNM-7 tumour staging was recoded according to TNM-6. Patients were considered potentially resectable if they had no distant metastasis (cM1) and no infiltration into surrounding organs (cT4 according to TNM-6). Patients with a cT1N0 tumour were also excluded as they were not eligible for perioperative chemotherapy according to the Dutch guidelines (A STROBE diagram of the study population is presented in figure 1). Patients with unknown clinical distant metastasis (cMX) were considered as having a cM0 and were therefore included in the study. Prior to 2010 coding regulations to register a cM0 or cM1 status into the NCR were strict and patients who were treated as cM0 were sometimes registered as cMX (due to certain coding regulations). As of 2010 the coding regulations were less strict which resulted in almost no cMX patients since 2010 and an increase in cM0 patients (with virtually no increase in cM1 patients). Therefore, to avoid bias due to changing regulations, all patients with cMX were included.

Treatment definitions

Perioperative treatment was defined as preoperative chemotherapy followed by a surgical resection and postoperative chemotherapy or chemoradiotherapy. As information on the number of received cycles was not available in the NCR for the study period, preoperative and postoperative chemotherapy were defined as receiving at least one dose of chemotherapy pre- and/or postoperative. Surgical resection was defined as a subtotal or total gastrectomy. Surgery alone was defined as receiving surgery without preoperative or postoperative treatment. Patients who did not undergo surgery were allocated to the groups 'preoperative chemotherapy without surgery' or 'neither chemotherapy nor surgery', whichever was appropriate. As the intention of chemotherapy (preoperative or palliative) was not registered in the NCR, we assumed that patients who were potentially resectable and received chemotherapy without surgery, had started with preoperative chemotherapy with curative intent and were therefore allocated to the group 'preoperative chemotherapy without surgery'.

Subgroup analysis were performed to estimate the number of cycles received for patients diagnosed between 2010 and 2014 based on the number of days between start of chemotherapy and end of chemotherapy. This period was chosen as the date of end of chemotherapy was not routinely registered prior to 2010. Treatment duration of 1-20 days was defined as 1 cycle, 21-41 days as 2 cycles, and 42-70 days as 3 cycles, whereas all other treatment durations were defined as unknown.

Statistical analysis

Descriptive statistics were used to characterise the patients according to type of treatment i.e. perioperative treatment, preoperative chemotherapy with surgery, surgery alone, preoperative chemotherapy without surgery and neither chemotherapy nor surgery. Differences in

characteristics between treatment groups were analysed by means of chi-squared tests for nominal data and ANOVA for continuous data.

Kaplan-Meier curves were generated to examine overall survival according to type of treatment for all potentially resectable patients and were compared with the log-rank test. For this analysis, survival time was defined from diagnosis until death or until February 1st 2017. Survival curves were also generated for patients who underwent surgery with or without pre- and/or postoperative treatment using the Kaplan-Meier method. For this and all other survival analyses survival time was defined as time from four months after surgery to death or until February 1st 2017 for patients who were still alive. This landmark at four months postoperative addressed immortal time bias of patients receiving postoperative treatment, which starts 6 to 8 weeks after surgery and takes approximately 9 weeks to complete the three cycles.

Differences in overall survival were compared between patients who underwent perioperative treatment and patients who underwent only preoperative chemotherapy (comparison 1) as well as between patients who underwent only preoperative chemotherapy versus patients who underwent surgery alone using multivariable Cox regression analyses (comparison 2). Furthermore, propensity score matching was performed to minimise confounding due to nonrandomised assignment of treatment. Selection of covariates for matching unrelated to survival was avoided, even though they were associated with the treatment received, as this may increase bias.[14, 15] For comparison 1 a logistic regression was used to determine the probability of perioperative treatment, i.e. the propensity score, based on gender, age, period of diagnosis, tumour location, pT classification, pN classification, tumour grade, type of surgery, margin involvement and duration of postoperative hospital stay. For comparison 2 a logistic regression was used to determine the probability of only preoperative chemotherapy, i.e. the propensity score, based on gender, age, period of diagnosis, tumour location, cT classification, cN classification and tumour grade. On the basis of propensity scores patients were then 1:1 matched within tight bound of the propensity scores; predicted probabilities could vary by no more than 0.01 (1%) on a scale of 0 to 1. Subsequently, Cox regression analyses were also performed for the propensity matched sample to investigate the prognostic impact of the treatment received. Reported *p* values of <0.05 were considered statistically significant. Analyses were conducted using SAS version 9.4 (Statistical Analysis System).

Results

Patients

Between January 2006 and December 2014, 12 117 patients were diagnosed with non-cardia gastric adenocarcinoma. Based on our inclusion and exclusion criteria a study population of 5824 patients was identified (Figure 1). Patient characteristics were summarised in table 1.

Perioperative treatment was administered in 962 patients (17%) and preoperative chemotherapy without postoperative treatment was administered in 724 patients (12%). Surgery alone was performed in 2114 patients (36%). Patients who underwent perioperative treatment were more often younger than patients who underwent only preoperative chemotherapy followed by surgery or surgery alone (Table 1).

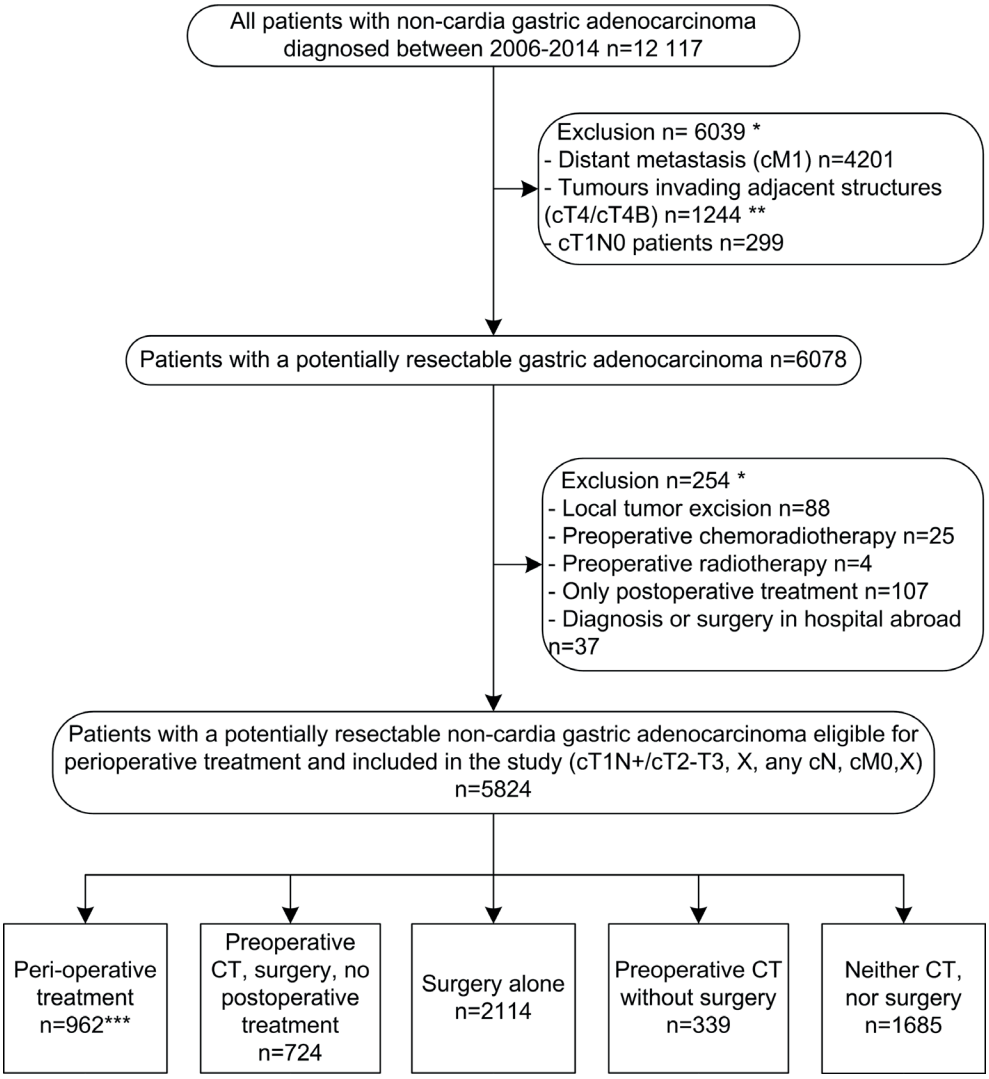


Figure 1 STROBE diagram of the study population.
* The sum of the excluded patients per exclusion criteria is larger than the total number of excluded patients because some patients met two exclusion criteria.
** cT4 according to TNM-6 and cT4B according to TNM-7. Patients with a cT4A tumour according to TNM-7 were recoded as having a cT3 tumour according to TNM-6.
***Perioperative treatment was defined as preoperative chemotherapy followed by a surgical resection and postoperative chemotherapy or chemoradiotherapy
CT= chemotherapy.

Table 1 Characteristics of patients with potentially resectable non-cardia gastric adenocarcinoma (cT1N+/T2-T3,X, any cN, cM0,X), diagnosed in the period 2006-2014 in the Netherlands (n=5824).

	Perioperative treatment		Preoperative CT, surgery, no postoperative treatment		Surgery alone		Preoperative CT without surgery		Neither CT nor surgery		*P* value	All patients	
	n	%**	n	%**	n	%**	n	%**	n	%**		n	%*
All patients	962	17%	724	12%	2114	36%	339	6%	1685	29%		5824	100%
Gender											<0.01		
Male	620	18%	437	13%	1272	37%	221	6%	927	27%		3477	60%
Female	342	15%	287	12%	842	36%	118	5%	758	32%		2347	40%
Age (median yrs., IQR)	62	54-69	67	60-72	76	69-81	68	60-74	83	77-87	<0.01	74	65-81
Age (yrs.)											<0.01		
< 60	398	46%	162	19%	172	20%	78	9%	59	7%		869	15%
60- 74	502	24%	448	21%	719	34%	188	9%	241	11%		2098	36%
≥ 75	62	2%	114	4%	1223	43%	73	3%	1385	48%		2857	49%
Period of diagnosis											<0.01		
2006-2008	187	9%	167	8%	993	48%	105	5%	599	29%		2051	35%
2009-2011	341	18%	268	14%	608	32%	133	7%	564	29%		1914	33%
2012-2014	434	23%	289	16%	513	28%	101	5%	522	28%		1859	32%
Tumour location											<0.01		
Proximal/ middle [a]	331	20%	266	16%	562	33%	90	5%	446	26%		1695	29%
Antrum	319	17%	232	12%	815	43%	72	4%	471	25%		1909	33%
Pyloric	69	15%	46	10%	236	50%	11	2%	106	23%		468	8%
Overlapping, unknown	243	14%	180	10%	501	29%	166	9%	662	38%		1752	30%
cT classification											<0.01		
cT1	11	16%	4	6%	19	28%	3	4%	31	46%		68	1%
cT2	434	25%	316	18%	525	30%	143	8%	328	19%		1746	30%
cT3	55	19%	33	11%	93	32%	32	11%	74	26%		287	5%
cTX	462	12%	371	10%	1477	40%	161	4%	1252	34%		3723	64%

cN classification											<0.01		
cN0	536	19%	395	14%	1274	46%	111	4%	438	16%		2754	47%
cN+	296	21%	218	15%	414	29%	157	11%	327	23%		1412	24%
cNX	130	8%	111	7%	426	26%	71	4%	920	55%		1658	28%
cM classification											<0.01		
cM0	943	98%	700	97%	1952	92%	297	88%	1314	78%		5206	89%
cMX	19	2%	24	3%	162	8%	42	12%	371	22%		618	11%
Tumour grade											<0.01		
Moderate/ well differentiated	115	11%	83	8%	599	57%	33	3%	229	22%		1059	18%
Poorly differentiated or anaplastic	430	16%	366	14%	1165	43%	143	5%	604	22%		2708	46%
Unknown	417	20%	275	13%	350	17%	163	8%	852	41%		2057	35%
Type of surgery													
Total gastrectomy	388	33%	296	25%	498	42%	n.a.	n.a.	n.a.	n.a.		1182∞	31%
Subtotal gastrectomy	544	23%	378	16%	1474	62%	n.a.	n.a.	n.a.	n.a.		2396∞	63%
Multi-organ surgery	30	14%	50	23%	142	64%	n.a.	n.a.	n.a.	n.a.		222∞	6%
Margin involvement													
No tumour residue	820	27%	560	18%	1704	55%	n.a.	n.a.	n.a.	n.a.		3084∞	81%
Microscopic tumour residue	99	20%	123	25%	272	55%	n.a.	n.a.	n.a.	n.a.		494∞	13%
Macroscopic tumour residue	8	13%	17	27%	39	61%	n.a.	n.a.	n.a.	n.a.		64∞	2%
Unknown	35	2%	24	1%	99	5%	n.a.	n.a.	n.a.	n.a.		158∞	4%
Duration of postoperative hospital stay													
<14 days	579	35%	346	21%	721	44%	n.a.	n.a.	n.a.	n.a.		1646∞	43%
≥14 days	115	17%	162	24%	400	59%	n.a.	n.a.	n.a.	n.a.		677∞	18%
Unknown	268	8%	216	6%	993	28%	n.a.	n.a.	n.a.	n.a.		1477∞	39%

CT= chemotherapy.

[a] Proximal / middle = Fundus, corpus and greater and lesser curvature.

* column percentage ** row percentage.

∞ This figure is based on patients who underwent surgery (with or without chemotherapy).

Trends in treatment

Administration of perioperative treatment increased over time (Figure 2). In 2006 3% of the patients underwent perioperative treatment and in 2014 26% underwent perioperative treatment. The number of patients who started with preoperative chemotherapy followed by surgery regardless of receiving postoperative treatment, increased from 6% in 2006 to 42% in 2014. Of the patients who underwent preoperative chemotherapy and surgery, 43% did not commence postoperative treatment in 2014.

In line with these findings, the percentage of patients who underwent surgery alone decreased from 60% in 2006 to 26% in 2014. The percentage of patients who started with preoperative chemotherapy and did not undergo surgery remained stable over the study period varying from respectively 4% to 7%. Similarly, the percentage of patients who received neither chemotherapy nor surgery also remained stable over time varying from 28% to 32%.

Subgroup analysis among patients who underwent preoperative chemotherapy with or without postoperative treatment in the period 2010-2014 showed that 89% of the patients who underwent perioperative treatment received 3 cycles of chemotherapy preoperatively, whereas patients who underwent preoperative treatment without postoperative treatment received less often 3 cycles of chemotherapy preoperatively (58%, Appendix 1).

Survival

Kaplan Meier survival curves of all potentially resectable patients showed that overall survival was worst for patients who received preoperative chemotherapy without surgery and for patients who received neither chemotherapy nor surgery with an almost equal 1-year overall survival rate of 22% and 21%, respectively (Figure 3).

Among patients who underwent surgery and survived the first four months after surgery, univariable overall survival was most favourable for patients who underwent perioperative treatment with a 5-year overall survival rate of 48% (P<0.01). Patients who underwent only preoperative chemotherapy had an 5-year overall survival comparable to patients who underwent surgery alone, respectively 43% and 39% (P=0.22; Figure 4).

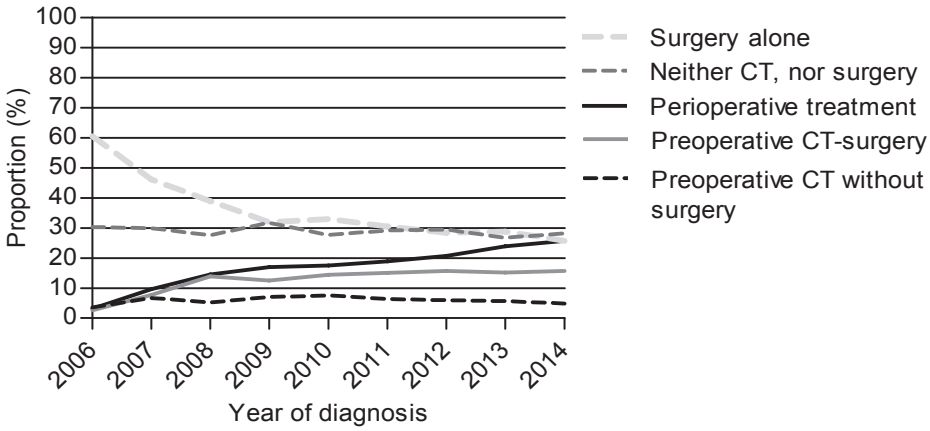
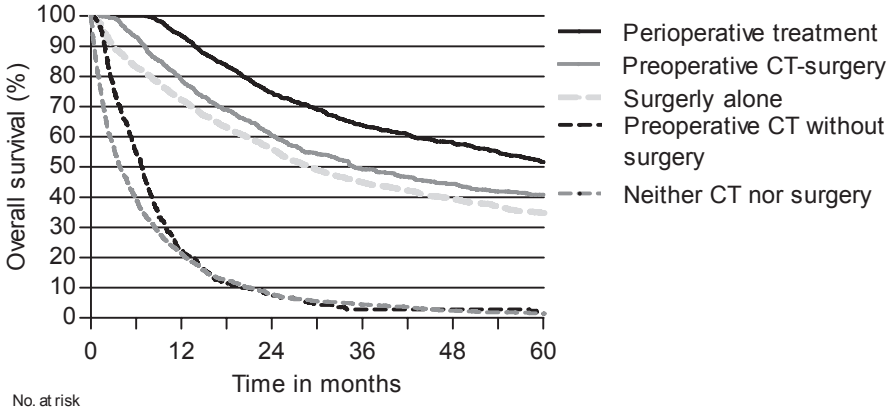
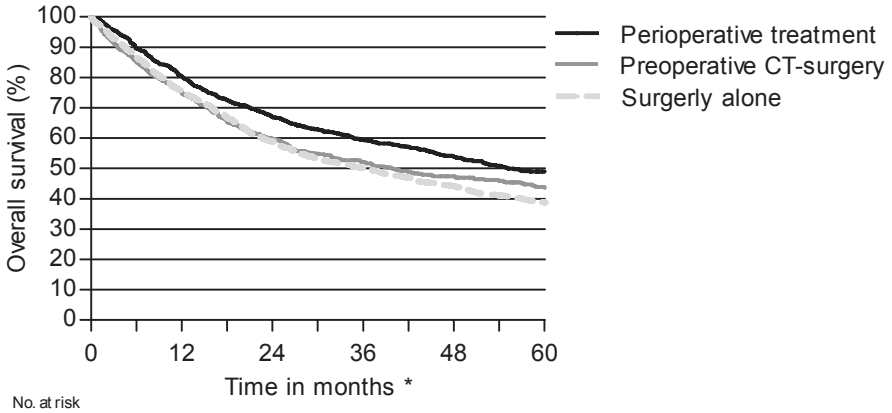


Figure 2 Trends in multimodality treatment among patients with potentially resectable non-cardia gastric adenocarcinoma (cT1N+/cT2-T3,X, any cN, cM0,X) diagnosed in the period 2006-2014 (n=5824).
CT= chemotherapy.



No. at risk						
Peri CT	962	901	716	519	385	286
Pre CT-surgery	724	571	437	313	241	178
Surg alone	2114	1524	1181	885	707	564
Pre CT-no surg	339	74	24			
Neither CT / surg	1685	355	129	68	34	17

Figure 3 Overall survival among patients with potentially resectable non-cardia gastric adenocarcinoma (cT1N+/cT2-3,X, any cN, cM0,X) diagnosed in the period 2006-2014 (n=5824).
Survival time was defined as time from diagnosis to death or 1nd of February 2017 for patients who were still alive. CT= chemotherapy.



No. at risk						
Peri CT	960	771	578	415	316	231
Pre CT-surgery	638	480	349	261	197	143
Surg alone	1791	1353	1030	799	642	506

Figure 4 Overall survival among patients with potentially resectable non-cardia gastric adenocarcinoma (cT1N+/cT2-T3,X, any cN, cM0,X) who underwent surgery with or without pre- and/or postoperative treatment and were diagnosed in the period 2006-2014 (n=3389; *P* <0.01).
*Survival time was defined as time from four months after surgery to death or 1nd of February 2017 for patients who were still alive. Patients who died within 4 months after surgery were excluded from the analysis.
CT= chemotherapy.

Multivariable Cox regression analysis also showed a favourable survival for patients who underwent perioperative treatment compared to patients who underwent only preoperative chemotherapy (HR=0.80 95%CI 0.70-0.93; Table 2a). A similar association was investigated among the propensity score matched sample. Characteristics of the matched patients were comparable and shown in appendix 2. After adjustment for confounders, the Cox regression analysis among the propensity score matched sample showed that perioperative treatment was associated with a better overall survival (HR=0.84 95%CI 0.71-0.99; Table 2a).

Multivariable Cox regression analysis demonstrated no significant difference in overall survival for patients who underwent only preoperative chemotherapy and for patients who underwent surgery alone (HR=0.89 95%CI 0.77-1.02; Table 2b). Survival analysis for the propensity score matched sample also showed no significant difference in survival (HR=0.85 95%CI 0.72-1.01 (Table 2b). Characteristics of the matched patients were comparable and shown in appendix 3.

Table 2a Multivariable Cox proportional hazards analyses of overall survival for potentially resectable non-cardia gastric adenocarcinoma patients who underwent preoperative chemotherapy followed by surgery with or without postoperative treatment for all patients and for the propensity score matched sample.

	All patients n=1598			Propensity score matched sample** n=1062		
	Crude 2-year OS	Multivariable analysis *		Crude 2-year OS	Multivariable analysis*	
	%	HR	95% CI	%	HR	95% CI
Treatment						
Perioperative treatment	67	0.80	0.70-0.93	67	0.84	0.71-0.99
Preoperative chemotherapy - surgery	60	ref		61	ref	

OS=overall survival. Patients who died within 4 months after surgery were excluded from the analysis.
*Adjusted for gender, age ,period of diagnosis, tumour location, pT classification, pN classification, tumour grade, type of surgery, margin involvement and duration of postoperative hospital stay.
**Characteristics of the propensity score matched sample were demonstrated in appendix 2.

Table 2b Multivariable Cox proportional hazards analyses of overall survival for potentially resectable non-cardia gastric adenocarcinoma patients who underwent preoperative chemotherapy followed by surgery without postoperative treatment and for patients who underwent surgery alone; for all patients and for the propensity score matched sample.

	All patients n=2429			Propensity score matched sample** n=967		
	Crude 2-year OS	Multivariable analysis *		Crude 2-year OS	Multivariable analysis *	
	%	HR	95% CI	%	HR	95% CI
Treatment						
Preoperative chemotherapy - surgery	60	0.89	0.77-1.02	61	0.85	0.72-1.01
Surgery alone	59	ref		58	ref	

OS=overall survival. Patients who died within 4 months after surgery were excluded from the analysis.
*Adjusted for gender, age ,period of diagnosis, tumour location, cT classification, cN classification and tumour grade.
**Characteristics of the propensity score matched sample were demonstrated in appendix 3.

Discussion

This population-based study of potentially resectable gastric cancer patients has demonstrated an increase in the administration of perioperative treatment of 3% to 26% in the course of time which may have led to a survival benefit compared to treatment with only preoperative chemotherapy followed by surgery. However, in 2014 still 74% of the patients was not treated with perioperative treatment. In addition, postoperative treatment was not administered to 43% of the patients who started with preoperative chemotherapy followed by surgery in 2014.

There are hypotheses that might explain the low percentage of resectable gastric cancer patients receiving perioperative treatment (26%), despite the publication of the MAGIC trial and the French FNCLCC/FFCD trial both demonstrating a significant survival benefit of perioperative treatment compared to surgery alone.[2, 4] Many patients with gastric cancer have an older age, comorbidities and suffer from malnutrition and weight loss which could preclude them from starting with the perioperative treatment regimen.[16] After preoperative chemotherapy there could be several reasons for not undergoing surgery such as disease progression, toxicity from chemotherapy, patient request and death.[2, 17] Moreover, gastric cancer surgery is associated with substantial morbidity and postoperative complications which could interfere with receiving postoperative treatment. [2,18-20] As only a minority of the patients is actually capable of receiving the full regimen, one could argue about the appropriateness of perioperative chemotherapy as a reference regime for patients with resectable gastric cancer.

In this observational study, many patients (43%) did not start postoperative treatment after preoperative chemotherapy followed by surgery. This percentage was somewhat higher compared to the results of the MAGIC trial [2] and CRITICS trial [21] but similar to the FLOT4-AIO trial [22], in which respectively 35%, 38% and 40%, of the patients did not start with postoperative treatment. However, the patients included in the trials were highly selected for trial eligibility and may therefore differ from the general gastric cancer patient population who probably have a worse performance status and are less ideal candidates for perioperative treatment. Another retrospective study found that 35% of the patients did not start with postoperative treatment after preoperative chemotherapy followed by surgery. [23]

Our survival results, based on real world data, support the survival benefits reported by the MAGIC trial and the French FNCLCC/FFCD trial.[2,4] Both trials reported an increase in 5-year overall survival of respectively 13% and 14% in the perioperative chemotherapy group compared to the surgery only group which is rather similar to the 10% increase found in the present study.[2,4] Multivariable Cox regression analyses, among all patients and the propensity score matched sample, indicated a favourable survival after perioperative treatment compared to only preoperative chemotherapy.

Even tough, propensity score matching was performed to minimise confounding due to nonrandomised assignment of treatment, groups may not be completely comparable and confounding due to nonrandomised assignment may still exists. For example, the differences in number of preoperative cycles received strongly suggests that patients who underwent only preoperative chemotherapy were less fit than patients who underwent perioperative treatment. This may, at least partially, explain why survival was comparable for patients who received only preoperative chemotherapy and patients who underwent surgery alone.

Furthermore, propensity score matching may amplify the risk of residual bias by unmeasured confounders as matching is only performed for measured confounders forcing balance of these confounders.[24] In addition, there could still be bias due to incomplete matching as 58% of the patients who received perioperative treatment, 77% of the patients who underwent only preoperative treatment and 26% of the patients who underwent surgery alone were excluded from the propensity score matched samples. Full matching instead of 1 to 1 matching seems a more appropriate method when performing survival analysis, however after full matching imbalance remained in characteristics between the treatment groups.[25] Although propensity score matching has uses and limitations, the authors decided to present the results of both the unmatched and propensity score matched analyses to facilitate the ongoing debate about the added value of propensity score matching to estimate causal effects.

Compliance to perioperative treatment in patients with resectable gastric cancer is poor, even in selected trial patients. Only 36% to 47% of all trial patients completed the entire treatment protocol.[2,4,22,26] As a substantial number of patients do not receive postoperative treatment, preoperative approaches may be particularly attractive.[27] Therefore, the CRITICS II trial which is a future Dutch multi-centre randomised phase II study that aims to assess the feasibility and safety of three preoperative treatment approaches (chemotherapy vs chemoradiotherapy vs chemotherapy plus chemoradiotherapy) will include no additional postoperative treatment.

This study has some limitations. First, information was not available about performance status, comorbidities and postoperative complications. However, age and duration of postoperative hospital stay may be proxies for comorbidities and postoperative complications, respectively. Second, because endoscopic ultrasonography is not always performed in patients with gastric cancer, clinical stage was unknown in a relatively high percentage of patients (64% cTX stage and 28% cNX stage; Table 1). Missing data for cT and cN might have led to an underestimation of the proportion of patients who underwent perioperative chemotherapy as inclusion of patients is based on clinical stage. However, the underestimation may only be to a small extent as most patients who were not eligible for perioperative chemotherapy were excluded from the study based on cM stage (67%) which is less often missing compared to cT and cN stage (Figure 1). Moreover, the missing values for cT and cN stage provide valuable information on care in daily clinical practice. Third, the number of cycles of preoperative or postoperative chemotherapy received was unknown for the total study period and was therefore not included in the analysis. Finally, if patients were treated with preoperative intent but failed to undergo surgery, these patients were assigned to preoperative chemotherapy without surgery, and as a consequence the patients treated with preoperative intent followed by surgery may represent a selection of the fittest patients.

To conclude, this study, based on real world data, highlights that a significant proportion of the patients did not receive perioperative treatment. More research is necessary to elucidate the importance of the individual components of perioperative treatment.

References

1. Allemani C, Weir HK, Carreira H, Harewood R, Spika D, Wang XS, Bannon F, Ahn JV, Johnson CJ, Bonaventure A, Marcos-Gragera R, Stiller C, Azevedo e Silva G, Chen WQ, Ogunbiyi OJ, Rachet B, Soeberg MJ, You H, Matsuda T, Bielska-Lasota M, Storm H, Tucker TC, Coleman MP. Global surveillance of cancer survival 1995-2009: analysis of individual data for 25,676,887 patients from 279 population-based registries in 67 countries (CONCORD-2), 2015. Lancet;385:977-1010.
2. Cunningham D, Allum WH, Stenning SP, Thompson JN, Van de Velde CJ, Nicolson M, Scarffe JH, Lofts FJ, Falk SJ, Iveson TJ, Smith DB, Langley RE, Verma M, Weeden S, Chua YJ, Participants MT. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer, 2006. N Engl J Med;355:11-20.
3. Macdonald JS, Smalley SR, Benedetti J, Hundahl SA, Estes NC, Stemmermann GN, Haller DG, Ajani JA, Gunderson LL, Jessup JM, Martenson JA. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction, 2001. N Engl J Med;345:725-730.
4. Ychou M, Boige V, Pignon JP, Conroy T, Bouche O, Lebreton G, Ducourtieux M, Bedenne L, Fabre JM, Saint-Aubert B, Geneve J, Lasser P, Rougier P. Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCD multicenter phase III trial, 2011. J Clin Oncol;29:1715-1721.
5. Ajani JA, D'Amico TA, Almhanna K, Bentrem DJ, Chao J, Das P, Denlinger CS, Fanta P, Farjah F, Fuchs CS, Gerdes H, Gibson M, Glasgow RE, Hayman JA, Hochwald S, Hofstetter WL, Ilson DH, Jaroszewski D, Johung KL, Keswani RN, Kleinberg LR, Korn WM, Leong S, Linn C, Lockhart AC, Ly QP, Mulcahy MF, Orringer MB, Perry KA, Poultsides GA, Scott WJ, Strong VE, Washington MK, Weksler B, Willett CG, Wright CD, Zelman D, McMillian N, Sundar H. Gastric Cancer, Version 3.2016, NCCN Clinical Practice Guidelines in Oncology, 2016. J Natl Compr Canc Netw;14:1286-1312.
6. Japanese Gastric Cancer A. Japanese gastric cancer treatment guidelines 2014 (ver. 4), 2017. Gastric Cancer;20:1-19.
7. Smyth EC, Verheij M, Allum W, Cunningham D, Cervantes A, Arnold D, Committee EG. Gastric cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up, 2016. Ann Oncol;27:v38-v49.
8. National clinical practice guideline gastric cancer 2009, Oncoline. http://www.oncoline.nl/maagcarcinoom. Accessed on: 23-6-2016.
9. Dassen AE, Dikken JL, van de Velde CJ, Wouters MW, Bosscha K, Lemmens VE. Changes in treatment patterns and their influence on long-term survival in patients with stages I-III gastric cancer in The Netherlands, 2013. Int J Cancer;133:1859-1866.
10. Trip AK, Stiekema J, Visser O, Dikken JL, Cats A, Boot H, van Sandick JW, Jansen EP, Verheij M. Recent trends and predictors of multimodality treatment for oesophageal, oesophagogastric junction, and gastric cancer: A Dutch cohort-study, 2015. Acta Oncol:1-9.
11. Fritz A, Percy C, Jack A, Shanmugaratnam K, Sobin L, Parkin DM, Whelan S, editors. International Classification of Diseases for Oncology, third edition., 2000ed. Geneva: World Health Organization.
12. UICC. TNM classification of malignant tumours, 2002, 6th ed. New York: Wiley-Liss.
13. UICC. TNM classification of malignant tumours, 2009, 7th ed. New York: Wiley-Liss.
14. Patrick AR, Schneeweiss S, Brookhart MA, Glynn RJ, Rothman KJ, Avorn J, Sturmer T. The implications of propensity score variable selection strategies in pharmacoepidemiology: an empirical illustration, 2011. Pharmacoepidemiol Drug Saf;20:551-559.
15. Wyss R, Girman CJ, LoCasale RJ, Brookhart AM, Sturmer T. Variable selection for propensity score models when estimating treatment effects on multiple outcomes: a simulation study, 2013. Pharmacoepidemiol Drug Saf;22:77-85.
16. Deans DA, Tan BH, Wigmore SJ, Ross JA, de Beaux AC, Paterson-Brown S, Fearon KC. The influence of systemic inflammation, dietary intake and stage of disease on rate of weight loss in patients with gastro-oesophageal cancer, 2009. Br J Cancer;100:63-69.

17. Reece-Smith AM, Saha S, Cunnell ML, Hameed K, Bessell EM, Duffy JP, Madhusudan S, Parsons SL. MAGIC in practice: experience of peri-operative ECF/X chemotherapy in gastro-esophageal adenocarcinomas, 2012. J Surg Oncol;106:748-752.

18. Bartlett EK, Roses RE, Kelz RR, Drebin JA, Fraker DL, Karakousis GC. Morbidity and mortality after total gastrectomy for gastric malignancy using the American College of Surgeons National Surgical Quality Improvement Program database, 2014. Surgery;156:298-304.

19. Luc G, Durand M, Chiche L, Collet D. Major post-operative complications predict long-term survival after esophagectomy in patients with adenocarcinoma of the esophagus, 2015. World J Surg;39:216-222.

20. Luc G, Gersen-Cherdieu H, Degrandi O, Terrebonne E, Chiche L, Collet D. Impact of postoperative chemotherapy in patients with locally advanced gastroesophageal adenocarcinoma treated with perioperative chemotherapy strategy, 2015. Am J Surg;210:15-23.

21. Snyder RA, Penson DF, Ni S, Koyama T, Merchant NB. Trends in the use of evidence-based therapy for resectable gastric cancer, 2014. J Surg Oncol;110:285-290.

22. Al-Batran S, Homann N, Schmalemberg H. Perioperative chemotherapy with docetaxel, oxaliplatin, and fluorouracil/leucovorin (FLOT) versus epirubicin, cisplatin, and fluorouracil or capecitabine (ECF/ECX) for resectable gastric or gastroesophageal junction (GEJ) adenocarcinoma (FLOT4-AIO): a multicenter, randomized phase 3 trial, 2017, ed. ASCO 2017 Annual Meeting; June 2-6, 2017; Chicago. Abstract no. 4004.

23. Mirza A, Pritchard S, Welch I. The postoperative component of MAGIC chemotherapy is associated with improved prognosis following surgical resection in gastric and gastrooesophageal junction adenocarcinomas, 2013. Int J Surg Oncol;2013:781742.

24. Brooks JM, Ohsfeldt RL. Squeezing the balloon: propensity scores and unmeasured covariate balance, 2013. Health Serv Res;48:1487-1507.

25. Austin PC, Stuart EA. Optimal full matching for survival outcomes: a method that merits more widespread use, 2015. Stat Med;34:3949-3967.

26. Verheij M, Jansen E, Cats A. A multicenter randomized phase III trial of neo-adjuvant chemotherapy followed by surgery and chemotherapy or by surgery and chemoradiotherapy in resectable gastric cancer: First results from the CRITICS study., 2016, ed. Oral presentation at ASCO 2016 Annual Meeting; June 3-7, 2016; Chicago. Abstract no. 4000.

27. Newton AD, Datta J, Loaiza-Bonilla A, Karakousis GC, Roses RE. Neoadjuvant therapy for gastric cancer: current evidence and future directions, 2015. J Gastrointest Oncol;6:534-543.

Appendix 1 Number of cycles received preoperatively for patients who underwent preoperative chemotherapy followed by surgery with or without postoperative treatment in the period 2010-2014.

	Perioperative treatment n=570**		Preoperative CT and surgery n=350**	
	n	%	n	%
Preoperative number of cycles *				
1	13	2%	52	15%
2	50	9%	94	27%
3	507	89%	204	58%

*The number of cycles was based on the number of days between start and end date of chemotherapy.
**The number of cycles was unknown for 223 patients (20%) in the period 2010-2014.

Appendix 2 Characteristics of potentially resectable non-cardia gastric adenocarcinoma patients who underwent preoperative chemotherapy followed by surgery with or without postoperative treatment for all patients (n=1686) and the propensity score matched sample (n=1118).

	All patients					Propensity score matched sample				
	Perioperative treatment		Preoperative CT- surgery			Perioperative treatment		Preoperative CT- surgery		
	n	%	n	%	*P* value	n	%	n	%	*P* value
Total	962	100%	724	100%		559	100%	559	100%	
Gender					0.09					0.99
Male	620	64%	437	60%		349	62%	349	62%	
Female	342	36%	287	40%		210	38%	210	38%	
Age in years (median, IQR)	62	54-69	67	60-72	<0.01	66	59-71	66	59-71	0.12
Period of diagnosis					0.06					0.73
2006-2008	187	19%	167	23%		126	23%	122	22%	
2009-2011	341	35%	268	37%		205	37%	196	35%	
2012-2014	434	45%	289	40%		228	41%	241	43%	
Tumour location					0.75					0.60
Proximal/ middle	331	34%	266	37%		191	34%	208	37%	
Antrum	319	33%	232	32%		188	34%	182	33%	
Pyloric	69	7%	46	6%		32	6%	36	6%	
Overlapping, unknown	243	25%	180	25%		148	26%	133	24%	
pT classification					0.06					0.92
pT0	58	6%	47	6%		37	7%	40	7%	
pT1	128	13%	94	13%		74	13%	75	13%	
pT2	558	58%	401	55%		322	58%	314	56%	
pT3	178	19%	134	19%		99	18%	104	19%	
pT4	21	2%	36	5%		15	3%	18	3%	
pTX	19	2%	12	2%		12	2%	8	1%	
pN classification					0.23					0.79
pN0	422	44%	339	47%		266	48%	261	47%	
pN+	532	55%	375	52%		286	51%	293	52%	
pNX	8	<1%	10	1%		7	1%	5	<1%	

Tumour grade					0.05					0.97
Moderate/ well differentiated	115	12%	83	11%		68	12%	66	12%	
Poorly differentiated or anaplastic	430	45%	366	51%		260	47%	259	46%	
Unknown	417	43%	275	38%		231	41%	234	42%	
Type of surgery					<0.01					0.98
Total gastrectomy	388	40%	296	41%		223	40%	220	39%	
Subtotal gastrectomy	544	57%	378	52%		310	55%	313	56%	
Multi-organ surgery	30	3%	50	7%		26	5%	26	5%	
Margin involvement					<0.01					0.86
No tumour residue	820	85%	560	77%		465	83%	456	82%	
Microscopic tumour residue	99	10%	123	17%		70	13%	77	14%	
Macroscopic tumour residue	8	<1%	17	2%		7	1%	6	1%	
Unknown	35	4%	24	3%		17	3%	20	4%	
Duration of postoperative hospital stay					<0.01					0.77
<14 days	579	60%	346	48%		295	53%	307	55%	
≥14 days	115	12%	162	22%		91	16%	86	15%	
Unknown	268	28%	216	30%		173	31%	166	30%	

CT=chemotherapy

Appendix 3 Characteristics of potentially resectable non-cardia gastric adenocarcinoma patients who underwent preoperative chemotherapy followed by surgery without postoperative treatment and for patients who underwent surgery alone; for all patients (n=2838) and the propensity score matched sample (n=1108).

	All patients					Propensity score matched sample				
	Preoperative CT- surgery		Surgery alone			Preoperative CT- surgery		Surgery alone		
	n	%	n	%	*P* value	n	%	n	%	*P* value
Total	724	100%	2114	100%		554	100%	554	100%	
Gender					0.93					0.67
Male	437	60%	1272	60%		334	60%	341	62%	
Female	287	40%	842	40%		220	40%	213	38%	
Age in years (median, IQR)	67	60-72	76	69-81	<0.01	69	63-73	70	61-77	0.44
Period of diagnosis					<0.01					0.67
2006-2008	167	23%	993	47%		157	28%	146	26%	
2009-2011	268	37%	608	29%		195	35%	193	35%	
2012-2014	289	40%	513	24%		202	36%	215	39%	
Tumour location					<0.01					0.54
Proximal/ middle	266	37%	562	27%		184	33%	175	32%	
Antrum	232	32%	815	39%		191	34%	185	33%	
Pyloric	46	6%	236	11%		40	7%	53	10%	
Overlapping, unknown	180	25%	501	24%		139	25%	141	25%	
cT classification					<0.01					0.22
cT1	4	<1%	19	<1%		4	<1%	3	<1%	
cT2	316	44%	525	25%		214	39%	222	40%	
cT3	33	5%	93	4%		22	4%	36	6%	
cTX	371	51%	1477	70%		314	57%	293	53%	
cN classification					<0.01					0.91
cN0	395	55%	1274	60%		319	58%	320	58%	
cN+	218	30%	414	20%		142	26%	146	26%	
cNX	111	15%	426	20%		93	17%	88	16%	
Tumour grade					<0.01					0.96
Moderate/ well differentiated	83	11%	599	28%		77	14%	74	13%	
Poorly differentiated or anaplastic	366	51%	1165	55%		301	54%	304	55%	
Unknown	275	38%	350	17%		176	32%	176	32%	

CT=chemotherapy

Chapter 7

Association between timing of adjuvant chemotherapy and overall survival in patients undergoing perioperative chemotherapy and gastrectomy for gastric cancer

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Abstract

Background
For patients who qualify for perioperative chemotherapy and gastrectomy, the optimal timing of adjuvant chemotherapy (aCTx) seems equivocal. The aim of this study was to assess the association between timing of aCTx and overall survival (OS) in patients receiving perioperative chemotherapy for gastric cancer.

Methods
Data from patients undergoing perioperative chemotherapy and gastrectomy for gastric adenocarcinoma with curative intent (2010-2014) were extracted from the nationwide population-based Netherlands Cancer Registry. Timing of aCTx was analysed as a linear and categorical variable (<6 weeks, 6-8 weeks, and >8 weeks). Multivariable regression was performed to identify risk factors for a late start of aCTx (≥6 weeks), and to assess the association between timing of aCTx and OS.

Results
Among 1066 patients who underwent neoadjuvant chemotherapy and gastrectomy, 463 (43%) patients started aCTx. aCTx was administered within 6 weeks in 208 (45%) patients, within 6-8 weeks in 155 (33%) patients, and after 8 weeks in 100 (22%) patients. A total of 419 (91%) and 351 (76%) patients finished all cycles of neoadjuvant and aCTx, respectively. A late start of aCTx was associated with a longer hospital stay (+1 hospital day: OR=1.15, 95%CI 1.08-1.23, *P*<0.001). Timing of aCTx was not associated with OS (6-8 weeks vs. <6 weeks, HR=1.14, 95%CI 0.79-1.65, *P*=0.471; >8 weeks vs. <6 weeks, HR=1.04, 95%CI 0.79-1.65, *P*=0.872).

Conclusion
This nationwide study demonstrates that timing of aCTx is not associated with OS. The results suggest that the early postoperative period may be safely used for recovery and optimising patients for the start of aCTx.

Introduction

In most European countries, the preferred treatment for patients with potentially curable gastric cancer is gastrectomy with perioperative chemotherapy.[1-3] Unfortunately, only 23% to 42% of the patients complete the total multimodality treatment regimen of gastrectomy and perioperative chemotherapy according to results from randomised controlled trials.[1,3] Discontinuation of treatment is mostly observed after gastrectomy; patients do not start with the adjuvant chemotherapy component of perioperative chemotherapy (aCTx), frequently due to gastrectomy related complications.[1,4]

For patients who are candidates for aCTx, optimal timing of aCTx seems equivocal. Initially, patients need time to recover from surgery, which can take up to several months depending on the postoperative course.[5] On the other hand, an early start of aCTx seems rational to achieve an optimal oncological result. For other cancer types, such as colon and breast cancer, studies indeed demonstrated that an early start of aCTx is associated with a better survival.[6-8]

Current studies on the association between timing of aCTx and survival for gastric cancer specifically are inconclusive.[9-11] However, these studies included patients receiving aCTx only, whereas perioperative chemotherapy is standard of care in most European countries. Moreover, (inter)national guidelines are lacking.[1] Therefore, the primary aim of this study was to assess the association between timing of aCTx and overall survival (OS) in a population of patients receiving perioperative chemotherapy and gastrectomy for cancer. Second, we aimed to identify risk factors for a late start of aCTx.

Methods

Study design

This study was conducted with data from the Netherlands Cancer Registry (NCR), which includes all newly diagnosed cancers in the Netherlands. The NCR is based on notification of all newly diagnosed malignancies by the national automated pathological archive (PALGA). Additional sources are the national registry of hospital discharge and radiotherapy institutions. Specifically trained data managers of the NCR extract information on diagnosis, staging and treatment from the medical records. This study was approved by the Privacy Review Board of the NCR.

Patient population

Patients who underwent neoadjuvant chemotherapy and gastrectomy for non-cardia gastric adenocarcinoma with curative intent based on clinical staging (cT1-4a-x, any cN, cM0-x) between 2010 and 2014 were selected from the NCR. Patients were not included if they had distant metastases (pM1) or infiltration into surrounding organs (pT4b), as these patients could most likely no longer receive aCTx with curative intent. Moreover, patients with cT1N0 tumours were not included, as guidelines do not recommend neoadjuvant chemotherapy for these patients. The study period was chosen as data on timing of aCTx before 2010 was not routinely registered. Patients who did not undergo aCTx, who underwent (neo)adjuvant (chemo)radiotherapy, or who had incomplete data on timing of aCTx or OS were excluded (Appendix 2). Furthermore, patients who started more than 12 weeks after surgery were excluded from the statistical

analysis to ensure that treatment had an adjuvant and not a palliative intention and since the MAGIC trial performed aCTx within 12 weeks after surgery.[1]

Tumour staging and treatment

According to the nationwide guidelines for patients with gastric cancer, tumour staging consists of gastroscopy and computed tomography in all patients.[12] Tumour staging was based on the American Joint Committee on Cancer TNM staging system (7th edition).[13] The guideline recommends perioperative chemotherapy (including epirubicin, cisplatin or oxalipatin, and capecitibine or fluorouracil)[1,14] and a (sub)total gastrectomy along with a D2 lymphadenectomy.[15,16] Topography and morphology were coded according to the International Classification of Diseases for Oncology (ICD-O-3).[17]

Definitions

Perioperative treatment was defined as neoadjuvant chemotherapy followed by a surgical resection and aCTx. As information on the number of received cycles was not available in the NCR, the number of days between start of chemotherapy and end of chemotherapy was used to determine by proxy the number of cycles received, based on the MAGIC regimen.[1] A treatment duration of 1-20 days was defined as 1 cycle, 21-41 days as 2 cycles, and 42-70 days as 3 cycles. All other treatment durations were defined as unknown. Timing of aCTx was defined as the interval between surgery and the start of aCTx. Patients were a priori divided into 3 groups according to the timing of aCTx (<6 weeks, 6-8 weeks, and >8 weeks). These groups were chosen based on consensus among the co-authors about clinically relevant groups and by evaluation of the dataset (to make the groups more or less equal in numbers).

Statistical analysis

Differences between groups were compared by using the chi-square or Fisher's exact test for categorical variables, and the one-way ANOVA or Kruskal-Wallis for continuous variables. Missing values for duration of hospital stay (7%), and duration of neoadjuvant treatment (14%) were considered at random and imputed by the median value. Missing categorical variables – most concerning tumour differentiation – were included in the analyses by creation of a dummy variable. Multivariable logistic regression was performed to identify risk factors associated with a late start (≥6 weeks) of aCTx. Kaplan-Meier curves were generated to examine OS according to timing of aCTx and were compared with the log-rank test. The association between timing of aCTx and OS was assessed using uni- and multivariable Cox regression analysis, providing hazard ratios (HRs) with 95% confidence intervals (CIs). To adjust for possible confounders, all baseline variables were entered in multivariable analysis. OS was defined as time from 5 months after surgery to death or until February 1st 2017 for patients who were still alive. This landmark at 5 months after surgery was chosen to address immortal time bias of patients receiving aCTx during the total period of the start (maximum of 12 weeks after surgery) and completion of all cycles of aCTx (9 weeks). The proportional hazard assumption was evaluated by constructing log minus log survival plots, and the assumption was met. Sensitivity analyses were performed to evaluate the association between timing of aCTx and OS for both early (pTNM-stage 0-I) and

advanced tumours (pTNM-stage II-III). All statistical analyses were performed using IBM SPSS version 21. All *P* values <0.05 were considered statistically significant.

Results

Study population

A total of 1066 patients underwent neoadjuvant chemotherapy and gastrectomy for non-cardia gastric adenocarcinoma with curative intent. After excluding patients who underwent (neo) adjuvant (chemo)radiotherapy (n=146), with incomplete data (n=15), or who did not undergo aCTx (n=341), 474 patients remained. Of these 474 patients, 463 (98%) patients started aCTx within 12 weeks and were included for the analysis (Appendix 2).

Patient characteristics

The majority of the 463 patients completed all 3 cycles of neoadjuvant chemotherapy (91%), and had a stage II or III tumour (69%). The median hospital stay was 8 days (interquartile range (IQR) 7-11 days), and all patients had a hospital stay ≤30 days. Some 351 patients (76%) who started with aCTx completed all 3 cycles. More patient characteristics are presented in appendix 1.

Timing of adjuvant chemotherapy

The median timing of start of aCTx was 6.1 weeks after gastrectomy (IQR 4.9-7.7 weeks) (Figure 1). The groups of timing of aCTx (<6 weeks, 6-8 weeks, and >8 weeks) consisted of 208 (45%), 155 (33%), and 100 (22%) patients, respectively (Table 1). Patients in the early timing groups more frequently underwent a partial gastrectomy (*P*=0.006), and had a shorter hospital stay (*P*<0.001). Furthermore, patients in the earlier timing groups more frequently completed all 3 cycles of aCTx (81% <6 weeks, 73% 6-8 weeks, 69% >8 weeks, *P*=0.007) (Table 2). In multivariable logistic regression analysis, a longer hospital stay was an independent predictor of late start of aCTx (each additional day OR=1.15, 95% CI 1.08-1.23, *P*<0.001; Table 2).

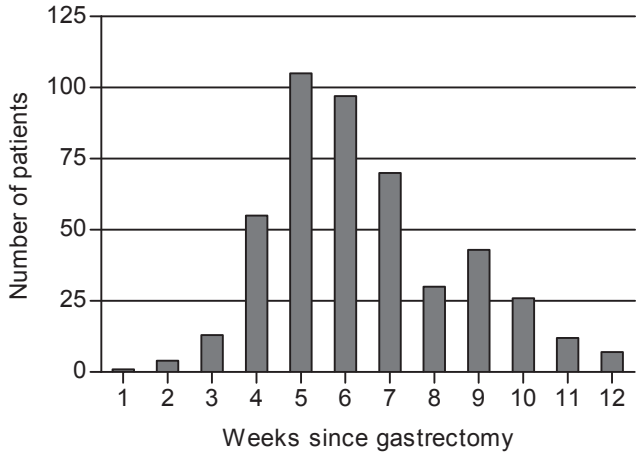


Figure 1 Histogram of the timing of aCTx in weeks (n=463).

Table 1 Baseline characteristics of 463 patients according to timing of aCTx.

	< 6 weeks n = 208		6 – 8 weeks n = 155		> 8 weeks n = 100		
	n	(%)	n	(%)	n	(%)	*P* value
Age in years (mean, SD)	61.0	10.0	62.0	±11.0	61.8	10.3	0.616
Gender							0.494
Male	130	(63)	103	(66)	69	(69)	
Female	78	(37)	52	(44)	31	(31)	
Year of diagnosis							0.061
2010	41	(20)	18	(12)	22	(22)	
2011	44	(21)	34	(22)	16	(16)	
2012	44	(21)	29	(19)	18	(18)	
2013	46	(22)	36	(23)	28	(28)	
2014	33	(16)	38	(24)	16	(16)	
cT stage							0.433
T1	3	(2)	0	(0)	1	(1)	
T2	57	(27)	52	(33)	31	(31)	
T3	44	(21)	31	(20)	24	(24)	
T4a	4	(2)	7	(5)	6	(6)	
Unknown	100	(48)	65	(42)	38	(38)	
cN stage							0.823
N0	126	(61)	96	(62)	58	(58)	
N1	40	(19)	37	(24)	23	(23)	
N2	20	(10)	19	(12)	16	(16)	
N3	1	(<1)	1	(1)	1	(1)	
Unknown	21	(10)	2	(1)	2	(2)	
Cycles of neoadjuvant CTx							0.259
1 cycle	0	(0)	0	(0)	3	(3)	
2 cycles	19	(9)	7	(5)	5	(5)	
3 cycles	187	(90)	143	(92)	89	(89)	
Unknown*	2	(1)	5	(315)	3	(3)	
Surgical type							0.006
Partial gastrectomy	133	(64)	77	(50)	47	(47)	
Total gastrectomy	75	(36)	77	(50)	51	(51)	
Multi-organ surgery*	0	(0)	1	(<1)	2	(2)	
Surgical approach							0.108
Open	171	(82)	117	(75)	72	(72)	
Laparoscopic	34	(16)	34	(22)	26	(26)	
Unknown*	3	(1)	4	(3)	2	(2)	
Radicality							0.616
R0	184	(89)	143	(92)	90	(90)	
R+	15	(7)	8	(5)	8	(8)	
Unknown*	9	(4)	4	(3)	2	(2)	

Table 1 continues on next page.

Continuation of Table 1.

	< 6 weeks n = 208		6 – 8 weeks n = 155		> 8 weeks n = 100		
	n	(%)	n	(%)	n	(%)	*P* value
ypT stage							0.164
T0	15	(7)	16	(10)	1	(1)	
T1	28	(14)	20	(13)	17	(17)	
T2	39	(19)	25	(16)	15	(15)	
T3	102	(49)	70	(45)	51	(51)	
T4a	21	(10)	23	(15)	15	(15)	
Unknown*	3	(1)	1	(1)	1	(1)	
ypN stage							0.414
N0	94	(45)	76	(49)	41	(41)	
N1	47	(23)	33	(21)	19	(19)	
N2	27	(13)	22	(14)	19	(19)	
N3	39	(19)	23	(15)	21	(21)	
Unknown*	1	(<1)	1	(1)	0	(0)	
Pathological tumour stage							0.191
0	15	(7)	15	(10)	1	(1)	
I	48	(23)	33	(21)	22	(22)	
II	77	(37)	61	(39)	39	(39)	
III	64	(31)	44	(28)	37	(37)	
Unknown*	4	(2)	2	(1)	1	(1)	
Tumour location							0.760
Proximal/middle	80	(38)	59	(38)	43	(43)	
Antrum	68	(33)	46	(30)	30	(30)	
Pyloric	16	(8)	9	(6)	4	(4)	
Overlapping or not otherwise specified	44	(21)	41	(26)	23	(23)	
Tumour differentiation							0.287
Well	1	(1)	2	(1)	1	(2)	
Moderate	29	(14)	13	(8)	8	(8)	
Poor	82	(39)	67	(43)	47	(47)	
Unknown*	96	(46)	73	(47)	44	(44)	
Hospital stay (median, IQR)	8	(6-10)	9	(7-12)	9	(7-14)	<0.001
Cycles of aCTx							0.007
1 cycle	11	(5)	11	(7)	8	(8)	
2 cycles	20	(10)	28	(18)	23	(23)	
3 cycles	169	(81)	113	(73)	69	(69)	
Unknown*	8	(4)	3	(2)	0	(0)	
Referral for aCTx to other hospital as surgical hospital	147	(71)	106	(68)	71	(71)	0.747

*Excluded from statistical analysis in this table. Percentages may not add up to 100 due to rounding.

Table 2 Univariable and multivariable logistic regression analysis on risk factors for late start (≥6 weeks) of adjuvant chemotherapy (n=463).

	Univariable			Multivariable		
	OR	95% CI	*P* value	OR	95% CI	*P* value
Gender						
Male	ref			ref		
Female	0.80	0.55-1.18	0.266	0.72	0.48-1.10	0.131
Additional year of age	1.01	0.99-1.03	0.328	1.01	0.99-1.03	0.520
Additional year of diagnosis	1.13	0.99-1.29	0.071	1.15	0.98-1.36	0.087
Surgical approach						
Open	ref			ref		
Minimally invasive	1.60	1.00-2.55	0.050	1.40	0.82-2.40	0.221
Surgical extent						
Partial gastrectomy	ref			ref		
Total gastrectomy	1.91	1.32-2.75	0.001	1.40	0.91-2.15	0.123
Tumour differentiation						
Well-moderate	ref			ref		
Poor-undifferentiated	1.74	0.95-3.19	0.074	1.80	0.93-3.35	0.082
ypT-stage						
T0-2	ref			ref		
T3-4	1.13	0.77-1.65	0.534	1.02	0.66-1.59	0.929
ypN-stage						
N0	ref			ref		
N+	0.97	0.67-1.41	0.889	0.81	0.53-1.25	0.347
Radicality						
R0	ref			ref		
R+	0.84	0.41-1.75	0.645	0.80	0.36-1.78	0.585
Additional day of hospital stay	1.15	1.09-1.22	<0.001	1.15	1.08-1.23	<0.001
Referral for aCTx						
Surgical hospital	ref			ref		
Other hospital	0.94	0.62-1.40	0.744	0.95	0.63-1.56	0.954

HR: Hazard ratio, CI: confidence interval.

Overall survival

Median follow-up length after gastrectomy of all patients treated with aCTx was 34.1 months (IQR 20.9 – 53.0 months), and the 1- and 3-year survival rates were 80% and 62%, respectively. The landmark at 5 months after surgery to compare OS between different timing of aCTx, excluded 4 patients (aCTx <6 weeks n=3, aCTx 6-8 weeks n=1). Kaplan-Meier survival curves demonstrated that timing of aCTx was not associated with OS (*P*=0.199, Figure 2). In multivariable survival analysis, timing of aCTx did not significantly influence OS using both timing as categorised variable (6-8 weeks vs. <6 weeks, HR=1.14, 95% CI 0.79-1.65, *P*=0.471; >8 weeks vs. <6 weeks, HR=1.04, 95% CI 0.68-1.57, *P* =0.872) and as linear variable (per additional week of timing, HR=1.02, 95% CI 0.95-1.11, *P* =0.549; Table 3). Sensitivity analyses demonstrated that the association between timing of aCTx and OS was non-significant for both early gastric cancer and advanced gastric cancer (stage II and III, data not shown).

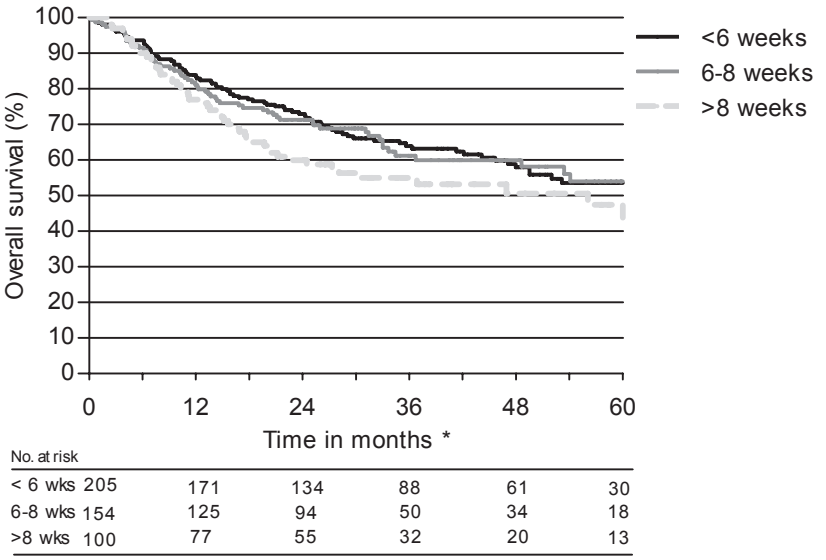


Figure 2 Kaplan-Meier survival curves according to timing of aCTx (n=459; *P*=0.199).
*Survival was defined as time from five months after surgery to death or 1nd of February 2017 for patients who were still alive. Patients who died within 5 months after surgery were excluded from the analysis (n=4).

Table 3 Univariable and multivariable Cox regression analyses on the influence of timing of aCTx on overall survival in patients treated with gastrectomy for cancer (n=459).

	Univariable			Multivariable*		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Each additional week	1.06	0.99 – 1.13	0.114	1.02	0.95 – 1.11	0.549
<6 weeks (n = 205)	ref			ref		
6-8 weeks (n = 154)	1.02	0.73 – 1.43	0.914	1.14	0.79 – 1.65	0.471
>8 weeks (n = 100)	1.36	0.95 – 1.94	0.092	1.04	0.68 – 1.57	0.872

*Adjusted for age, gender, year of diagnosis, number of neoadjuvant CTx cycles, type of surgery, surgical approach, tumour differentiation, radicality, ypT-stage, ypN-stage, length of hospital stay, and number of aCTx cycles. HR: Hazard ratio, CI: confidence interval. Patients who died within 5 months after surgery were excluded from the analysis (n=4).

Discussion

This population-based study among patients with gastric cancer who received perioperative chemotherapy and gastrectomy with curative intent demonstrated that the timing of aCTx was not associated with overall survival. Patients who started within 6 weeks had a comparable survival compared to patients who started between 6-8 weeks and >8 weeks after surgery. Furthermore, a later start of aCTx was associated with a longer hospital stay and completion of less aCTx cycles.

Value of adjuvant therapy

Only 76% of patients who started aCTx were able to complete all 3 cycles in the present study. These numbers are similar to the MAGIC-trial.[1] In the MAGIC-trial, discontinuation of perioperative chemotherapy was mostly observed after surgery, indicating that patients do not start with aCTx. This led to a discussion about the relevance of aCTx in the perioperative chemotherapy regimen. Although there is evidence that omitting aCTx impairs oncologic outcomes in patients receiving aCTx after gastrectomy without neoadjuvant chemotherapy[18], there is limited evidence in patients who received neoadjuvant chemotherapy. In a recent study from our group, a propensity score matched analysis was performed to compare patients who received the complete perioperative chemotherapy and patients who received only the neoadjuvant component (chapter 6). This study demonstrated that patients who received perioperative chemotherapy had a better OS compared to patients who only received neoadjuvant chemotherapy. However, even after propensity score matching it is still possible that patient groups were not completely comparable due to selection bias. In continuation of this study, the question raised whether the timing of aCTx was of importance for oncological outcomes.

Optimal timing of adjuvant therapy

For patients who qualify for aCTx after gastrectomy, the optimal timing of aCTx is under debate. On the one hand, it seems rational to start with aCTx as early as possible for an optimal oncological result. The goal of aCTx is to eradicate microscopic disease that may exist after neoadjuvant treatment and gastrectomy. Previous translational research has demonstrated that surgical resection may enhance growth of remaining tumour cells, thus early start of treatment may be favourable.[19,20] For colon and breast cancer, early timing of aCTx has indeed proven to benefit oncological outcomes.[6-8] However, these tumours have a relatively higher response rate to chemotherapy than gastric cancer, which may increase the importance for early timing of aCTx.[20-22] Moreover, these tumours generally only receive aCTx, whereas patients in this study already received neoadjuvant treatment.

On the other hand, late start of aCTx might even be favourable. Gastrectomy is considered as a major surgical procedure, and patients need time to recover from surgery, which may take up to several months depending on the postoperative course.[5] Indeed, the present study found a longer hospital stay to be an independent factor associated with a late start of aCTx. Hospital stay was used as a proxy for a complicated postoperative course, indicating that patients who experience complications have a higher risk for later start of aCTx. There may be more factors

related to a late start of aCTx, which were not taken into account in this study, such as dietary problems after surgery.[23,24] Furthermore, patients need to be fit for the start of aCTx, since the chemotherapy regimen is associated with considerable toxicity.[1] Last, it is questionable whether the time frames (weeks) of the delay in start of aCTx are relevant for oncologic outcomes. Cancer development generally involves months to years, which are longer than the time frames that delay the start of aCTx.

Comparison to other studies

To our knowledge, no studies evaluated the impact of timing of aCTx on OS in patients who received perioperative chemotherapy and gastrectomy for cancer. Our group previously demonstrated that the time between diagnosis and start of neoadjuvant treatment was not associated with worse OS for gastric cancer.[25] Other studies have focused on the timing of aCTx in patients receiving gastrectomy and aCTx only.[9-11] Two Korean studies demonstrated that OS of patients was impaired if aCTx was not started within 4 and 8 weeks after surgery.[9,10] On the contrary, a more recent American study found no relation between timing of aCTx and OS in patients starting aCTx up to 6 months after surgery.[11] These studies differed from each other and the present study. The Korean studies included only stage 2-3 tumours, and the American study also included stage 1 tumours. The present study included all tumour stages and performed sensitivity analyses in order to detect a difference between early and advanced tumours. As no difference was seen between tumour stages, taking the American study into account, it seems that in Western countries timing of aCTx does not impair survival for any tumour stage, and in any chemotherapeutic setting.

Guidelines

Dutch guidelines advise to start treatment within 5-6 weeks after diagnosis, but there is no advice for the start of adjuvant therapy for gastric cancer.[26,27] In the MAGIC-trial however, which led to the introduction of perioperative treatment in most European countries, aCTx was administered within 12 weeks after surgery.[1] The present study demonstrates that in the Netherlands only 45% of the patients received aCTx within 6 weeks, and in 98% of the patients aCTx was administered within 12 weeks after surgery. Possibly, physicians may have omitted aCTx in patients who were unable to start aCTx within 12 weeks after surgery due to limited evidence of the effect on survival.[1] The results of this study are therefore restricted to the time frame of 12 weeks after gastrectomy.

Limitations

This study has some limitations that need to be addressed. First, performance status, comorbidities and data on postoperative complications and recurrence patterns were not available in the NCR. However, age and duration of postoperative hospital stay may be proxies for comorbidities and postoperative complications, respectively. The use of hospital stay as a proxy for complications has probably worked well, since including this variable in multivariable analysis affected the association between timing of aCTx and OS demonstrated in univariable analysis, indicating that it is a confounder. Secondly, the study is limited by its observational design; the results may be highly susceptible to selection bias, e.g. fragile patients receiving aCTx

later. Although we adjusted for several confounding factors, results may be subjected to residual confounding. Nevertheless, a strong bias most likely would have led to significant differences in OS between the groups. As this was not the case, the data used for this study is probably of high quality. Moreover, the current study may have used the best available methodology, as a randomised trial for this type of research would face ethical problems. Strengths of this study include its large nationwide population-based design and being the first study to examine the effect of timing of adjuvant chemotherapy on survival in patients treated with perioperative chemotherapy and gastrectomy for gastric cancer.

Conclusion

If started within 12 weeks after surgery, timing of aCTx is not associated with overall survival in patients undergoing perioperative chemotherapy and gastrectomy for gastric cancer. These results suggest that the early period after surgery may be safely used for recovery and optimising patients for the start of aCTx.

References

1. Cunningham D, Allum WH, Stenning SP, Thompson JN, Van de Velde CJ, Nicolson M, Scarffe JH, Lofts FJ, Falk SJ, Iveson TJ, Smith DB, Langley RE, Verma M, Weeden S, Chua YJ, Participants MT. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer, 2006. N Engl J Med;355:11-20.
2. Brenkman HJ, Haverkamp L, Ruurda JP, van Hillegersberg R. Worldwide practice in gastric cancer surgery, 2016. World J Gastroenterol;22:4041-4048.
3. Ychou M, Boige V, Pignon JP, Conroy T, Bouche O, Lebreton G, Ducourtieux M, Bedenne L, Fabre JM, Saint-Aubert B, Geneve J, Lasser P, Rougier P. Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCD multicenter phase III trial, 2011. J Clin Oncol;29:1715-1721.
4. Busweiler LA, Schouwenburg MG, van Berge Henegouwen MI, Kolfschoten NE, de Jong PC, Rozema T, Wijnhoven BP, van Hillegersberg R, Wouters MW, van Sandick JW, Dutch Upper Gastrointestinal Cancer Audit g. Textbook outcome as a composite measure in oesophagogastric cancer surgery, 2017. Br J Surg;104:742-750.
5. Brenkman HJF, Ruurda JP, Verhoeven RHA, van Hillegersberg R. Safety and feasibility of minimally invasive gastrectomy during the early introduction in the Netherlands: short-term oncological outcomes comparable to open gastrectomy, 2017. Gastric Cancer;20:853-860.
6. Hershman D, Hall MJ, Wang X, Jacobson JS, McBride R, Grann VR, Neugut AI. Timing of adjuvant chemotherapy initiation after surgery for stage III colon cancer, 2006. Cancer;107:2581-2588.
7. Czaykowski PM, Gill S, Kennecke HF, Gordon VL, Turner D. Adjuvant chemotherapy for stage III colon cancer: does timing matter?, 2011. Dis Colon Rectum;54:1082-1089.
8. Lohrisch C, Paltiel C, Gelmon K, Speers C, Taylor S, Barnett J, Olivotto IA. Impact on survival of time from definitive surgery to initiation of adjuvant chemotherapy for early-stage breast cancer, 2006. J Clin Oncol;24:4888-4894.
9. Park HS, Jung M, Kim HS, Kim HI, An JY, Cheong JH, Hyung WJ, Noh SH, Kim YI, Chung HC, Rha SY. Proper timing of adjuvant chemotherapy affects survival in patients with stage 2 and 3 gastric cancer, 2015. Ann Surg Oncol;22:224-231.
10. Kang SY, Ahn MS, Song GW, Choi YW, Lee HW, Jeong SH, Park JS, Cho YK, Han SU, Sheen SS, Han JH, Choi JH. Does the timing of adjuvant chemotherapy for gastric cancer influence patient outcome?, 2015. Acta Oncol;54:1231-1234.
11. Greenleaf EK, Kulaylat AN, Hollenbeak CS, Almhanna K, Wong J. Timing of Adjuvant Chemotherapy and Impact on Survival for Resected Gastric Cancer, 2016. Ann Surg Oncol;23:4203-4213.
12. Vereniging integrale kankercentra. diagnostiek, behandeling en follow-up van het maagcarcinoom http://www.oncoline.nl/uploaded/docs/Maagcarcinoom/Richtlijn%20maagcarcinoom.pdf. Updated 2009. Accessed 01/31, 2017.
13. Edge S, Byrd D, Compton C, Fritz A, Greene F, Trotti A. AJCC cancer staging manual. 7th edition ed. New York: Springer; 2010.
14. Cunningham D, Okines AF, Ashley S. Capecitabine and oxaliplatin for advanced esophagogastric cancer, 2010. N Engl J Med;362:858-859.
15. Japanese Gastric Cancer Association. Japanese gastric cancer treatment guidelines 2010 (ver. 3). Gastric Cancer. 2011;14(2):113-123.
16. Japanese Gastric Cancer Association. Japanese classification of gastric carcinoma: 3rd english edition. Gastric Cancer. 2011;14(2):101-112.
17. Fritz A, Percy C, Jack A, Shanmugaratnam K, Sobin L, Parkin DM, Whelan S, editors. International Classification of Diseases for Oncology, third edition., 2000ed. Geneva: World Health Organization.

18. Jin LX, Sanford DE, Squires MH, 3rd, Moses LE, Yan Y, Poultsides GA, Votanopoulos KI, Weber SM, Bloomston M, Pawlik TM, Hawkins WG, Linehan DC, Schmidt C, Worhunsky DJ, Acher AW, Cardona K, Cho CS, Kooby DA, Levine EA, Winslow E, Saunders N, Spolverato G, Colditz GA, Maithel SK, Fields RC. Interaction of Postoperative Morbidity and Receipt of Adjuvant Therapy on Long-Term Survival After Resection for Gastric Adenocarcinoma: Results From the U.S. Gastric Cancer Collaborative, 2016. Ann Surg Oncol;23:2398-2408.

19. Gunduz N, Fisher B, Saffer EA. Effect of surgical removal on the growth and kinetics of residual tumor, 1979. Cancer Res;39:3861-3865.

20. Fisher B, Gunduz N, Saffer EA. Influence of the interval between primary tumor removal and chemotherapy on kinetics and growth of metastases, 1983. Cancer Res;43:1488-1492.

21. Mansour JC, Tang L, Shah M, Bentrem D, Klimstra DS, Gonen M, Kelsen DP, Brennan MF, Coit DG. Does graded histologic response after neoadjuvant chemotherapy predict survival for completely resected gastric cancer?, 2007. Ann Surg Oncol;14:3412-3418.

22. Adlard JW, Richman SD, Seymour MT, Quirke P. Prediction of the response of colorectal cancer to systemic therapy, 2002. Lancet Oncol;3:75-82.

23. Aoyama T, Yoshikawa T, Shirai J, Hayashi T, Yamada T, Tsuchida K, Hasegawa S, Cho H, Yukawa N, Oshima T, Rino Y, Masuda M, Tsuburaya A. Body weight loss after surgery is an independent risk factor for continuation of S-1 adjuvant chemotherapy for gastric cancer, 2013. Ann Surg Oncol;20:2000-2006.

24. Aoyama T, Kawabe T, Fujikawa H, Hayashi T, Yamada T, Tsuchida K, Yukawa N, Oshima T, Rino Y, Masuda M, Ogata T, Cho H, Yoshikawa T. Loss of Lean Body Mass as an Independent Risk Factor for Continuation of S-1 Adjuvant Chemotherapy for Gastric Cancer, 2015. Ann Surg Oncol;22:2560-2566.

25. Brenkman HJF, Visser E, van Rossum PSN, Siesling S, van Hillegersberg R, Ruurda JP. Association Between Waiting Time from Diagnosis to Treatment and Survival in Patients with Curable Gastric Cancer: A Population-Based Study in the Netherlands, 2017. Ann Surg Oncol;24:1761-1769.

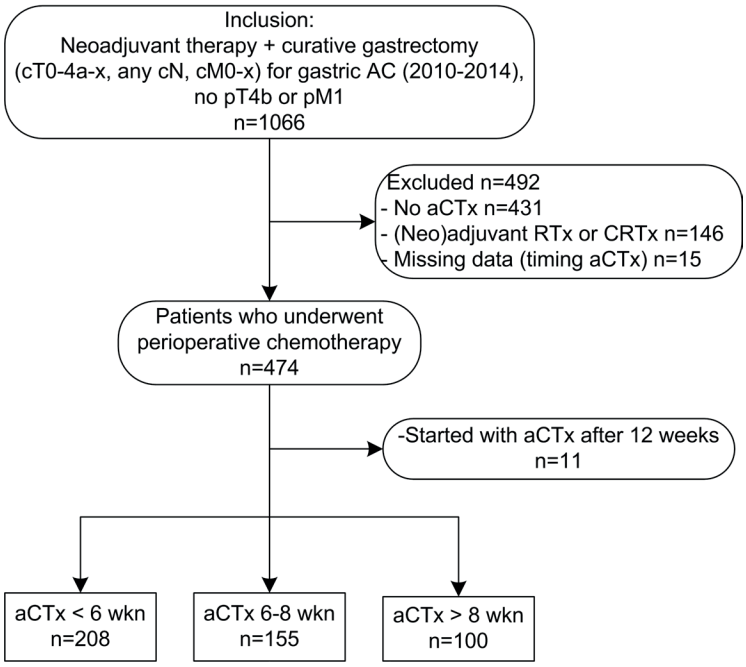
26. Stichting Oncologische Samenwerking. Normeringsrapport SONCOS 2017, versie 5. http://www.soncos.org/. Accessed July, 10, 2017.

27. Dutch Upper GI Cancer Audit. DUCA jaarrapportage 2016. https://www.dica.nl/jaarrapportage-2016/duca. Updated 2017. Accessed July, 10, 2017.

Appendix 1 Baseline characteristics of 463 patients with gastric cancer who underwent perioperative chemotherapy and gastrectomy in the period 2010-2014.

	All patients n = 463	
	n	(%)
Age in years (mean, SD)	61.5	10.4
Gender		
Male	302	(65)
Female	161	(35)
Year of diagnosis		
2010	81	(17)
2011	94	(20)
2012	91	(20)
2013	111	(24)
2014	87	(19)
cT stage		
T1	4	(1)
T2	140	(30)
T3	99	(21)
T4a	17	(3)
Unknown	203	(44)
cN stage		
N0	280	(60)
N1	100	(22)
N2	55	(12)
N3	3	(1)
Unknown	25	(5)
Cycles of neoadjuvant CTx		
1 cycle	3	(1)
2 cycles	31	(7)
3 cycles	419	(90)
Unknown	10	(2)
Surgical type		
Partial gastrectomy	257	(55)
Total gastrectomy	203	(44)
Multi-organ surgery	3	(1)
Surgical approach		
Open	360	(78)
Laparoscopic	94	(20)
Unknown	9	(2)
Radicality		
R0	417	(90)
R+	31	(7)
Unknown	15	(3)

ypT stage		
T0	32	(7)
T1	65	(14)
T2	79	(17)
T3	223	(48)
T4a	59	(13)
Unknown	5	(1)
ypN stage		
N0	211	(46)
N1	99	(21)
N2	68	(15)
N3	83	(18)
Unknown	2	(<1)
Pathological tumour stage		
0	31	(7)
I	103	(22)
II	177	(38)
III	145	(31)
Unknown	7	(2)
Tumour location		
Proximal/middle (fundus/corpus/curvatures)	182	(39)
Antrum	144	(31)
Pyloric	29	(6)
Overlapping or not otherwise specified	108	(23)
Tumour differentiation		
Well	4	(1)
Moderate	50	(11)
Poor	196	(42)
Unknown	213	(46)
Duration of hospital stay (median, IQR)	8	(7-11)
Cycles of aCTx		
1 cycle	30	(7)
2 cycles	71	(15)
3 cycles	351	(76)
Unknown	11	(2)
Referral for aCTx to other hospital as surgical hospital	324	(70)



Appendix 2 Flowchart of the study population.

Chapter 8

Impact of age and comorbidity on choice and outcome of two different treatment options for patients with potentially curable oesophageal cancer

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Abstract

Background
Definitive chemoradiotherapy is an alternative treatment option in patients with potentially curable oesophageal cancer who are not eligible for surgery. The aim of this study was to assess the impact of age and comorbidity on choice and outcome of two different types of curative treatment and long-term survival among these patients.

Methods
All patients with potentially curable oesophageal cancer (cT1N+/cT2-3,TX, any cN, cM0) diagnosed in the South East of the Netherlands between 2004 and 2014 treated with definitive chemoradiotherapy or neoadjuvant chemoradiotherapy plus surgery were included. Multivariable logistic regression analysis was used to examine the probability to undergo definitive chemoradiotherapy or neoadjuvant chemoradiotherapy plus surgery. Kaplan-Meier method with log-rank tests and multivariable Cox regression analysis were used to compare overall survival.

Results
A total of 702 patients was included. Age ≥75 years and multiple comorbidities were associated with a higher probability for definitive chemoradiotherapy (OR=8.58; 95% CI 4.72-15.58; and OR=3.09; 95% CI 1.93-4.93, respectively). The strongest associations were found for the combination of hypertension plus diabetes (OR=3.80; 95% CI 1.97-7.32) and the combination of cardiovascular with pulmonary co-morbidity (OR=3.18; 95% CI 1.57-6.46). Patients with oesophageal cancer who underwent definitive chemoradiotherapy had a poorer prognosis than those who underwent neoadjuvant chemoradiotherapy plus surgery, irrespective of age, number and type of co-morbidities . In contrast, for patients with squamous cell carcinoma having ≥2 comorbidities or being ≥75 years of age, overall survival was comparable between both groups (HR=1.52; 95% CI 0.78-2.97; and HR=0.73; 95% CI 0.13-4.14, respectively).

Conclusions
Histological tumour type should be acknowledged in treatment choices for patients with oesophageal cancer. Neoadjuvant chemoradiotherapy plus surgery should be the choice of treatment for operable oesophageal adenocarcinoma patients, regardless of age, number and type of comorbidity. For patients with oesophageal squamous cell carcinoma having ≥2 comorbidities or being 75 years or older, definitive chemoradiotherapy may be the preferred strategy.

Introduction

For potentially curable oesophageal cancer, radical surgery after neoadjuvant chemoradiotherapy is standard of care in the Netherlands since 2008.[1] However, surgery is associated with postoperative morbidity in up to 60% of patients and a 90-day mortality rate of 7-13%.[2-6] In general, comorbidity and older age are related to early postoperative mortality after gastrointestinal cancer surgery.[7] A less aggressive treatment approach may well be considered in these patients.[8] Definitive chemoradiotherapy is an alternative treatment option in elderly patients and in patients with severe comorbidities.[3,9-11] Similar survival rates have been reported after chemoradiotherapy with or without surgery for patients with oesophageal squamous cell carcinoma (OSCC).[11,12] In patients with oesophageal adenocarcinoma (OAC), surgery is recommended unless there is a high risk for postoperative complications and/or mortality.[13-16]

Long-term outcome data following definitive chemoradiotherapy for potentially curable oesophageal cancer are scarce and guidelines for selecting the appropriate treatment in patients with severe comorbidity and older age are not available.[13,17] Therefore, the aim of this retrospective observational study was to assess the impact of age and comorbidity on the choice of treatment and long-term overall survival among patients with potentially curable oesophageal cancer.

Methods

Data from all patients with a primary oesophageal cancer (C15.1-C15.9), diagnosed between 2004 and 2014 in the South East of the Netherlands were obtained from the population-based nationwide Netherlands Cancer Registry (NCR). Data from this region was used, as data on comorbidities was not routinely registered in other parts of the Netherlands during the study period. Trained data managers of the NCR routinely extract information on diagnosis, tumour stage, comorbidity and treatment from the medical hospital records, using a strict registration and coding manual. Tumours were clinically staged according to the UICC/AJCC TNM classification that was valid at the time of diagnosis.

Patients with potentially curable oesophageal cancer (cT1N+/cT2-3,TX, any cN , cM0) and treated with definitive chemoradiotherapy or neoadjuvant chemoradiotherapy plus surgery were eligible for this study (Figure 1). Patient were classified as cTX when the tumour could not be adequately subcategorised, for example due to an obstructing tumour that could not be passed during endoscopic ultrasonography. Patients were considered potentially curable if they had no clinically distant metastasis (cM0 and cM1a i.e. positive coeliac nodes, according to TNM-6 and cM0 according to TNM-7) and no tumour invasion into surrounding organs (no cT4 according to TNM-6 and no cT4a or cT4b according to TNM-7). Although patients with a cT4a tumour could theoretically be treated with curative intent, all cT4 tumours were excluded, as T4a and T4b were only distinguished after 2010 by TNM-7. For the analysis, patients with a cM1a tumour according to TNM-6 were categorised as having cN+ according to TNM-7. As of 2010, coding regulations to register a cM0 or cM1 status into the NCR were less strict than prior to 2010. As a consequence, since 2010, relatively more patients were registered with no (cM0) rather than unknown (cMX) clinical distant metastases into the NCR. To account for this,

we decided to include all patients with cMX. Patients with cancer of the cervical oesophagus (C15.0) as well as patients with a cT1N0 tumour were excluded as surgery was not standard of care in these patients.

Definitive chemoradiotherapy was defined as concurrent chemotherapy and radiotherapy not followed by surgical resection. Neoadjuvant chemoradiotherapy, which was introduced more recently, was usually given according to the CROSS regimen.1 Patients who underwent palliative or other treatment were excluded from the analysis (Figure 1).

In the NCR, comorbidities are registered according to a slightly modified version of the Charlson Co-morbidity index.[18] The Charlson comorbidity index is most widely used for recording comorbidity and was validated in various studies. Comorbidity was defined as life-shortening diseases that were present at the time of cancer diagnosis.[19,20] The following groups of comorbidities were included in our analyses: pulmonary disease (COPD, emphysema, chronic bronchitis), cardiovascular disease (vascular disease, angina pectoris, myocardial infarction, cardiomyopathy, myocarditis, TIA, CVA), hypertension, diabetes mellitus (non-insulin-dependent, insulin-dependent) and previous malignancies. Patients with no serious co-morbidity in the medical file were registered as having no co-morbidity. Patients were excluded if comorbidity status was not registered.

Statistics Netherlands developed an indicator of Socio-Economic Status Score (SES), using individual fiscal data based on the economic value of the home and household income.[21] This SES indicator is provided at an aggregated level for each postal code (covering an average of 17 households). SES was categorised as low (deciles 1–3), medium (deciles 4–7) or high (deciles 8–10). A separate category was made for postal codes of care-providing institutions because assigning SES for those living in nursing home or other care providing institutions is difficult.

Statistical analysis

Differences between patient groups were analysed by using Chi-square tests. Multivariable logistic regression analyses were performed to examine the impact of clinicopathological factors on the choice of treatment (definitive chemoradiotherapy versus neoadjuvant chemoradiotherapy followed by surgery). Survival time was defined as time from 6 months after diagnosis until death or until February 2017 for patients who were still alive. Thus, patients who died within 6 months after diagnosis were excluded from survival analysis. This was done in order to deal with immortal time bias of patients undergoing neoadjuvant treatment plus surgery, as total treatment duration for those who underwent definitive chemoradiotherapy is shorter. Overall survival was calculated with the Kaplan Meier analysis and log-rank tests were performed to test for differences between groups. Multivariable survival analyses were performed using the Cox proportional hazards model (HR and 95% confidence intervals) to investigate the prognosis after definitive chemoradiotherapy versus neoadjuvant chemoradiotherapy plus surgery after adjustment for confounders. According to histological tumour type separate models were performed for age categories, number of comorbidities and for each type of comorbidity. All analyses were performed in SAS version 9.4 and 2-sided *P* values of <0.05 were considered statistically significant.

Results

Clinicopathological characteristics

A total of 702 patients was included in the study (Figure 1). Neoadjuvant chemoradiotherapy with surgery was performed in 386 patients (55%) and definitive chemoradiotherapy in 316 patients (45%). Frequently reported comorbidities were cardiovascular disease (33%), hypertension (33%), pulmonary disease (15%) and diabetes (15%) (Table 1). Most tumours were adenocarcinomas (65%) and in a locally advanced stage with cT3 (65%) and cN1-3 (60%). About 81% of the patients were treated after 2008.

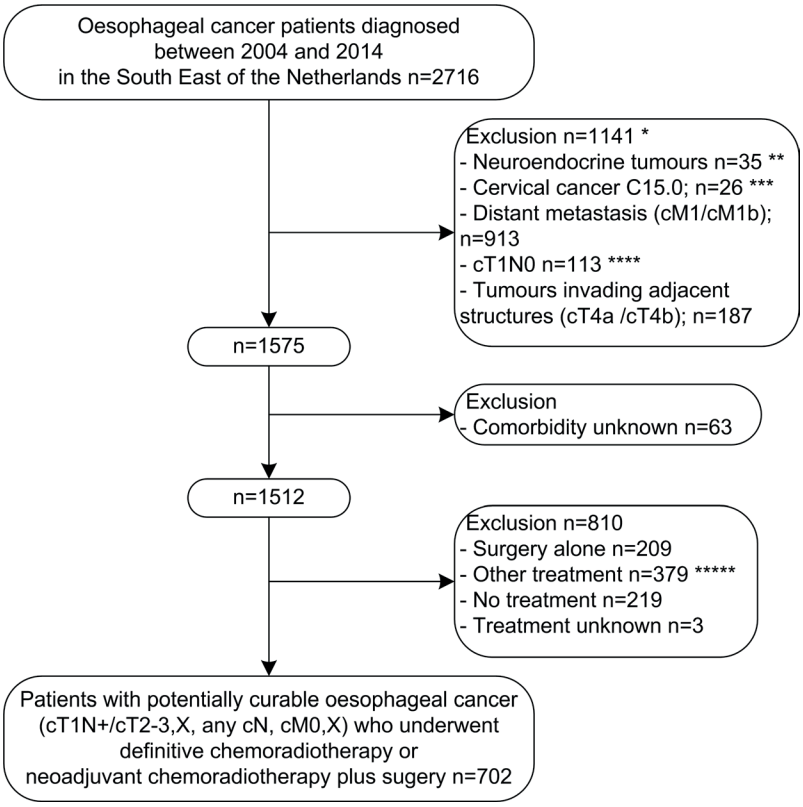


Figure 1 Flowchart of study population.

*The sum of excluded patients per exclusion criteria is larger than the total number of excluded patients because some patients met 2 exclusion criteria. ** Lymphoma, melanoma were already excluded. ***Not eligible for surgery. ****Eligible for endoscopic resection. ***** 74% underwent radiotherapy only.

Table 1 Characteristics of oesophageal cancer patients (cT1N+/cT2-3,TX, any cN , cM0) treated with definitive chemoradiotherapy or neoadjuvant chemoradiotherapy followed by surgery diagnosed in the South East of the Netherlands in the period 2004-2014 (n=702).

	All patients (n=702)	
	n	%
Treatment		
Definitive chemoradiotherapy	316	45%
Neoadjuvant chemoradiotherapy followed by surgery	386	55%
Gender		
Male	535	76%
Female	167	24%
Age (in years)		
< 60	184	26%
60-74	387	55%
≥75	131	19%
Number of comorbidities		
0	211	30%
1	218	31%
≥2	273	39%
Type of comorbidity		
Cardiovascular	231	33%
Pulmonary	108	15%
Hypertension	232	33%
Previous malignancies	72	10%
Diabetes	102	15%
Socio-economic status		
Low	153	22%
Intermediate	277	39%
High	219	31%
Care providing institution	21	3%
Unknown	32	5%
Tumour Localisation		
Proximal	38	5%
Mid	92	13%
Distal	544	77%
Overlapping/ not otherwise specified	28	4%
Histology		
OAC	457	65%
OSCC	230	33%
Other/unknown	15	2%

Table 1 continues on next page

Continuation of table 1

	All patients (n=702)	
	n	%
cT classification		
T1	6	<1%
T2	138	20%
T3	455	65%
TX	103	15%
cN classification		
N0	259	37%
N+	423	60%
NX	20	3%
Period of diagnosis		
2004 – 2008	133	19%
2009 – 2014	569	81%

OAC= oesophageal adenocarcinoma, OSSC=oesophageal squamous cell carcinoma
dCRT = definitive chemoradiotherapy, nCRT=neoadjuvant chemoradiotherapy

The association between age and treatment

Of the patients treated with neoadjuvant chemoradiotherapy and surgery less than 8% (29 of 386 patients) were 75 years or older (Table 2). On the other hand, of the patients who were treated with definitive chemoradiotherapy, 19% (60 of 316 patients) were younger than 60 years. About 78% (102 of 131 patients) of the elderly (≥75 years) patients were treated with definitive chemoradiotherapy, whereas only 33% (60 of 184 patients) of the patients younger than 60 years underwent definitive chemoradiotherapy.

The association between comorbidity and treatment

Patients with multiple comorbidities underwent more often definitive chemoradiotherapy (160 of 273 patients; 59%) whereas patients without comorbidities underwent more often neoadjuvant chemoradiotherapy plus surgery (142 of 211 patients; 67%; Table 2). Multivariable logistic regression analysis confirmed the associations of age and comorbidities with type of treatment. Patients ≥75 years of age (OR=8.58; 95% CI 4.72-15.58) and patients with multiple comorbidities (OR=3.09; 95%CI 1.93-4.93) had a higher probability to receive definitive chemoradiotherapy than neoadjuvant chemoradiotherapy plus surgery. Regarding type of comorbidity and the likelihood to receive definitive chemoradiotherapy, the association was higher for the combination hypertension and diabetes (OR=3.80; 95% CI 1.97-7.32) and for cardiovascular and pulmonary comorbidity (OR=3.18; 95% CI 1.57-6.46) (Table 2).

Table 2 Multivariable logistic regression analysis of clinicopathological factors upon the likelihood of treatment with definitive chemoradiotherapy versus neoadjuvant chemoradiotherapy followed by surgery among patients with potentially curable oesophageal cancer (cT1N+/cT2-3,Tx, any cN , cM0) diagnosed in the South East of the Netherlands in the period 2004-2014 (n=702).

	Patients					Multivariable analysis	
	Definitive chemoradiotherapy (n=316)		Neoadjuvant chemoradiotherapy + surgery (n=386)			Definitive chemoradiotherapy vs. neoadjuvant chemoradiotherapy + surgery	
	n	%	n	%	*P* value	OR	95% CI
Gender					<0.01		
Male	218	69%	317	82%		1.0	
Female	98	31%	69	18%		1.38	0.88-2.17
Age (in years)					<0.01		
< 60	60	19%	124	32%		1.0	
60-74	154	49%	233	60%		1.08	0.69-1.68
≥75	102	32%	29	8%		8.58	4.72-15.58
Number of comorbidities					<0.01		
0	69	22%	142	37%		1.0	
1	87	28%	131	34%		1.34	0.84-2.15
≥2	160	51%	113	29%		3.09	1.93-4.93
Type of comorbidity [a]							
Cardiovascular	132	42%	99	26%	<0.01	1.74	1.18-2.57
Pulmonary	63	20%	45	12%	<0.01	2.08	1.28-3.38
Hypertension	118	37%	114	30%	0.03	1.40	0.95-2.06
Previous malignancies	44	14%	28	7%	<0.01	1.55	0.86-2.80
Diabetes	60	19%	42	11%	<0.01	2.39	1.45-3.92
Cardiovascular and pulmonary	34	11%	17	4%	<0.01	3.18	1.57-6.46
Hypertension and diabetes	40	13%	18	5%	<0.01	3.80	1.97-7.32
Socio-economic status					0.05		
Low	79	25%	74	19%		1.0	
Intermediate	125	40%	152	39%		0.67	0.42-1.06
High	84	27%	135	35%		0.57	0.35-0.93
Care providing institution / unknown	28	9%	25	6%		0.72	0.34-1.55
Tumour Localisation					<0.01		
Proximal/ Mid	98	31%	32	8%		1.0	
Distal	204	65%	340	88%		0.23	0.13-0.40
Overlapping/ not otherwise specified	14	4%	14	4%		0.37	0.14-0.98
Histology [b]					<0.01		
OAC	158	50%	299	77%		1.0	
OSCC	149	47%	81	21%		1.95	1.24-3.06

Table 2 continues on next page

Continuation of table 2

	Patients					Multivariable analysis	
	Definitive chemoradiotherapy (n=316)		Neoadjuvant chemoradiotherapy + surgery (n=386)			Definitive chemoradiotherapy vs. neoadjuvant chemoradiotherapy + surgery	
	n	%	n	%	*P* value	OR	95% CI
cT classification					<0.01		
cT1-2	70	22%	74	19%		1.0	
cT3	184	58%	271	70%		0.66	0.42-1.03
cTX	62	20%	41	11%		1.34	0.72-2.48
cN classification					0.07		
cN0	112	35%	147	38%		1.0	
cN+	190	60%	233	60%		1.76	1.17-2.66
cNX	14	4%	6	2%		3.36	1.03-10.97
Period of diagnosis					0.01		
2004 – 2008	60	23%	73	16%		1.0	
2009 – 2014	326	77%	243	84%		0.48	0.35-0.76

OAC= oesophageal adenocarcinomas, OSSC=oesophageal squamous cell carcinoma

[a] The effects of type of comorbidity on treatment allocation were evaluated in separated models, which are adjusted for all variables in Table 2 expect number of comorbidities. Reference category for effects of type of co-morbidity: No co-morbidity.

[b] Category unknown is not shown.

Long-term overall survival

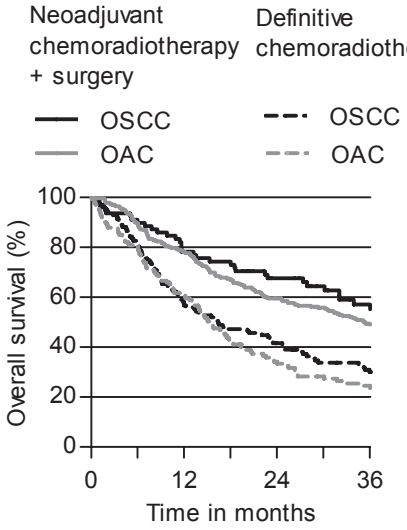
Two-year overall survival of all patients was significantly better following neoadjuvant chemoradiotherapy plus surgery compared to definitive chemoradiotherapy (61% versus 38% *P* <0.01). Even after stratification for histological tumour type, the survival differences remained statistically significant (OAC: 60% versus 33% respectively *P* <0.01; OSSC: 68% versus 42% respectively *P*<0.01; Figure 2a).

Impact of age and comorbidity on long-term overall survival

Kaplan Meier survival analysis showed that the 2-year overall survival was worse among patients with OAC who underwent definitive chemoradiotherapy compared to those who underwent neoadjuvant chemoradiotherapy plus surgery, regardless of the number of comorbidities (Figure 2b). In contrast, the 2-year overall survival for OSCC patients with multiple comorbidities after definitive chemoradiotherapy (46%) was comparable to the 2-year overall survival (51%) following neoadjuvant chemoradiotherapy plus surgery (Figure 2c).

Multivariable Cox regression analyses showed that OAC patients had a poorer prognosis following definitive chemoradiotherapy compared to neoadjuvant chemoradiotherapy plus surgery, irrespective of age and number of comorbidities (Table 3). Especially, among patients with cardiovascular diseases, hypertension or diabetes survival was poorer after definitive chemoradiotherapy.

In contrast, among OSCC patients with at least 2 comorbidities or being 75 years or older, overall survival after definitive chemoradiotherapy was comparable to the overall survival after neoadjuvant chemoradiotherapy plus surgery. This was especially the case among OSCC patients with cardiovascular diseases or previous malignancies. However, OSCC patients with hypertension had a poorer overall survival after definitive chemoradiotherapy compared to neoadjuvant chemoradiotherapy plus surgery. The impact of pulmonary diseases or diabetes could not be assessed accurately due to the small number of patients (Table 3).

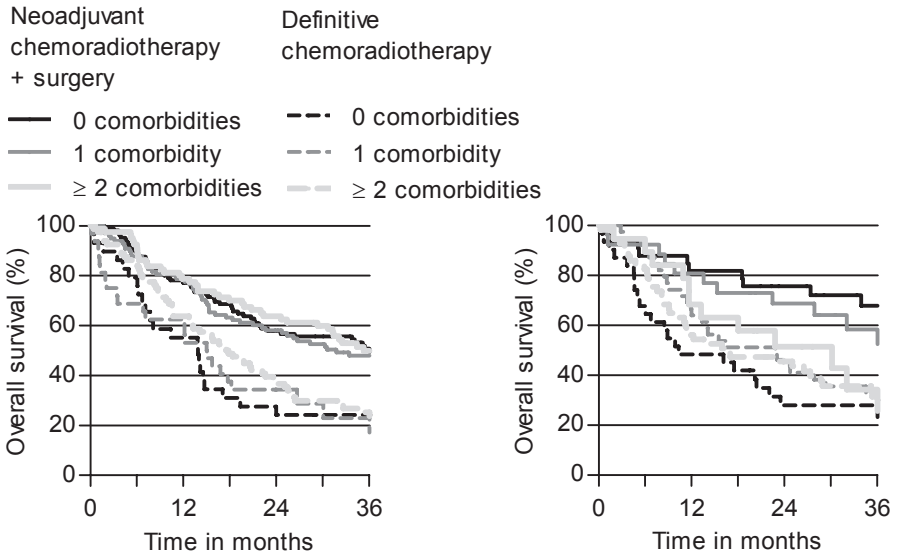


a OAC and OSCC

No. at risk				
Neo CRT				
OAC	283	221	160	109
OSCC	78	61	46	29
Def CRT				
OAC	141	87	40	25
OSCC	127	72	50	32

2-year overall survival	Neoadjuvant chemorad + surgery	Definitive chemoradiotherapy	*P* value
Whole group	61%	38%	<0.01
OAC	60%	33%	<0.01
OSCC	68%	42%	<0.01

Figure 2a Overall survival of oesophageal cancer patients (cT1N+/cT2-3,Tx, any cN , cM0) according to morphology following definitive chemoradiotherapy or neoadjuvant chemoradiotherapy plus surgery.
Patients who died within the first 6 months after diagnosis were excluded from the analysis.
OAC= oesophageal adenocarcinomas, OSSC=oesophageal squamous cell carcinoma



b OAC

No. at risk

Neo CRT				
0 co	105	81	54	39
1 co	98	77	55	39
≥ 2 co	80	63	51	31
Def CRT				
0 co	29	16	7	5
1 co	32	20	6	4
≥ 2 co	80	51	27	16

2-year overall survival	Neoadjuvant chemorad + surgery	Definitive chemoradiotherapy	*P* value
0 comorb	58%	24%	<0.01
1 comorb	58%	34%	<0.01
≥ 2 comorb	64%	37%	<0.01

c OSCC

No. at risk

Neo CRT				
0 co	33	27	22	15
1 co	26	21	16	10
≥ 2 co	19	13	8	4
Def CRT				
0 co	31	15	8	6
1 co	39	25	18	11
≥ 2 co	57	32	24	15

2-year overall survival	Neoadjuvant chemorad + surgery	Definitive chemoradiotherapy	*P* value
0 comorb	76%	28%	<0.01
1 comorb	69%	46%	0.02
≥ 2 comorb	51%	46%	0.32

Figure 2b and c Overall survival of oesophageal cancer patients (cT1N+/cT2-3,Tx, any cN , cM0) according to number of comorbidities following definitive chemoradiotherapy or neoadjuvant chemoradiotherapy plus surgery, stratified for morphology (b; n=424 and c; n=205).

Discussion

The results of this population-based study support the use of neoadjuvant chemoradiotherapy plus surgery in operable patients with OAC, regardless of age, number and type of comorbidity. The administration of definitive chemoradiotherapy was preferable in patients with OSCC having at least 2 comorbidities or being 75 years or older. This was seen particularly among those with cardiovascular disease or previous malignancies as their overall survival after definitive chemoradiotherapy was comparable to the overall survival of patients after neoadjuvant chemoradiotherapy plus surgery.

Table 3 Multivariable Cox regression analyses to examine overall survival differences among patients who underwent definitive chemoradiotherapy versus patients who underwent neoadjuvant chemoradiotherapy followed by surgery according to age, number and type of comorbidity, stratified for histology.

	OAC			OSSC		
	Definitive chemoradiotherapy vs. neoadjuvant chemoradiotherapy + surgery			Definitive chemoradiotherapy vs. neoadjuvant chemoradiotherapy + surgery		
	n	HR	95% CI	n	HR	95% CI
Patients who died within 6 months after diagnosis were excluded to reduce immortal time bias.						
Number of comorbidities *						
0 comorbidities	134	3.21	1.85-5.57	64	4.14	1.80-9.52
1 comorbidity	130	2.99	1.73-5.19	65	2.31	1.10-4.89
≥2 comorbidities	160	2.67	1.75-4.09	76	1.52	0.78-2.97
Age (in years) **						
< 60	116	4.95	2.63-9.32	55	2.30	1.09-4.85
60-74	230	2.33	1.63-3.34	117	2.72	1.58-4.69
75 +	78	2.17	1.09-4.30	33	0.73	0.13-4.14
Type of comorbidity [a]						
Cardiovascular diseases	131	2.32	1.42-3.77	67	1.68	0.83-3.40
Pulmonary	64	1.84	0.90-3.78	32	n.a.	
Hypertension	142	3.34	2.10-5.34	62	3.22	1.22-8.50
Previous malignancies	33	1.30	0.36-4.67	28	0.98	0.25-3.90
Diabetes	69	2.95	1.50-5.81	16	n.a.	

OAC= oesophageal adenocarcinomas, OSSC=oesophageal squamous cell carcinoma, n.a. =not assessed (too small number of patients).

* Adjusted for gender, age, tumour stage and period of diagnosis.

** Adjusted for gender, tumour stage, number of comorbidities and period of diagnosis

[a] Models for type of comorbidity were adjusted for gender, age, tumour stage, period of diagnosis and number of comorbidities.

In the Netherlands, neoadjuvant chemoradiotherapy in combination with surgery is the standard potentially curative treatment for locally advanced oesophageal cancer. This treatment potentially downstages the tumour and increases the radical resectability rate, which in turn reduces locoregional recurrences with improved long-term survival.[1] Moreover, the CROSS trial also showed a distant disease control beyond the first 24 months after neoadjuvant chemoradiotherapy followed by surgery, supporting a direct systemic effect of this regimen.[22] Of great importance for a prolonged survival is a pathological complete response following neoadjuvant chemoradiotherapy, which occurred in about 49% of the patients with OSSC included in the CROSS trial and in 23% of those with OAC.[22]

In our study, 78% of the elderly patients were treated with definitive chemoradiotherapy and survival in elderly patients with OSCC was equal for both treatment modalities. Elderly patients are generally regarded as less suitable for surgery because of an advanced age, severe comorbidity or decreased performance status. Moreover, definitive chemoradiotherapy seems a well-tolerated alternative for patients with oesophageal cancer who are not fit enough to

undergo surgery.[11,12,23-24] Nevertheless, selecting the appropriate treatment for elderly patients requires an adequate multidisciplinary board with the presence and consultation of a geriatric physician.[25]

Several studies have reported relatively good outcome after definitive chemoradiotherapy in a selected groups of patients.[11,12,26-27] Two previous studies have found a comparable overall survival after definitive chemoradiotherapy compared with surgery alone for patients with resectable OSCC.[11,12] However, in these studies, survival differences were not investigated according to number and type of comorbidities. In our study no significant difference was found in overall survival following definitive chemoradiotherapy or neoadjuvant chemoradiotherapy plus surgery in patients with OSCC having at least 2 comorbidities. This suggests that patients derive the same benefits from both treatment methods, although the type of comorbidity may have an impact on the outcome.

In patients with OAC, the standard approach of neoadjuvant chemoradiotherapy followed by surgery indeed resulted in a better survival. A better overall survival was found for OAC patients with diabetes mellitus, hypertension or cardiovascular disease. Tougeron et al. reported a more frequent use of definitive chemoradiotherapy in advanced staged OAC, in elderly patients and patients with comorbidities of ≥ Charlson score 2.[13] Although selection bias may be present in this previous study, survival after surgery was better compared to survival after definitive chemoradiotherapy (median overall survival 36.2 months vs. 16.5 months; *P*=0.02). Another study has also found a significant improvement in median survival for patients with locally advanced OAC treated with neoadjuvant chemoradiotherapy followed by surgery compared to definitive chemoradiotherapy.[14]

The differences in treatment response between patients with OAC and OSCC may be associated with tumour aggressiveness and different carcinogenesis pathways.[13] Moreover, tumour site (distal versus proximal) and pulmonary based differences with a larger field of radiotherapy in lower oesophageal tumours, may also play a role in the different outcomes between OAC and OSCC following definitive chemoradiotherapy.[28] With current radiation techniques, including intensity-modulated radiotherapy, respiratory gated radiotherapy and intensity-modulated proton therapy the radiation dose can be delivered more accurately with less damage to normal tissue.[15,29-31] Moreover, in diminishing toxicity of chemotherapy regimens, the combination of carboplatin/paclitaxel can be a good alternative or even standard approach, especially in patients with cardiovascular and pulmonary comorbidities.[32]

Our study has some limitations. First, the intent of treatment with chemoradiotherapy (curative or palliative) was unknown. As only potentially curable oesophageal cancer patients were included it was assumed that these patients underwent chemoradiotherapy with curative intent (neoadjuvant or definitive). Second, the group of patients who underwent definitive chemoradiotherapy may be heterogeneous as patients who were unable to undergo surgery after neoadjuvant chemoradiotherapy were allocated to this group. Furthermore, patients in this group may also had a complete clinical response after chemoradiotherapy and may have refused surgery. Third, little information was given about the radiotherapy techniques and schedule of the given chemoradiotherapy. Fourth, the impact of type of some comorbidities could not be assessed accurately due to a small number of patients. Moreover, information about performance status was not registered for the study period. Finally, because endoscopic

ultrasonography was not always performed in patients with oesophageal cancer, clinical T-stage was unknown in 15% of the patients. A strength of this population-based study is that the results are based on patients diagnosed in ten hospitals providing an overview of everyday clinical practice, rather than in a single institution in which patients are possibly more carefully selected,

In conclusion, neoadjuvant chemoradiotherapy plus surgery should be performed in operable patients with oesophageal adenocarcinoma regardless of age, number and type of comorbidities. Definitive chemoradiotherapy may be preferred in patients with oesophageal squamous cell carcinoma having at least 2 comorbidities or being older than 75 years. Prospective studies are needed to assess more accurately which patients may benefit from definitive chemoradiotherapy.

References

1. van Hagen P, Hulshof MC, van Lanschot JJ, Steyerberg EW, van Berge Henegouwen MI, Wijnhoven BP, Richel DJ, Nieuwenhuijzen GA, Hospers GA, Bonenkamp JJ, Cuesta MA, Blaisse RJ, Busch OR, ten Kate FJ, Creemers GJ, Punt CJ, Plukker JT, Verheul HM, Spillenaar Bilgen EJ, van Dekken H, van der Sangen MJ, Rozema T, Biermann K, Beukema JC, Piet AH, van Rij CM, Reinders JG, Tilanus HW, van der Gaast A. Preoperative chemoradiotherapy for esophageal or junctional cancer, 2012. N Engl J Med;366:2074-2084.
2. Gwynne S, Hurt C, Evans M, Holden C, Vout L, Crosby T. Definitive chemoradiation for oesophageal cancer--a standard of care in patients with non-metastatic oesophageal cancer, 2011. Clin Oncol (R Coll Radiol);23:182-188.
3. Morgan MA, Lewis WG, Casbard A, Roberts SA, Adams R, Clark GW, Havard TJ, Crosby TD. Stage-for-stage comparison of definitive chemoradiotherapy, surgery alone and neoadjuvant chemotherapy for oesophageal carcinoma, 2009. Br J Surg;96:1300-1307.
4. In H, Palis BE, Merkow RP, Posner MC, Ferguson MK, Winchester DP, Pezzi CM. Doubling of 30-Day Mortality by 90 Days After Esophagectomy: A Critical Measure of Outcomes for Quality Improvement, 2016. Ann Surg;263:286-291.
5. Walters DM, McMurry TL, Isbell JM, Stukenborg GJ, Kozower BD. Understanding mortality as a quality indicator after esophagectomy, 2014. Ann Thorac Surg;98:506-511; discussion 511-502.
6. Pultrum BB, Bosch DJ, Nijsten MW, Rodgers MG, Groen H, Slaets JP, Plukker JT. Extended esophagectomy in elderly patients with esophageal cancer: minor effect of age alone in determining the postoperative course and survival, 2010. Ann Surg Oncol;17:1572-1580.
7. van Gestel YR, Lemmens VE, de Hingh IH, Steevens J, Rutten HJ, Nieuwenhuijzen GA, van Dam RM, Siersema PD. Influence of comorbidity and age on 1-, 2-, and 3-month postoperative mortality rates in gastrointestinal cancer patients, 2013. Ann Surg Oncol;20:371-380.
8. Koppert LB, Lemmens VE, Coebergh JW, Steyerberg EW, Wijnhoven BP, Tilanus HW, Janssen-Heijnen ML. Impact of age and co-morbidity on surgical resection rate and survival in patients with oesophageal and gastric cancer, 2012. Br J Surg;99:1693-1700.
9. Chuang WY, Yeh CJ, Wu YC, Chao YK, Liu YH, Tseng CK, Chang HK, Liu HP, Hsueh C. Tumor cell expression of podoplanin correlates with nodal metastasis in esophageal squamous cell carcinoma, 2009. Histol Histopathol;24:1021-1027.
10. Muijs CT, Beukema JC, Mul VE, Plukker JT, Sijtsema NM, Langendijk JA. External beam radiotherapy combined with intraluminal brachytherapy in esophageal carcinoma, 2012. Radiother Oncol;102:303-308.
11. Stahl M, Stuschke M, Lehmann N, Meyer HJ, Walz MK, Seeber S, Klump B, Budach W, Teichmann R, Schmitt M, Schmitt G, Franke C, Wilke H. Chemoradiation with and without surgery in patients with locally advanced squamous cell carcinoma of the esophagus, 2005. J Clin Oncol;23:2310-2317.
12. Bedenne L, Michel P, Bouche O, Milan C, Mariette C, Conroy T, Pezet D, Roullet B, Seitz JF, Herr JP, Paillot B, Arveux P, Bonnetain F, Binquet C. Chemoradiation followed by surgery compared with chemoradiation alone in squamous cancer of the esophagus: FFCD 9102, 2007. J Clin Oncol;25:1160-1168.
13. Tougeron D, Scotte M, Hamidou H, Di Fiore F, Paillot B, Michot F, Michel P. Definitive chemoradiotherapy in patients with esophageal adenocarcinoma: an alternative to surgery?, 2012. J Surg Oncol;105:761-766.
14. Murphy CC, Correa AM, Ajani JA, Komaki RU, Welsh JW, Swisher SG, Hofstetter WL. Surgery is an essential component of multimodality therapy for patients with locally advanced esophageal adenocarcinoma, 2013. J Gastrointest Surg;17:1359-1369.
15. Crehange G, Conroy T. The SCOPE of definitive chemoradiotherapy in locally advanced esophageal cancer: what direction for the future?, 2016. J Thorac Dis;8:1014-1018.
16. Lordick F, Mariette C, Haustermans K, Obermannova R, Arnold D, Committee EG. Oesophageal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up, 2016. Ann Oncol;27:v50-v57.

17. Kristjansson SR, Nesbakken A, Jordhoy MS, Skovlund E, Audisio RA, Johannessen HO, Bakka A, Wyller TB. Comprehensive geriatric assessment can predict complications in elderly patients after elective surgery for colorectal cancer: a prospective observational cohort study, 2010. Crit Rev Oncol Hematol;76:208-217.

18. Janssen-Heijnen ML, Houterman S, Lemmens VE, Louwman MW, Maas HA, Coebergh JW. Prognostic impact of increasing age and co-morbidity in cancer patients: a population-based approach, 2005. Crit Rev Oncol Hematol;55:231-240.

19. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation, 1987. J Chronic Dis;40:373-383.

20. Bosch DJ, Pultrum BB, de Bock GH, Oosterhuis JK, Rodgers MG, Plukker JT. Comparison of different risk-adjustment models in assessing short-term surgical outcome after transthoracic esophagectomy in patients with esophageal cancer, 2011. Am J Surg;202:303-309.

21. van Duijn C, Keij I. Sociaal-economische status indicator op postcode niveau (in Dutch). Maandstatistiek van de bevolking 2002;50:32-35.

22. Shapiro J, van Lanschot JJ, Hulshof MC, van Hagen P, van Berge Henegouwen MI, Wijnhoven BP, van Laarhoven HW, Nieuwenhuijzen GA, Hospers GA, Bonenkamp JJ, Cuesta MA, Blaisse RJ, Busch OR, Ten Kate FJ, Creemers GJ, Punt CJ, Plukker JT, Verheul HM, Bilgen EJ, van Dekken H, van der Sangen MJ, Rozema T, Biermann K, Beukema JC, Piet AH, van Rij CM, Reinders JG, Tilanus HW, Steyerberg EW, van der Gaast A, group Cs. Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): long-term results of a randomised controlled trial, 2015. Lancet Oncol;16:1090-1098.

23. Sabel MS, Smith JL, Nava HR, Mollen K, Douglass HO, Gibbs JF. Esophageal resection for carcinoma in patients older than 70 years, 2002. Ann Surg Oncol;9:210-214.

24. Cronin-Fenton DP, Sharp L, Carsin AE, Comber H. Patterns of care and effects on mortality for cancers of the oesophagus and gastric cardia: a population-based study, 2007. Eur J Cancer;43:565-575.

25. Stairmand J, Signal L, Sarfati D, Jackson C, Batten L, Holdaway M, Cunningham C. Consideration of comorbidity in treatment decision making in multidisciplinary cancer team meetings: a systematic review, 2015. Ann Oncol;26:1325-1332.

26. Rebecca WO, Richard MA. Combined chemotherapy and radiotherapy (without surgery) compared with radiotherapy alone in localized carcinoma of the esophagus, 2003. Cochrane Database Syst Rev:CD002092.

27. Wong RK, Malthaner RA, Zuraw L, Rumble RB, Cancer Care Ontario Practice Guidelines Initiative Gastrointestinal Cancer Disease Site G. Combined modality radiotherapy and chemotherapy in nonsurgical management of localized carcinoma of the esophagus: a practice guideline, 2003. Int J Radiat Oncol Biol Phys;55:930-942.

28. Muijs C, Smit J, Karrenbeld A, Beukema J, Mul V, van Dam G, Hospers G, Kluin P, Langendijk J, Plukker J. Residual tumor after neoadjuvant chemoradiation outside the radiation therapy target volume: a new prognostic factor for survival in esophageal cancer, 2014. Int J Radiat Oncol Biol Phys;88:845-852.

29. Kole TP, Aghayere O, Kwah J, Yorke ED, Goodman KA. Comparison of heart and coronary artery doses associated with intensity-modulated radiotherapy versus three-dimensional conformal radiotherapy for distal esophageal cancer, 2012. Int J Radiat Oncol Biol Phys;83:1580-1586.

30. Welsh J, Gomez D, Palmer MB, Riley BA, Mayankkumar AV, Komaki R, Dong L, Zhu XR, Likhacheva A, Liao Z, Hofstetter WL, Ajani JA, Cox JD. Intensity-modulated proton therapy further reduces normal tissue exposure during definitive therapy for locally advanced distal esophageal tumors: a dosimetric study, 2011. Int J Radiat Oncol Biol Phys;81:1336-1342.

31. Langendijk JA, Lambin P, De Ruysscher D, Widder J, Bos M, Verheij M. Selection of patients for radiotherapy with protons aiming at reduction of side effects: the model-based approach, 2013. Radiother Oncol;107:267-273.

32. Honing J, Smit JK, Muijs CT, Burgerhof JG, de Groot JW, Paardekooper G, Muller K, Woutersen D, Legdeur MJ, Fiets WE, Slot A, Beukema JC, Plukker JT, Hospers GA. A comparison of carboplatin and paclitaxel with cisplatinum and 5-fluorouracil in definitive chemoradiation in esophageal cancer patients, 2014. Ann Oncol;25:638-643.

Chapter 9

Definitive chemoradiation or surgery in elderly patients with potentially curable oesophageal cancer in the Netherlands: a nationwide population-based study on patterns of care and survival

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Abstract

Background
The aim of our study was to describe treatment patterns and the impact on overall survival among elderly patients (75 years and older) with potentially curable oesophageal cancer.

Methods
Between 2003 and 2013, 13 244 patients from the nationwide population-based Netherlands Cancer Registry were diagnosed with potentially curable oesophageal cancer (cT2-3,X, any cN, cM0,X) of which 34% were elderly patients (n=4501).

Results
Surgical treatment with or without neoadjuvant treatment remained stable among elderly patients (around the 16% between 2003-2013). However, among younger patients surgical treatment increased from 60.2% to 67.0%. The use of definitive chemoradiation (dCRT) increased in elderly patients from 1.9% to 19.5% and in younger patients from 5.2% to 17.2%. Due to the increase in dCRT, treatment with curative intent doubled in the elderly from 17% to 37.1%. Multivariable Cox regression revealed that elderly patients with an adenocarcinoma receiving surgery alone or dCRT had a significantly worse overall survival compared to those receiving surgery with neoadjuvant chemo(radio)therapy (nCRT/CT)(HR: 1.7 95%CI 1.4-2.0 and HR=1.9 95%CI 1.5-2.3). However, among elderly with squamous cell carcinoma overall survival was comparable between dCRT, surgery alone and surgery with nCRT/CT.

Conclusions
Survival was comparable among elderly patients with squamous cell carcinoma who underwent surgery with nCRT/CT, surgery alone or received dCRT, while elderly patients with an adenocarcinoma who underwent surgery with nCRT/CT had a better overall survival, when compared with surgery alone or dCRT. Therefore, dCRT can be considered as a reasonable alternative for surgery among potentially curable elderly patients with oesophageal squamous cell carcinoma. However in elderly patients with oesophageal adenocarcinoma surgery with nCRT/CT is still preferable regarding overall survival.

Introduction

The incidence of oesophageal cancer, especially adenocarcinoma, has increased dramatically over the past four decades in the Western world and is still rising but at a slower rate than previously.[1,2] Oesophageal cancer is mainly a disease of the elderly as a significant number of patients is aged between 60 and 85 year at time of diagnosis.[3,4] In the Netherlands approximately 30% of all newly diagnosed patients with oesophageal cancer is 75 years or older.[5]

According to the Dutch clinical practice guidelines, the preferred treatment for patients with potentially curable oesophageal cancer is neoadjuvant chemoradiation followed by a subsequent oesophagectomy. Early oesophageal cancer (T1a) can be treated with Endoscopic Mucosal Resection (EMR).[6] Frail patients unfit for surgery, such as some elderly patients, can be treated alternatively with a curative intention using definitive chemoradiation (dCRT).[7,8] Furthermore, histological subtype plays a role in treatment of patients with potentially curable oesophageal cancer. For example, patients with squamous cell carcinoma seem to have a better response to dCRT compared to patients with an adenocarcinoma.[9-11]

Surgical treatment of oesophageal cancer is complex with a high post-operative complication rate, especially in elderly patients with multiple co-morbidities, which might be an argument to withhold some patients from surgical treatment.[12,13] A previous study has shown an increase in 30-day postoperative mortality from 4.9% in patients younger than 65 years to 10.3% in patients older than 75 years.[14]

However, most treatment strategies and guidelines are based on clinical trials in which elderly patients are excluded. Therefore, it is of significant importance to investigate the effect of different treatment options on survival in this specific group of patients. The aim of our study was to describe treatment patterns and the impact on overall survival in elderly patients (75 years and older) with potentially curable oesophageal cancer (adenocarcinoma or squamous cell carcinoma) in the Netherlands.

Methods

Data collection

Nationwide population-based data from the Netherlands Cancer Registry (NCR) were used. The NCR is based on notification of all newly diagnosed malignancies in the Netherlands by the national automated pathological archive (PALGA). Additional sources are the national registry of hospital discharge, radiotherapy institutions and diagnosis therapy combinations (specific codes for reimbursement purposes). Specially trained data managers of the NCR routinely extracted information on diagnosis, tumour stage and treatment from the medical records. Information on vital status was obtained through an annual linkage with the Municipal Administrative Database, in which all deceased and emigrated persons in the Netherlands were registered. Institutional Review Board approval was obtained from the NCR.

Patients

Between January 2003 and December 2013, 25 638 patients were diagnosed with an adenocarcinoma or squamous cell carcinoma of the oesophagus or gastro-oesophageal junction

in the Netherlands. The topography and morphology of the tumours were coded according to the International Classification of Diseases for Oncology (ICD-O-3).[15] Subsite distribution was divided as: proximal (C15.0, C15.3), mid (C15.4), distal (C15.5), overlapping or not otherwise specified (C15.8, C15.9) and gastro-oesophageal junction (GEJ) (C16.0). Patients diagnosed from 2003 to 2009 were staged according to TNM-6, whereas patients diagnosed from 2010-2013 were staged according to TNM-7.[16,17]

Patients with potentially curable oesophageal tumours were eligible for this study (Figure 1). Patients were considered potentially curable in this study if they had no clinically distant metastasis (cM1b for TNM-6 and cM1 for TNM 7) (n=8009) and no tumours infiltrating surrounding organs (cT4 according to TNM-6 and cT4A and cT4B according to TNM-7) (n=1368). We excluded patients with tumours infiltrating surrounding organs since it was uncertain whether or not these patients were eligible for curative treatment. For the analyses, patients with a cM1A tumour according to TNM-6 were categorized as having cN+ as most patients with a cM1A tumour had a distal tumour with coeliac lymph nodes which can be considered as having cN+ according to TNM-7. Furthermore, patients with unknown clinical distant metastases (cMX) were included. It should be noted that as of 2010 coding regulations to register a cM0 or cM1 status into the NCR were less strict than before 2010, and therefore as of 2010 relatively more patients were registered with a cM0 rather than a cMX into the NCR. To account for this, we decided to include all patients with cMX. Patients with an in-situ or a cT1 tumour (n=1002) were also excluded since these tumours are treated predominantly with an Endoscopic Mucosal Resection (EMR) rather than surgical treatment. In addition, patients with missing/unknown treatment (n=92) and patients receiving EMR alone (n=350) were excluded. This resulted in 13244 patients with a potentially curable oesophageal carcinoma (cT2, 3, X, any cN, cM0, X). Of these patients 4501 (34%) were elderly patients being 75 years and older (Figure 1).

Treatment

Surgery with potentially curative intent was defined as an transhiatal oesophagectomy or transthoracic oesophagectomy. Definitive chemoradiation (dCRT) was defined as the combination of radiotherapy and chemotherapy as primary treatment without surgery. Curative treatment was defined as dCRT, surgery alone or surgery with neoadjuvant chemoradiotherapy or chemotherapy (nCRT/CT). All other treatments were defined as "other" therapy.

Statistical analysis

Differences in patient and tumour characteristics between elderly patients with an adenocarcinoma and squamous cell carcinoma were described and compared using the Pearson's chi-square test for nominal data. For differences in continuous variables, the independent T-test was used. Survival time was defined as time from diagnosis to death or until February 1st 2016 for patients who were still alive. Survival curves per treatment option were obtained using the Kaplan-Meier method for elderly patients according to histology. Differences in overall survival according to treatment were assessed by using log-rank tests. Multivariable Cox regression analyses were performed to evaluate independent prognostic factors for overall survival. All statistical analyses were performed using Statistical Package for Social Sciences version 22.0

(IBM Corporation, Armonk, NY, USA) and *P*-values less than 0.05 were considered statistically significant.

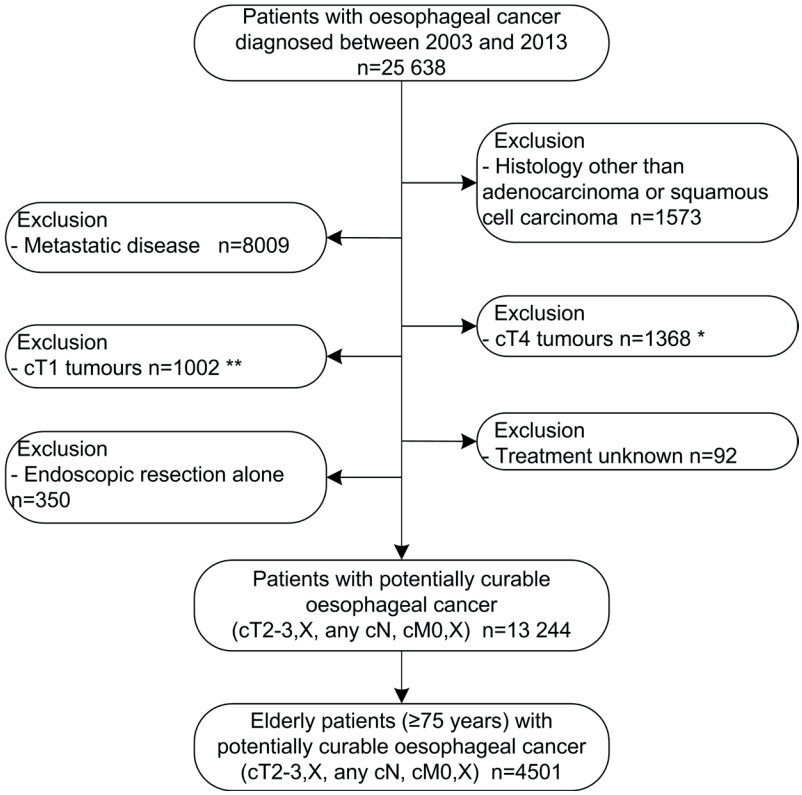

Figure 1 Flowchart of the study population.
*cT4 according to TNM-6 and cT4a and cT4b according to TNM-7.
**cT1 according to TNM-6 and cT1a and cT1b according to TNM-7.

Results

Patient characteristics

Of the potentially curable elderly patients of 75 years and older diagnosed with a oesophageal carcinoma, 75.6% (n=3402) was diagnosed with an adenocarcinoma and 24.4% (n=1099) with a squamous cell carcinoma. There were no significant differences in age, cT- stage, cN-stage and cM-stage between both histology groups. However, patients with an adenocarcinoma had more often a distally located tumour and a poor tumour differentiation. Furthermore, elderly patients with an adenocarcinoma more often received surgical treatment (21.3%) than dCRT (7.7%), whereas patients with a squamous cell carcinoma more often received dCRT (13.1%) than surgery (10.4%) (Table 1).

Of all elderly patients diagnosed with potentially curable oesophageal carcinoma, 6.9% received surgery with nCRT/CT, 11.8% received surgery alone, 18.6% received surgery, 9.0% received dCRT and 72.4% received other/no treatment.

Trends in treatment

From 2003 until 2013, the use of surgery with nCRT/CT among the elderly (≥75 years) and the younger patients (<75 years) increased over time from 0.5% to 13.5% and from 14.4% to 63.3% respectively. In line with these findings, the proportion of patients with underwent surgery alone decreased among both the elderly and the younger patients from respectively 14.5% to 4.2% and from 45.8% to 3.7%. The use of surgical treatment (surgery with nCRT/CT or surgery alone) among all elderly patients (≥75 years) remained relatively stable over time from 15.0% in 2003 to 17.7% in 2013, whereas among the younger patients (≥75 years) the use of surgical treatment increased over time from 60.2% in 2003 to 67.0% in 2013. Furthermore, there was an increase in administration of dCRT in elderly patients from 1.9% to 19.5% as well as in the younger patients from 5.2% to 17.2% (Figure 2a).

The increase in dCRT was most prominent among elderly patients with a squamous cell carcinoma in which treatment with dCRT increased from 3.5% to 30.7%, while among younger patients with squamous cell carcinoma an increase from 9.5% to 29.3% was observed (Figure 2b). In patients with an adenocarcinoma, the increase in use of dCRT was comparable in the elderly patients compared to the increase among younger patients (Figure 2c). Mainly due to the increase in dCRT, the administration of treatment with curative intent (surgery or dCRT) doubled over time in all elderly patient from 17% to 37.1%. The increase of treatment with a curative intent quadrupled over time in the elderly patient with squamous cell carcinoma from 10.5% to 41.2%. However, the increase in the use of treatment with curative intent was less prominent in the younger patients (Figure 2).

Table 1 Patient characteristics of the elderly patient (≥75 years) diagnosed with potentially curable oesophageal cancer in the period 2003-2013 (n=4501).

	Adenocarcinoma	Squamous cell carcinoma	
	n (%)	n (%)	*P* value
Total	3402 (75.6)	1099 (24.4)	
Age in years (mean, SD)	81.6 (4.9)	81.3 (5.0)	0.051
Gender			<0.001
Male	2374 (69.8)	514 (46.8)	
Female	1028 (30.2)	585 (53.2)	
cT-stage			0.163
T2	582 (17.1)	171 (15.6)	
T3	863 (25.4)	308 (28.0)	
Unknown	1957 (57.5)	620 (56.4)	
cN-stage			0.302
N0	1167 (34.3)	388 (35.3)	
N+	1173 (34.5)	395 (35.9)	
Unknown	1062 (31.2)	316 (28.8)	
cM-stage			0.174
M0	2790 (82.0)	921 (83.8)	
Unknown	612 (18.0)	178 (16.2)	
Tumour location			<0.001
Proximal	38 (1.1)	164 (14.9)	
Mid	208 (6.1)	398 (36.2)	
Distal	1983 (58.3)	454 (41.3)	
GOJ	1040 (30.6)	7 (0.6)	
Overlapping/NOS	133 (3.9)	76 (6.9)	
Tumour differentiation			<0.001
Well	67 (2.0)	31 (2.8)	
Moderate	677 (19.9)	296 (26.9)	
Poor	1147 (33.7)	254 (23.1)	
Unknown	1511 (44.4)	518 (47.1)	
Type of treatment			<0.001
Surgery with nCRT/CT *	250 (7.3)	59 (5.4)	
Surgery alone	475 (14.0)	55 (5.0)	
Definitive chemoradiation	261 (7.7)	144 (13.1)	
Other/no treatment	2416 (71.0)	841 (76.5)	

GOJ: Gastro-oesophageal junction. NOS: Not otherwise specified.
* Among this group of patients 77.3% received nCRT and 22.7% received nCT. Two patients received chemoradiation postoperatively.

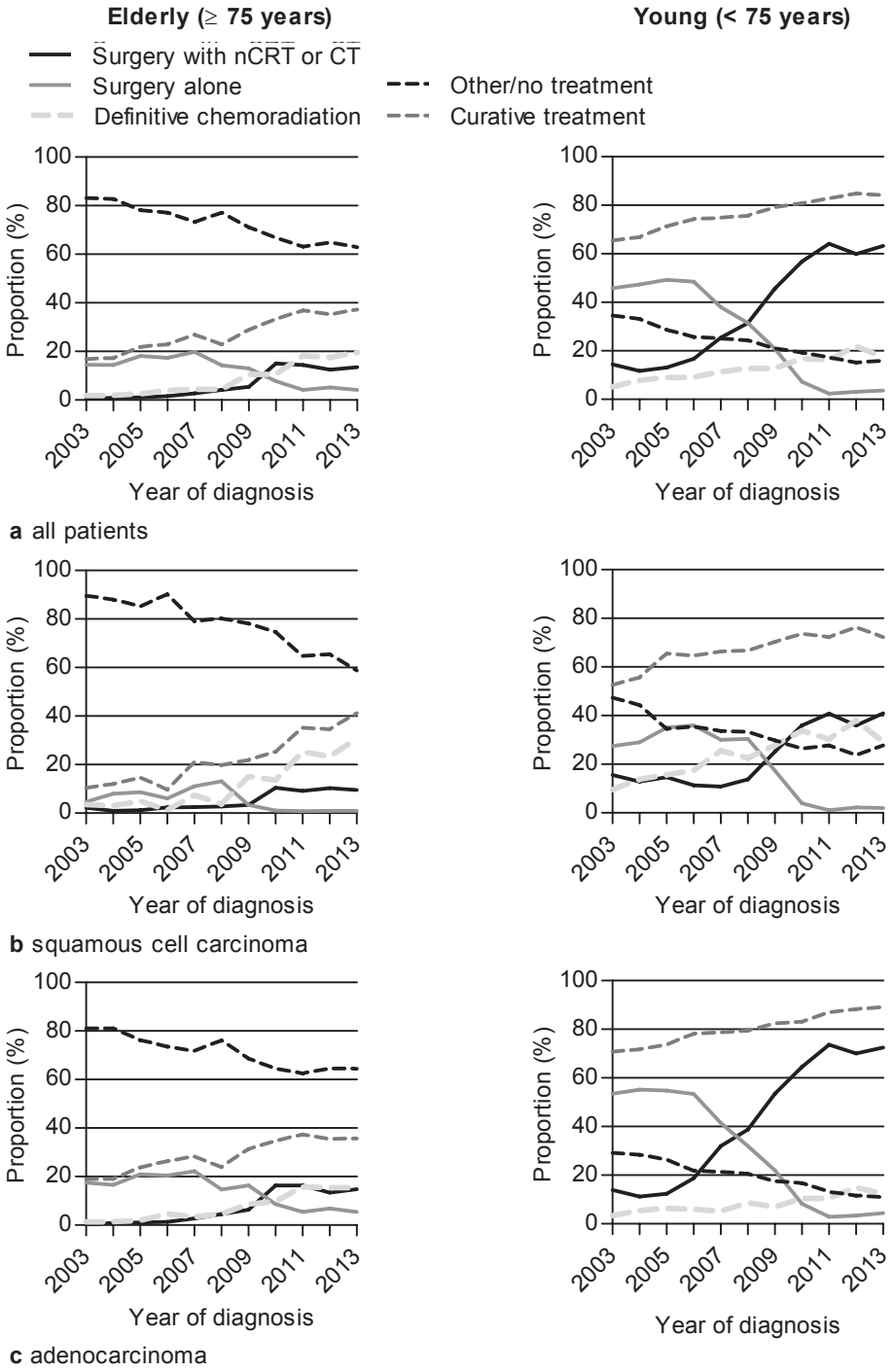

Figure 2 Trends in treatment for oesophageal cancer according to age for a all patients (n=4501), b squamous cell carcinoma (n=3402) and c adenocarcinoma (n=1099).

Survival

Overall, elderly patients with a potentially curable adenocarcinoma had a comparable 1- and 3-year overall survival rate compared to elderly patients with a potentially curable squamous cell carcinoma with 1-year overall survival rates of 40.8% vs. 36.5% and 3-year survival rates of 12.0% vs. 14.1%, respectively (log rank *P*=0.621). Furthermore, the 1- year overall survival in elderly patients with an adenocarcinoma treated with surgery and nCRT/CT was 79.6% which was comparable to the overall survival of patients treated with surgery alone (64.8%) or dCRT (72.4%) whereas 3-year overall survival was significantly better for patients who underwent surgery with nCRT/CT (51.2%) compared to patients receiving surgery alone (29.5%) or dCRT (11.6%)(*P*<0.001)(Figure 3a). Among elderly patients with a squamous cell carcinoma, patients receiving surgery with nCRT/CT had a better 3-year overall survival (50.2%) compared to surgery alone (40.0%) and dCRT (36.8%) however this difference was not statistically significant (*P*=0.267) (Figure 3b).

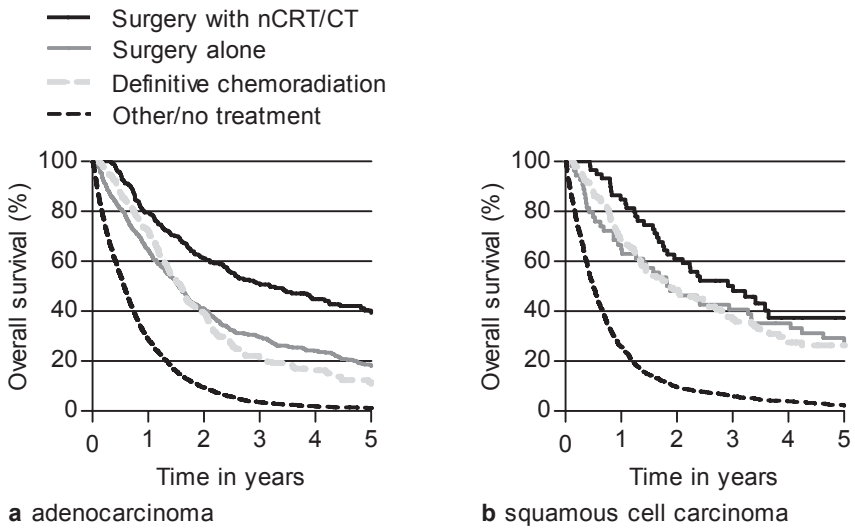

Figure 3 Kaplan-Meier survival analysis among elderly patients with oesophageal cancer according to treatment, stratified for histology; a adenocarcinoma (n=3402), b squamous cell carcinoma (n=1099).

Multivariable Cox regression analyses showed that patients with male gender, a poor tumour differentiation, an overlapping tumour/not otherwise specified tumour location, cT3 tumours, regional lymph nodes metastasis and a squamous cell histology had a significantly worse overall survival. Regarding the treatment strategy, the multivariable Cox regression analysis which included both histology groups showed that elderly patients who received surgery alone (HR=1.6, 95%CI 1.3-1.9), dCRT (HR=1.7, 95%CI 1.4-2.0) or other/no treatment (HR=4.1, 95%CI 3.5-4.8) had a significantly worse overall survival compared to patients who underwent surgery with nCRT/CT (Table 2).

Comparable results were found for elderly patients with an adenocarcinoma. Among elderly patients with an adenocarcinoma, patients receiving surgery alone (HR=1.7, 95%CI 1.4-2.0),

dCRT (HR=1.9, 95%CI 1.5-2.3) or other/no treatment (HR=4.3, 95%CI 3.6-5.1) had a significantly worse overall survival compared to patients receiving surgery with nCRT/CT. However, among elderly patients with a squamous cell carcinoma overall survival was comparable for patients who underwent surgery alone (HR=1.3, 95%CI 0.8-2.1), dCRT (HR=1.4, 95%CI 0.9-2.0) or surgery with nCRT/CT (Table 2).

Table 2 Multivariable Cox regression analysis for all elderly patients and stratified for histology.

	All elderly patients n=4501			Adenocarcinoma n=3402			Squamous cell carcinoma n=1099		
	HR*	95%CI	*P* value	HR*	95%CI	*P* value	HR*	95%CI	*P* value
Gender									
Male	1.0			1.0			1.0		
Female	0.9	0.8-1.0	0.001	0.9	0.8-1.0	0.015	0.8	0.7-0.9	0.003
Period of diagnosis									
2003-2006	0.9	0.9-1.0	0.084	0.9	0.9-1.0	0.058	1.0	0.8-1.1	0.581
2007-2010	0.9	0.9-1.0	0.085	1.0	0.9-1.0	0.304	0.9	0.8-1.0	0.132
2011-2013	1.0			1.0			1.0		
Tumour differentiation									
Well	0.8	0.6-1.0	0.031	0.6	0.5-0.8	0.001	1.7	1.1-2.5	0.009
Moderate	0.9	0.8-0.9	<0.001	0.8	0.7-0.9	<0.001	1.1	0.9-1.3	0.269
Poor	1.0			1.0			1.0		
Unknown	0.8	0.7-0.9	<0.001	0.8	0.7-0.8	<0.001	1.0	0.8-1.2	0.922
Tumour location									
Proximal	0.8	0.7-0.9	0.008	1.0	0.7-1.4	0.954	0.7	0.6-0.9	0.002
Mid	0.9	0.8-1.0	0.041	1.0	0.8-1.1	0.721	0.9	0.7-1.0	0.030
Distal	1.0			1.0			1.0		
GOJ	1.0	0.9-1.1	0.828	1.0	0.9-1.1	0.997	1.9	0.9-4.0	0.104
Overlapping/ NOS	1.3	1.1-1.5	0.001	1.2	1.0-1.4	0.042	1.4	1.1-1.8	0.008
cT-stage									
cT2	0.9	0.8-1.0	0.019	0.9	0.8-1.0	0.019	0.9	0.7-1.1	0.411
cT3	1.0			1.0			1.0		
Unknown	1.2	1.1-1.3	<0.001	1.2	1.1-1.3	0.002	1.4	1.2-1.7	<0.001
cN-stage									
cN0	1.0			1.0			1.0		
cN+	1.2	1.1-1.3	<0.001	1.2	1.1-1.3	<0.001	1.2	1.0-1.4	0.057
Unknown	1.6	1.4-1.7	<0.001	1.5	1.4-1.7	<0.001	1.8	1.5-2.1	<0.001
Type of treatment									
Surgery with nCRT/CT	1.0			1.0			1.0		
Surgery alone	1.6	1.3-1.9	<0.001	1.7	1.4-2.0	<0.001	1.3	0.8-2.1	0.222
Definitive chemoradiation	1.7	1.4-2.0	<0.001	1.9	1.5-2.3	<0.001	1.4	0.9-2.0	0.123
Other/no treatment	4.1	3.5-4.8	<0.001	4.3	3.6-5.1	<0.001	3.8	2.7-5.4	<0.001
Histology									
Squamous cell	1.1	1.0-1.2	0.037	n.a.			n.a.		
Adenocarcinoma	1.0								

* Adjusted for all variables listed in table 2. GOJ: Gastro-oesophageal junction. NOS: Not otherwise specified. HR=Hazard ratio. CI=confidence interval. n.a.= non-applicable.

Discussion

This large nationwide population-based study among elderly patients with potentially curable oesophageal cancer who were 75 years or older revealed an increase in treatment with a curative intent, with a consistent use of surgical treatment and a significant increase in the use of dCRT among all elderly patients in the period 2003-2013. The increase in administration of dCRT was most prominent in elderly patients with a squamous cell carcinoma. Furthermore, multivariable analysis showed no difference in overall survival for elderly patients with a squamous cell carcinoma who received surgery with nCRT/CT or surgery alone or dCRT. However, elderly patients with an adenocarcinoma who underwent surgery with nCRT/CT had a significantly better overall survival compared to patients who underwent surgery alone or dCRT.

Despite the increase in the use of treatment with curative intent among potentially curable elderly patients, explained by the increase in dCRT, there is still a large proportion of patients that were not treated with curative intent (72.4%).This study demonstrates that the elderly patients with potentially curable tumours received less often surgical treatment compared to younger patients (17.7% vs. 67.0%), whereas the use of dCRT was slightly higher in the elderly patients compared to the younger patients (19.5% vs. 17.2%). These findings may be explained by the fact that an older age is a risk factor for post-operative morbidity and mortality after oesophagectomy.[12,18-20] Although, other studies have shown that age alone should not be regarded as a predictor for worse overall survival after oesophagectomy, in daily practice it appears that advanced age is a significant factor in decision making whether or not patients are proposed for surgery.[12,13]

Our study revealed a relatively stable use of surgical treatment and a significant increase in use of dCRT among all elderly patients during the study period especially after 2010. This striking increase in administration of dCRT is higher compared to another study in the Netherlands in an earlier period (1989-2008) in which they reported an increase from 0.2% to 2.2%.[21] The increase in use of dCRT is probably caused by the increasing awareness that dCRT has a favourable survival, especially among patients with squamous cell carcinoma, and is often well tolerated, even in patients with considerable co-morbidity.[7,8] Although toxicity after chemoradiation is occurring frequently, with 75% of the patients experiencing toxicity of grade 3 or greater, especially in the elderly patients, it is often manageable.[22,23]

This study showed that elderly patients with an adenocarcinoma received more often surgical treatment compared to patients with a squamous cell carcinoma which received more often dCRT especially after 2010. These result are in line with result from a large population based study in the United States.[9] The observed difference in treatment could be explained by the fact that most studies show a better response to dCRT of squamous cell carcinomas when compared to adenocarcinoma, with a better overall survival and disease free survival in good responders.[10] On the other hand, a study from the United Kingdom on dCRT revealed a comparable overall survival and disease free survival between both histological subtypes. However patients with squamous cell carcinoma had significantly more advanced stages of disease.[24] Furthermore, a significant difference in relapse pattern has been described, with adenocarcinomas being more likely to relapse in distant sites and squamous cell carcinoma more likely to recur locally.[8,24]

The multivariable Cox survival analysis revealed that elderly patients with an adenocarcinoma who received surgery with nCRT/CT have a better overall survival compared to the patients receiving surgery alone or dCRT. However, among elderly patient with squamous cell carcinomas there was no significant difference in overall survival between patients who underwent surgery with nCRT/CT, surgery alone or patients who received dCRT. Currently, there are only three randomised control trials which have directly compared dCRT with surgical treatment in patients with squamous cell carcinoma. These trials have shown comparable survival rates in patients treated with definitive chemoradiation or chemoradiation followed by surgery.[11,25,26] However, in two of the three trials elderly patients were excluded and in the third trial results were not reported for elderly patients as a separate group. Furthermore, a recent Cochrane review states that there is only low quality evidence in the literature which showed that chemoradiation appears to be equivalent to surgery in squamous cell carcinoma who are responsive to chemoradiation, however in adenocarcinoma there is uncertainty whether or not patients receiving definitive chemoradiation benefit compared to surgery.[27] Our results provide more arguments for the equivalence of definitive chemoradiation to surgery in squamous cell carcinoma and confirm their statement on adenocarcinoma. The results of our study advocate for further research in which the use of dCRT and surgery are compared for disease free survival and quality of life.

Univariable and multivariable survival analysis also revealed a similar overall survival for patients with oesophageal squamous cell carcinoma who underwent surgery with or without nCRT/CT. Although there seems to be immortal time bias, the Kaplan-Meier curves for these treatment groups were parallel, assuming overall survival is comparable (Figure 3b). Immortal time bias exists of patients receiving nCRT/CT which takes more time to receive than surgery alone. However, no landmark analysis was performed as this would result in exclusion of many patients in the 'other/no treatment' group. Multivariable analysis confirmed the non-significant difference in overall survival between squamous cell carcinoma patients with and without nCRT/CT. These results are in contrast with results from the CROSS trial[28,29], which showed an improved survival for patients who received surgery with nCRT compared to patients who received surgery alone. Moreover, the difference in overall survival was higher for squamous cell carcinoma compared to adenocarcinoma. However, most elderly patients did not meet the eligibility criteria from the CROSS trial. Therefore, further research should investigate the difference in outcomes between surgery with or without nCRT/CT among elderly patients with oesophageal squamous cell carcinoma.

A limitation of this study is that the NCR did not register nationwide information on comorbidity or performance status during the study period. This might have influenced the survival analyses since comorbidity and performance status play an important role in the clinical decision making, especially among the elderly patients and has a significant influence on overall survival. However, the survival benefit for dCRT might even be more than observed, because especially unfit patients with multiple comorbidities and an a priori unfavourable prognosis receive dCRT. Thus, the lack of comorbidity data might even lead to an underestimation of the potential favourable impact of dCRT on overall survival. This study has also several strengths, such as its observational nature resulting in a representative nationwide population and therefore enabling the demonstration of current patterns of care and its impact on overall survival among elderly patients with oesophageal cancer in daily clinical practice.

In conclusion, this large nationwide population-based study revealed that there was a consistent use of surgical treatment and a major increase in use of dCRT among all elderly patients with potentially curable oesophageal cancer in the period 2003 to 2013. The increase in dCRT was most prominent among patients with squamous cell carcinoma. Survival was comparable among elderly patients with squamous cell carcinoma who underwent surgery with nCRT/CT, surgery alone or received dCRT, while elderly patients with an adenocarcinoma who underwent surgery with nCRT/CT had a better overall survival, when compared with surgery alone or dCRT. Therefore, dCRT can be considered as a reasonable alternative for surgery among potentially curable elderly patients with oesophageal squamous cell carcinoma. However in elderly patients with oesophageal adenocarcinoma surgery with nCRT/CT is still preferable regarding overall survival.

References

1. Pohl H, Sirovich B, Welch HG. Esophageal adenocarcinoma incidence: are we reaching the peak?, 2010. Cancer Epidemiol Biomarkers Prev;19:1468-1470.
2. Pennathur A, Gibson MK, Jobe BA, Luketich JD. Oesophageal carcinoma, 2013. Lancet;381:400-412.
3. Holmes RS, Vaughan TL. Epidemiology and pathogenesis of esophageal cancer, 2007. Semin Radiat Oncol;17:2-9.
4. Kocher HM, Linklater K, Patel S, Ellul JP. Epidemiological study of oesophageal and gastric cancer in south-east England, 2001. Br J Surg;88:1249-1257.
5. Cijfers over kanker., Netherlands Cancer Registry. www.cijfersoverkanker.nl. Accessed on: 1-7-2017.
6. National clinical practice guideline oesophageal cancer. www.oncoline.nl. Assessed on: 1-7-2017.
7. Crosby TD, Brewster AE, Borley A, Perschky L, Kehagioglou P, Court J, Maughan TS. Definitive chemoradiation in patients with inoperable oesophageal carcinoma, 2004. Br J Cancer;90:70-75.
8. Gwynne S, Hurt C, Evans M, Holden C, Vout L, Crosby T. Definitive chemoradiation for oesophageal cancer--a standard of care in patients with non-metastatic oesophageal cancer, 2011. Clin Oncol (R Coll Radiol);23:182-188.
9. Merkow RP, Bilimoria KY, McCarter MD, Chow WB, Gordon HS, Stewart AK, Ko CY, Bentrem DJ. Effect of histologic subtype on treatment and outcomes for esophageal cancer in the United States, 2012. Cancer;118:3268-3276.
10. Smit JK, Muijs CT, Burgerhof JG, Paardekooper G, Timmer PR, Muller K, Woutersen D, Mul VE, Beukema JC, Hospers GA, van Dijk BA, Langendijk JA, Plukker JT. Survival after definitive (chemo)radiotherapy in esophageal cancer patients: a population-based study in the north-East Netherlands, 2013. Ann Surg Oncol;20:1985-1992.
11. Stahl M, Stuschke M, Lehmann N, Meyer HJ, Walz MK, Seeber S, Klump B, Budach W, Teichmann R, Schmitt M, Schmitt G, Franke C, Wilke H. Chemoradiation with and without surgery in patients with locally advanced squamous cell carcinoma of the esophagus, 2005. J Clin Oncol;23:2310-2317.
12. Elsayed H, Whittle I, McShane J, Howes N, Hartley M, Shackcloth M, Page R. The influence of age on mortality and survival in patients undergoing oesophagogastrectomies. A seven-year experience in a tertiary centre, 2010. Interact Cardiovasc Thorac Surg;11:65-69.
13. Pultrum BB, Bosch DJ, Nijsten MW, Rodgers MG, Groen H, Slaets JP, Plukker JT. Extended esophagectomy in elderly patients with esophageal cancer: minor effect of age alone in determining the postoperative course and survival, 2010. Ann Surg Oncol;17:1572-1580.
14. van Gestel YR, Lemmens VE, de Hingh IH, Steevens J, Rutten HJ, Nieuwenhuijzen GA, van Dam RM, Siersema PD. Influence of comorbidity and age on 1-, 2-, and 3-month postoperative mortality rates in gastrointestinal cancer patients, 2013. Ann Surg Oncol;20:371-380.
15. Fritz A, Percy C, Jack A, S et al.: International Classification of Diseases for Oncology, third edition. Geneva: World Health Organisation; 2000.
16. Sobin LH, Wittekind C. TNM classification of malignant tumours, 2002, 6th ed.: Wiley-Liss.
17. Sobin LH, Gospodarowicz MK, Wittekind C. TNM classification of malignant tumours, 2009, 7th ed.: Wiley-Blackwell.
18. Koppert LB, Lemmens VE, Coebergh JW, Steyerberg EW, Wijnhoven BP, Tilanus HW, Janssen-Heijnen ML. Impact of age and co-morbidity on surgical resection rate and survival in patients with oesophageal and gastric cancer, 2012. Br J Surg;99:1693-1700.
19. Miyata H, Yamasaki M, Makino T, Miyazaki Y, Takahashi T, Kurokawa Y, Nakajima K, Takiguchi S, Mori M, Doki Y. Clinical Outcome of Esophagectomy in Elderly Patients With and Without Neoadjuvant Therapy for Thoracic Esophageal Cancer, 2015. Ann Surg Oncol;22 Suppl 3:S794-801.
20. Cijs TM, Verhoef C, Steyerberg EW, Koppert LB, Tran TC, Wijnhoven BP, Tilanus HW, de Jonge J. Outcome of esophagectomy for cancer in elderly patients, 2010. Ann Thorac Surg;90:900-907.

21. Faiz Z, Lemmens VE, Siersema PD, Nieuwenhuijzen GA, Wouters MW, Rozema T, Coebergh JW, Wijnhoven BP. Increased resection rates and survival among patients aged 75 years and older with esophageal cancer: a Dutch nationwide population-based study, 2012. World J Surg;36:2872-2878.

22. Mak RH, Mamon HJ, Ryan DP, Miyamoto DT, Ancukiewicz M, Kobayashi WK, Willett CG, Choi NC, Blaszkowsky LS, Hong TS. Toxicity and outcomes after chemoradiation for esophageal cancer in patients age 75 or older, 2010. Dis Esophagus;23:316-323.

23. Tepper J, Krasna MJ, Niedzwiecki D, Hollis D, Reed CE, Goldberg R, Kiel K, Willett C, Sugarbaker D, Mayer R. Phase III trial of trimodality therapy with cisplatin, fluorouracil, radiotherapy, and surgery compared with surgery alone for esophageal cancer: CALGB 9781, 2008. J Clin Oncol;26:1086-1092.

24. Reid TD, Davies IL, Mason J, Roberts SA, Crosby TD, Lewis WG. Stage for stage comparison of recurrence patterns after definitive chemoradiotherapy or surgery for oesophageal carcinoma, 2012. Clin Oncol (R Coll Radiol);24:617-624.

25. Bedenne L, Michel P, Bouche O, Milan C, Mariette C, Conroy T, Pezet D, Roullet B, Seitz JF, Herr JP, Paillot B, Arveux P, Bonnetain F, Binquet C. Chemoradiation followed by surgery compared with chemoradiation alone in squamous cancer of the esophagus: FFCD 9102, 2007. J Clin Oncol;25:1160-1168.

26. Chiu PW, Chan AC, Leung SF, Leong HT, Kwong KH, Li MK, Au-Yeung AC, Chung SC, Ng EK. Multicenter prospective randomized trial comparing standard esophagectomy with chemoradiotherapy for treatment of squamous esophageal cancer: early results from the Chinese University Research Group for Esophageal Cancer (CURE), 2005. J Gastrointest Surg;9:794-802.

27. Best LM, Mughal M, Gurusamy KS. Non-surgical versus surgical treatment for oesophageal cancer, 2016. Cochrane Database Syst Rev;3:CD011498.

28. Shapiro J, van Lanschot JJ, Hulshof MC, van Hagen P, van Berge Henegouwen MI, Wijnhoven BP, van Laarhoven HW, Nieuwenhuijzen GA, Hospers GA, Bonenkamp JJ, Cuesta MA, Blaisse RJ, Busch OR, Ten Kate FJ, Creemers GJ, Punt CJ, Plukker JT, Verheul HM, Bilgen EJ, van Dekken H, van der Sangen MJ, Rozema T, Biermann K, Beukema JC, Piet AH, van Rij CM, Reinders JG, Tilanus HW, Steyerberg EW, van der Gaast A, group Cs. Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): long-term results of a randomised controlled trial, 2015. Lancet Oncol;16:1090-1098.

29. van Hagen P, Hulshof MC, van Lanschot JJ, Steyerberg EW, van Berge Henegouwen MI, Wijnhoven BP, Richel DJ, Nieuwenhuijzen GA, Hospers GA, Bonenkamp JJ, Cuesta MA, Blaisse RJ, Busch OR, ten Kate FJ, Creemers GJ, Punt CJ, Plukker JT, Verheul HM, Spillenaar Bilgen EJ, van Dekken H, van der Sangen MJ, Rozema T, Biermann K, Beukema JC, Piet AH, van Rij CM, Reinders JG, Tilanus HW, van der Gaast A. Preoperative chemoradiotherapy for esophageal or junctional cancer, 2012. N Engl J Med;366:2074-2084.

Chapter 10

Effect of age on rates of palliative surgery and chemotherapy use in patients with locally advanced or metastatic gastric cancer

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Abstract

Background

This study assessed trends in the treatment and survival of palliatively treated patients with gastric cancer, with a focus on age-related differences.

Methods

For this retrospective, population-based, nationwide cohort study, all patients diagnosed between 1989 and 2013 with non-cardia gastric cancer with metastasised disease or invasion into adjacent structures were selected from the Netherlands Cancer Registry. Trends in treatment and 2-year overall survival were analysed and compared between younger (age less than 70 years) and older (aged 70 years or more) patients. Analyses were done for five consecutive periods of 5 years, from 1989–1993 to 2009–2013. Multivariable logistic regression analysis was used to examine the probability of undergoing surgery. Multivariable Cox regression analysis was used to identify independent risk factors for death.

Results

Palliative resection rates decreased significantly in both younger and older patients, from 24.5 and 26.2 per cent to 3.0 and 5.0 per cent respectively. Compared with patients who received chemotherapy alone, both younger (21.6 versus 6.3 per cent respectively; $P < 0.001$) and older (14.7 versus 4.6 per cent; $P < 0.001$) patients who underwent surgery had better 2-year overall survival rates. Multivariable analysis demonstrated that younger and older patients who received chemotherapy alone had worse overall survival than patients who had surgery only (younger: hazard ratio (HR) 1.22, 95 per cent c.i. 1.12 to 1.33; older: HR 1.12, 1.01 to 1.24). After 2003 there was no association between period of diagnosis and overall survival in younger or older patients.

Conclusion

Despite changes in the use of resection and chemotherapy as palliative treatment, overall survival rates of patients with advanced and metastatic gastric cancer did not improve.

Introduction

Gastric cancer incidence rates are declining in the western world, including the Netherlands.[1] Survival rates of patients with gastric cancer have remained dismal through the years, despite developments in treatment.[1] One important reason for the generally poor prognosis is that a considerable proportion of patients (45 per cent) are diagnosed with metastatic disease (stage IV).[1,2] With a median overall survival of less than 4 months for patients with stage IV gastric cancer, their survival rate is amongst the lowest in gastrointestinal oncology.[3,4]

The preferred treatment approach for patients with stage IV or locally advanced gastric cancer is debated worldwide. In particular, the effect of palliative gastrectomy on survival and quality of life remains unclear.[5–7] This is particularly relevant as postoperative mortality rates in gastric cancer are amongst the highest of all gastrointestinal cancers.[8] In addition, the effect of palliative chemotherapy on survival and quality of life is debated.[4]

According to the national clinical practice guideline for treatment of gastric cancer[9], palliative gastrectomy can be performed to improve quality of life and/or survival. This guideline[9] and some previous studies[5,6] suggest that palliative resection should be performed only in patients aged less than 70 years. Although surgical morbidity and mortality are indeed higher in older patients with gastric cancer, palliative resection is suggested to have an equally positive effect on survival in both younger and older patients.[10–13]

The aim of the present study was to investigate trends and the incidence of palliative treatment among younger and older patients in a nationwide setting, and assess which patient, tumour and treatment characteristics are related to the likelihood of having a palliative resection. The study also investigated the survival of younger and older patients according to the type of treatment.

Methods

Data source

Data were obtained from the population-based Netherlands Cancer Registry (NCR). This registry serves the total Dutch population of almost 17 million. The NCR is based on notification of all newly diagnosed malignancies in the Netherlands by the national automated pathological archive (PALGA). Additional sources are the national registry of hospital discharge and radiotherapy institutions. Information on diagnosis, staging and treatment is extracted routinely from the medical records by specially trained data managers of the NCR. The information on vital status is obtained by annual linkage with the municipal administrative databases, which register all deceased and emigrated persons in the Netherlands. The study period was from January 1989 to December 2013.

Ethical approval

According to the Netherlands Central Committee on Research involving Human Subjects, this type of study does not require approval from an ethics committee in the Netherlands. This study was approved by the Privacy Review Board of the NCR. All procedures followed were in accordance with the Helsinki Declaration of 1964 and later versions.[14]

Patient selection criteria

The reporting of this study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[15] For this retrospective, population-based, nationwide cohort study, patients with non-cardia gastric cancer who received palliative treatment for clinically distant metastases or a tumour infiltrating surrounding organs were selected. Topography and morphology of the disease were coded according to ICD-O-3.[16]

Tumour location and stage

The distribution of the location in the stomach was considered as follows: proximal/middle (fundus, corpus and lesser and greater curvature: C16.1, C16.2, C16.5 and C16.6), pylorus and antrum (C16.3, C16.4), and overlapping or not otherwise specified (C16.8, C16.9).

Tumour staging was performed according to the fourth, fifth, sixth or seventh edition of the UICC TNM classification, as was valid at the time of diagnosis. An important change was made in the seventh UICC TNM classification. Before TNM-7 (which was implemented in the NCR in 2010) malignancies infiltrating surrounding organs were categorised as cT4, and since TNM-7 tumours infiltrating surrounding organs have been categorised as cT4B. cT4A in TNM-7 corresponds to tumours that perforate the gastric serosa, which were previously coded as cT3. Therefore, the present study included all cT4 tumours before 2010 and only cT4B tumours after 2010.

Hospital type

The three types of hospital in which diagnosis was made were academic, teaching and non-teaching hospitals. A hospital was considered a teaching hospital if it offered (part of) a surgical residency programme.

Age groups

Patients were analysed according to age (less than 70 years versus 70 years or above), in accordance with the guidelines proposed by the European Society of Medical Oncology and the Dutch clinical guideline.[8,9]

Statistical analysis

All analyses were conducted using SPSS® version 23 (IBM, Armonk, New York, USA). Analyses were performed for five consecutive periods of 5 years, from 1989–1993 to 2009–2013. To investigate trends over time in the proportion of patients treated with palliative intent, ratios of palliative patients for sequential time periods were calculated for all patients, and for both younger and older patients.

Descriptive statistics were used to characterise patients younger or older than 70 years, and compared using χ^2 test. Bar graphs were used to assess differences in treatment modalities throughout the years for the two groups of patients, and compared with the χ^2 test. Postoperative 30-day mortality rates were available in the NCR from 2005, and were calculated and compared using the χ^2 test. Univariable and multivariable logistic regression analyses were performed for younger and older patients to examine the influence of different clinicopathological factors associated with the receipt of palliative surgery. Results of these analyses were reported as odds ratios (ORs) with 95 per cent confidence intervals.

Survival time was defined as time from diagnosis to death, or until 1 January 2015 for patients who were still alive. Kaplan–Meier curves were generated and compared by log-rank testing to examine overall survival in younger and older patients according to treatment.
Multivariable Cox regression analyses were performed to investigate the prognostic impact of palliative treatment options on overall survival in both groups of patients after adjustment for patient, tumour and treatment characteristics. Results of survival analyses using Cox regression were reported as hazard ratios (HRs) with 95 per cent confidence intervals. $P <$ 0.050 was considered statistically significant.

Results

A total of 38 004 patients were diagnosed with non-cardia gastric cancer, of whom 15 011 were included in the study as they had clinically distant metastasis or a tumour infiltrating surrounding organs, and therefore were considered to have been treated with palliative intent (Figure 1; Appendix 1). The mean (s.d.) age was 58.2 (9.5) years for younger patients and 77.8(5.4) years for older patients. Median duration of follow-up was 4.4 (interquartile range 1.8–9.5) and 2.9 (1.2–6.6) months for younger and older patients respectively. The percentage of patients treated with palliative intent increased significantly over the years for both age groups ($P <$ 0.001) (Figure 1).

Some 8108 patients (51 per cent) were aged at least 70 years, and 6903 (49 per cent) patients were less than 70 years of age. The two groups were comparable (Table 1), except for more younger patients presenting with signet-ring cell carcinomas (23.1 versus 13.2 per cent; $P <$ 0.001). Younger patients were significantly more often treated with chemotherapy compared with older patients (28.0 versus 7.9 per cent respectively; $P < 0.001$). Older patients more often received supportive care alone (no surgery or chemotherapy) than younger patients (73.9 versus 52.5 per cent respectively; $P < 0.001$). Surgery alone was performed in 16.0 per cent of the younger patients and among 17.5 per cent of older patients ($P = 0.018$).

During the study interval, the proportion of patients undergoing palliative surgery decreased significantly in both younger and older patients, from 24.5 per cent in 1989–1993 to 3.0 per cent in 2009–2013 ($P < 0.001$), and from 26.2 per cent to 5.0 per cent, respectively ($P < 0.001$). Postoperative 30-day mortality rates in 2005–2008 and 2009–2013 were 12.1 and 11.3 per cent respectively ($P = 0.781$) (7.5 and 8.0 per cent for younger patients (P = 0.896) and 16.6 and 15.2 per cent for older patients ($P = 0.129$), respectively).

There was a significant increase in the proportion of patients treated with chemotherapy alone over the study interval (Figure 2). In 1989 –1993, 15.0 and 2.1 per cent of younger and older patients respectively received chemotherapy alone, compared with 51.3 and 20.8 per cent respectively in 2009–2013 ($P < 0.001$).

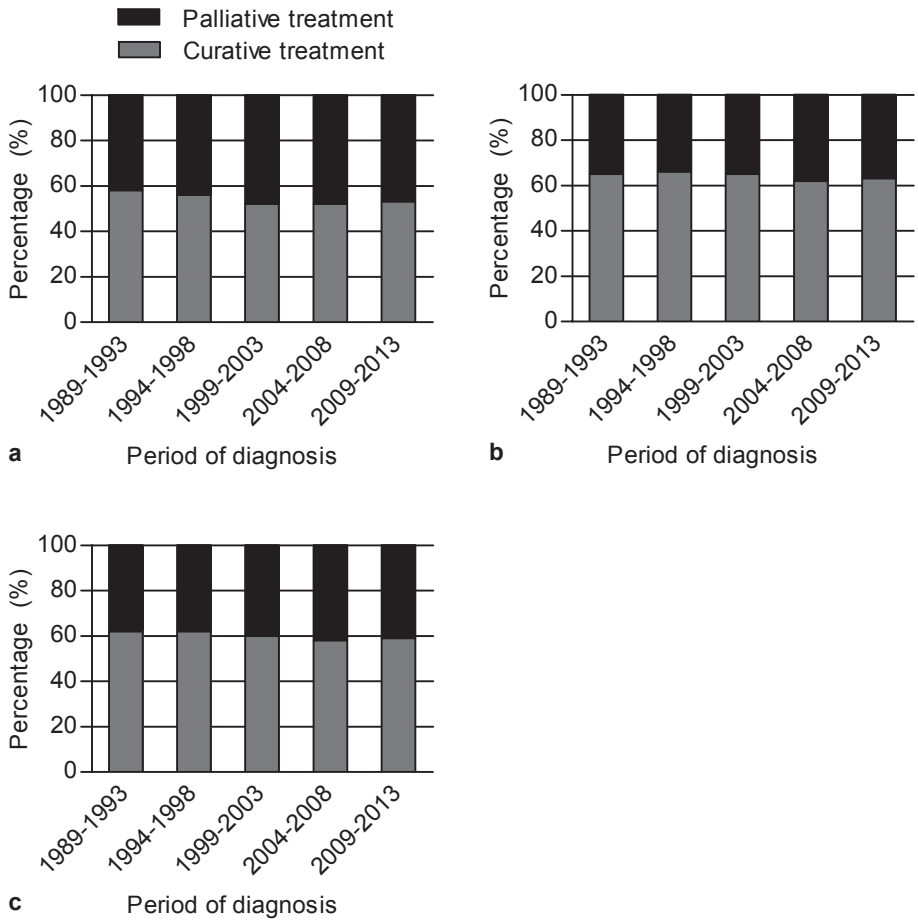

Figure 1 Proportions of a younger (aged less than 70 years), b older (aged 70 years or more) and c all patients, with non-cardia gastric cancer having a palliative disease (cT4(b) or cM1) according to period of diagnosis.

Probability of surgery

Multivariable logistic regression analyses showed that both younger and older patients with a more recent diagnosis had a significantly lower likelihood of having surgery: OR 0.42 (95 per cent c.i. 0.33 to 0.54) and 0.22 (0.17 to 0.28) respectively. Among younger patients, sex, period of diagnosis, tumour morphology, tumour differentiation, tumour location, cTNM status, chemotherapy, radiotherapy and type of diagnosing hospital were associated with a higher probability of undergoing surgery. In contrast, in older patients sex, tumour morphology and type of diagnosing hospital did not influence the probability of having surgery, but age did (Table 2).

Table 1 Characteristics of younger and older patients diagnosed between 1989 and 2013 who received palliative treatment (cM1 and cT4(b)).

	Younger patients (age < 70 years) n = 6903	Older patients (age ≥ 70 years) n = 8108
Sex ratio (M : F)	4347 : 2556	4832 : 3276
Period of diagnosis		
1989–1993	1589 (23.0)	1929 (23.8)
1994–1998	1400 (20.3)	1669 (20.6)
1999–2003	1393 (20.2)	1528 (18.8)
2004–2008	1268 (18.4)	1526 (18.8)
2009–2013	1253 (18.2)	1456 (18.0)
cT status		
0–3	926 (13.4)	1021 (12.6)
4	2515 (36.4)	2905 (35.8)
Unknown	3462 (50.2)	4182 (51.6)
cN status		
N0	703 (10.2)	897 (11.1)
N+	2757 (39.9)	2761 (34.1)
Unknown	3443 (49.9)	4450 (54.9)
cM status		
M0	973 (14.1)	1232 (15.2)
M1	5602 (81.2)	6452 (79.6)
Unknown	328 (4.8)	424 (5.2)
Tumour location		
Proximal and middle	1972 (28.6)	2139 (26.4)
Pyloric and antrum	1693 (24.5)	2444 (30.1)
Overlapping or unspecified	3238 (46.9)	3525 (43.5)
Tumour differentiation		
Well	111 (1.6)	148 (1.8)
Moderate	936 (13.6)	1495 (18.4)
Poor/undifferentiated	3524 (51.1)	3768 (46.5)
Unknown	2332 (33.8)	2697 (33.3)
Tumour morphology		
Adenocarcinoma	4274 (61.9)	6130 (75.6)
Non-adenocarcinoma	405 (5.9)	421 (5.2)
Linitis plastica	632 (9.2)	489 (6.0)
Signet-ring cell carcinoma	1592 (23.1)	1068 (13.2)
Hospital type		
Academic	571 (8.3)	460 (5.7)
Teaching	4067 (58.9)	4778 (58.9)
Non-teaching	2256 (32.7)	2867 (35.4)
Unknown	9 (0.1)	3 (0.0)

Table 1 continues on the next page

Treatment		
No resection or CT	3627 (52.5)	5995 (73.9)
Chemotherapy	1935 (28.0)	640 (7.9)
Resection	1106 (16.0)	1415 (17.5)
Resection + CT	235 (3.4)	58 (0.7)

Values in parentheses are percentages. CT= chemotherapy.

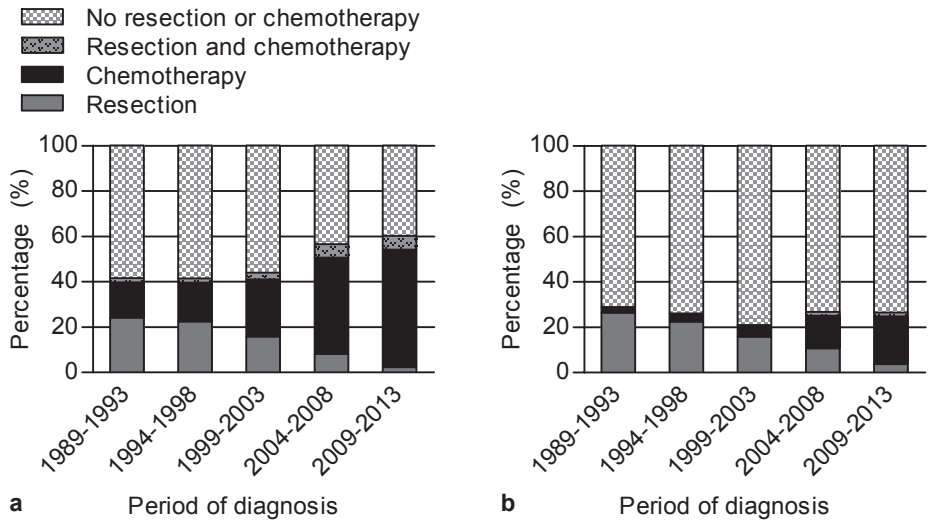

Figure 2 Treatment modality according to period of diagnosis for a younger (aged less than 70 years) and b older (aged 70 years or more) patients with non-cardia gastric cancer who received palliative treatment.

Table 2 Multivariable logistic regression analysis of factors related to the likelihood of having palliative surgery.

	Younger patients (age < 70 years) n = 6903		Older patients (age ≥ 70 years) n = 8108	
	Odds ratio	*P* value	Odds ratio	*P* value
Age	0.99 (0.99, 1.00)	0.066	0.97 (0.90, 0.98)	< 0.001
Sex				
M	1.00 (reference)		1.00 (reference)	
F	1.21 (1.05, 1.40)	0.007	1.13 (0.99, 1.29)	0.068
Period of diagnosis				
1989–1993	1.00 (reference)		1.00 (reference)	
1994–1998	0.94 (0.78, 1.14)	0.538	0.78 (0.65, 0.92)	0.004
1999–2003	0.66 (0.55, 0.81)	< 0.001	0.57 (0.47, 0.69)	< 0.001
2004–2008	0.58 (0.47, 0.73)	< 0.001	0.40 (0.33, 0.50)	< 0.001
2009–2013	0.42 (0.33, 0.54)	< 0.001	0.22 (0.17, 0.28)	< 0.001
Tumour morphology				
Adenocarcinoma	1.00 (reference)		1.00 (reference)	
Non-adenocarcinoma	0.93 (0.67, 1.29)	0.662	0.83 (0.59, 1.18)	0.303
Linitis plastica	1.51 (1.15, 1.98)	0.003	1.16 (0.85, 1.59)	0.343
Signet ring cell carcinoma	1.52 (1.28, 1.80)	< 0.001	1.12 (0.93, 1.36)	0.237
Tumour differentiation				
Well	1.37 (0.87, 2.16)	0.176	0.99 (0.65, 1.49)	0.946
Moderate	1.24 (1.02, 1.49)	0.029	0.89 (0.76, 1.05)	0.157
Poor/undifferentiated	1.00 (reference)		1.00 (reference)	
Unknown	0.37 (0.31, 0.44)	< 0.001	0.23 (0.19, 0.28)	< 0.001
Tumour location				
Proximal and middle	1.00 (reference)		1.00 (reference)	
Pylorus and antrum	1.49 (1.26, 1.77)	< 0.001	2.10 (1.78, 2.47)	< 0.001
Overlapping/unspecified	0.59 (0.50, 0.70)	< 0.001	0.89 (0.75, 1.05)	0.177
cT status				
0–3	1.62 (1.24, 2.11)	< 0.001	1.77 (1.37, 2.28)	< 0.001
4	1.00 (reference)		1.00 (reference)	
Unknown	1.32 (1.08, 1.62)	0.008	1.16 (0.95, 1.42)	0.152
cN status				
N0	1.46 (1.18, 1.81)	0.001	1.52 (1.24, 1.86)	< 0.001
N+	1.00 (reference)		1.00 (reference)	
Unknown	0.56 (0.48, 0.65)	< 0.001	0.44 (0.39, 0.51)	< 0.001
cM status				
M0	6.58 (5.24, 8.25)	< 0.001	4.91 (3.95, 6.10)	< 0.001
M1	1.00 (reference)		1.00 (reference)	
Unknown	2.91 (2.13, 3.98)	< 0.001	1.89 (1.40, 2.56)	< 0.001
Chemotherapy				
No	1.00 (reference)		1.00 (reference)	
Yes	0.48 (0.41, 0.57)	< 0.001	0.58 (0.43, 0.79)	< 0.001

Table 2 continues on the next page

Radiotherapy				
No	1.00 (reference)		1.00 (reference)	
Yes	0.53 (0.32, 0.89)	0.017	0.18 (0.08, 0.39)	< 0.001
Hospital type				
Academic	0.96 (0.74, 1.23)	0.736	1.07 (0.81, 1.41)	0.650
Teaching	1.00 (reference)		1.00 (reference)	
Non-Teaching	0.86 (0.74, 1.00)	0.045	1.08 (0.95, 1.24)	0.256
Unknown	1.59 (0.17, 14.40)	0.681	4.27 (0.25, 71.80)	0.313

Values in parentheses are 95 per cent confidence intervals.

Survival

Survival analyses showed that both younger and older patients who underwent surgery had better 2-year overall survival than those who received chemotherapy alone (younger group: 21.6 versus 6.3 per cent respectively, $P < 0.001$; older group: 14.7 versus 4.6 per cent, $P < 0.001$) (Figure 3). Overall survival at 2 years was lowest among patients who received only supportive care. Patients who had both surgery and chemotherapy had the most favourable survival.

Multivariable Cox regression analyses confirmed that younger and older patients who did not have chemotherapy or surgery had a worse overall survival than patients who had surgery alone (HR 2.77, 95 per cent c.i. 2.57 to 2.98, and 2.29, 2.15 to 2.45, respectively). Younger and older patients treated with chemotherapy had a worse overall survival than those treated with surgery (HR 1.22, 95 per cent c.i.1.12 to 1.33, and 1.12, 1.01 to 1.24). Survival was best among patients who received both chemotherapy and surgery versus surgery only (younger group: HR 0.76, 95 per cent 0.66 to 0.88; older group: HR 0.74, 0.57 to 0.97) (Table 3). Period of diagnosis was not associated with survival in older patients. Among younger patients, survival was better in 1994–1998 than in 1989–1993 (HR 0.92, 95 per cent c.i. 0.85 to 0.98). For all other periods there was no statistically significant difference in survival (Table 3). A subgroup analysis, in which multivariable Cox regression analysis was performed in younger patients who did not receive surgery, found no significant survival difference over the years, whereas the same analysis in younger patients who did have surgery showed a significant survival improvement in 2009–2013 compared with 1989–1993 (HR 0.71, 95 per cent 0.54 to 0.93) (Appendix 2). The same subgroup analysis in older patients treated with palliative intent who did or did not receive surgery showed no significant differences in survival over time.

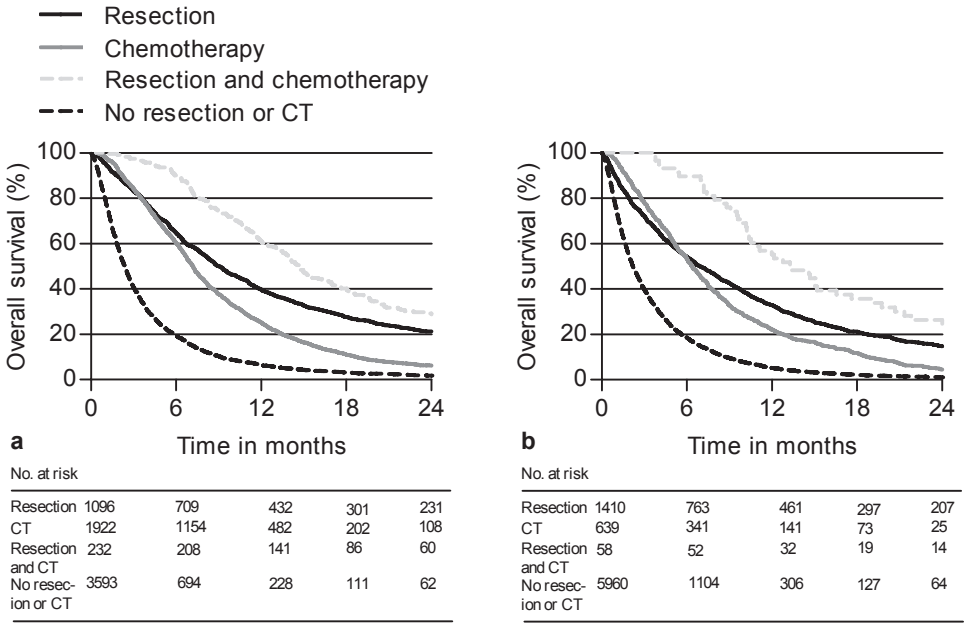

Figure 3 Kaplan–Meier 2-year survival curves according to treatment method in a younger (aged less than 70 years) and b older (aged 70 years or more) patients with non-cardia gastric cancer who received palliative treatment

Table 3 Multivariable Cox regression analysis of factors related to overall survival.

	Younger patients (age < 70 years) n = 6903		Older patients (age ≥ 70 years) n = 8108	
	Hazard ratio	*P* value	Hazard ratio	*P* value
Age	1.00 (1.00, 1.01)	0.036	1.01 (1.01, 1.02)	< 0.001
Sex				
M	1.00 (reference)		1.00 (reference)	
F	0.89 (0.84, 0.93)	< 0.001	0.91 (0.87, 0.95)	< 0.001
Period of diagnosis				
1989–1993	1.00 (reference)		1.00 (reference)	
1994–1998	0.92 (0.85, 0.98)	0.018	1.05 (0.98, 1.12)	0.173
1999–2003	0.93 (0.86, 1.00)	0.054	0.98 (0.92, 1.05)	0.632
2004–2008	0.99 (0.91, 1.07)	0.756	0.96 (0.89, 1.03)	0.224
2009–2013	1.03 (0.95, 1.12)	0.459	1.00 (0.93, 1.08)	0.981
Tumour location				
Proximal and middle	1.00 (reference)		1.00 (reference)	
Pylorus and antrum	1.01 (0.95, 1.08)	0.683	1.05 (0.99, 1.12)	0.084
Overlapping/unspecified	1.11 (1.05, 1.18)	< 0.001	1.14 (1.08, 1.21)	< 0.001

Table 3 continues on the next page

Tumour morphology				
Adenocarcinoma	1.00 (reference)		1.00 (reference)	
Non-adenocarcinoma	1.05 (0.94, 1.16)	0.384	1.33 (1.21, 1.47)	< 0.001
Linitis plastica	1.03 (0.94, 1.13)	0.483	1.07 (0.97. 1.17)	0.205
Signet-ring cell carcinoma	1.02 (0.96, 1.08)	0.551	1.04 (0.97, 1.11)	0.291
Tumour differentiation				
Well	0.76 (0.62, 0.92)	0.004	0.88 (0.74, 1.04)	0.130
Moderate	0.90 (0.84, 0.97)	0.008	0.82 (0.78, 0.88)	< 0.001
Poor/undifferentiated	1.00 (reference)		1.00 (reference)	
Unknown	0.98 (0.93, 1.04)	0.563	0.89 (0.85, 0.94)	< 0.001
cT status				
0–3	0.93 (0.85, 1.02)	0.105	0.96 (0.88, 1.04)	0.336
4	1.00 (reference)		1.00 (reference)	
Unknown	1.11 (1.04, 1.19)	0.002	1.11 (1.04, 1.18)	0.001
cN status				
N0	0.91 (0.83, 0.99)	0.023	0.81 (0.75, 0.88)	< 0.001
N+	1.00 (reference)		1.00 (reference)	
Unknown	1.09 (1.04, 1.15)	0.001	1.13 (1.08, 1.19)	< 0.001
cM status				
M0	0.64 (0.59, 0.70)	< 0.001	0.65 (0.60, 0.70)	< 0.001
M1	1.00 (reference)		1.00 (reference)	
Unknown	0.84 (0.74, 0.95)	0.006	0.89 (0.79, 0.99)	0.036
Hospital type				
Academic	1.06 (0.97, 1.16)	0.202	0.97 (0.88, 1.07)	0.537
Teaching	1.00 (reference)		1.00 (reference)	
Non-teaching	1.07 (1.02, 1.13)	0.011	1.04 (0.99, 1.09)	0.117
Unknown	0.93 (0.48, 1.80)	0.830	0.57 (0.18, 1.77)	0.328
Treatment				
Resection	1.00 (reference)		1.00 (reference)	
Chemotherapy	1.22 (1.12, 1.33)	< 0.001	1.12 (1.01, 1.24)	0.030
Resection + CT	0.76 (0.66, 0.88)	< 0.001	0.74 (0.57, 0.97)	0.027
No resection or CT	2.77 (2.57, 2.98)	< 0.001	2.29 (2.15, 2.45)	< 0.001

Values in parentheses are 95 per cent confidence intervals. CT= chemotherapy.

Discussion

In this population-based nationwide study, 45.2 per cent of younger patients and 35.7 per cent of older patients presented with locally advanced or metastasised gastric cancer at diagnosis. During the study interval, the proportion undergoing palliative surgery reduced significantly. However, both younger and older patients who underwent gastrectomy had a significantly better survival compared with patients treated with chemotherapy or supportive care alone.

An increased incidence of stage IV disease and decreased resection rates have been shown for other gastrointestinal cancers in the Netherlands.[17–19] This decrease in palliative resection suggests a better selection of patients as a result of improved diagnostic accuracy

and preoperative staging, and the availability of systemic treatment options.[18] The latter was also demonstrated in the present study, by a significant increase in use of chemotherapy, especially from 2005 onwards. In addition, the Dutch clinical guideline[9] on treatment of gastric cancer, implemented in 2009, advises that palliative gastrectomy should be performed only in patients under 70 years of age, who have no more than one item of incurability – either distant metastasis (M1 disease) or tumour infiltrating the surrounding organs (cT4 disease). This could also have led to a decrease in palliative gastrectomy. Finally, better understanding of postoperative morbidity and mortality in patients with stage IV gastric cancer may have led physicians to refrain from a surgical approach.[5,6] In the present study, especially in older patients, 30-day postoperative mortality rates were high, despite a substantial improvement in postoperative mortality compared with that in previous Dutch studies.[5,6] A Dutch study[5] of palliative gastrectomy reported a 30-day postoperative mortality rate of 20 per cent in 1989–1993, considerably higher than the 15.2 per cent found in the present study.

Despite increased use of chemotherapy, survival of all patients receiving palliative care for gastric cancer did not improve after adjustment for clinicopathological factors. However, in multivariable analysis overall survival increased between 2010 and 2013 for younger patients treated with gastrectomy, which may be due to centralisation of gastric cancer surgery as of 2012 in the Netherlands. An additional explanation may be better selection of younger patients with cancer, who are relatively fit for palliative surgery. The present study also showed that younger patients diagnosed in teaching hospitals had a significantly better overall survival than those diagnosed in non-teaching hospitals.

Previous studies from Germany[20,21] have suggested that tumour resection should be part of palliative therapy in gastric cancer, with prolongation of median survival up to 5 months, and acceptable perioperative morbidity and mortality rates of 47.7 and 11.6 per cent respectively. Other studies have shown a positive effect of palliative gastrectomy on overall survival in smaller groups and in a meta-analysis.[22] In line with this, the present study showed that survival of patients who had a palliative resection was higher than that in those receiving chemotherapy alone. The 2-year survival rate was 21.6 and 14.7 per cent in younger and older patients who underwent palliative surgery, compared with 6.3 and 4.6 per cent in patients who received chemotherapy alone . A positive effect of palliative resection on survival has been reported for various malignancies, although there has been no explanation as to why palliative resection is associated with improved overall survival.[23–28]

There are studies that have suggested a more positive or equal effect on survival compared with palliative surgery in patients with gastric cancer treated with palliative chemotherapy.[7,29,30] Recently an RCT comparing palliative gastrectomy and chemotherapy with chemotherapy alone (REGATTA trial)[29] showed no benefit for palliative gastrectomy. However, this trial involved an Asian population and, because of well known differences between Asian and European patients with gastric cancer, this finding should be treated with care.[31–33] Furthermore, the REGATTA trial included only patients with liver, peritoneal or para-aortic lymph node metastases, and thus the effect of palliative surgery on survival of patients with gastric cancer and a locally advanced (T4b) tumour remains unclear. The difference in survival between patients treated with chemotherapy alone and those who had surgery and chemotherapy in the present study is, however, noteworthy, and not in line with the findings of the REGATTA trial. An European

RCT evaluating the effect of palliative gastrectomy versus palliative chemotherapy on overall survival is thus needed.

The present study has some limitations. This was a retrospective cohort study in which there is a likelihood of selection bias. The survival difference between various treatment groups may be caused by selecting fitter patients for palliative gastrectomy. The absence of information on clinical symptoms, comorbidity, hospital resection volume, ASA fitness grade and therapeutic complication rates is another limitation. These data have only recently been included entirely in the NCR, and could therefore not be included in the present study. Furthermore, information regarding adherence to multidisciplinary team meetings, intention of treatment and therapeutic plans was not available. There was also a relatively large proportion of unknown characteristics (for instance cTNM status, tumour location and differentiation). This was because in the earlier periods clinical staging was not always available and a high proportion of patients did not undergo surgery. Finally, no adjustment was made for immortal time bias – the period during follow-up in which death cannot occur. For example, in the present study, patients who had been treated with chemotherapy and resection could not die within the first few weeks after diagnosis as otherwise they would not have been able to receive these treatments. However, taking immortal time bias into account would have meant excluding patients who had died in the initial months after diagnosis - mainly those treated with neither chemotherapy nor with resection. As these patients generally have the worst prognosis, skewness would have been created in the study population.

References

1. Dikken JL, Lemmens VE, Wouters MW, Wijnhoven BP, Siersema PD, Nieuwenhuijzen GA, van Sandick JW, Cats A, Verheij M, Coebergh JW, van de Velde CJ. Increased incidence and survival for oesophageal cancer but not for gastric cardia cancer in the Netherlands, 2012. Eur J Cancer;48:1624-1632.
2. Dassen AE, Dikken JL, Bosscha K, Wouters MW, Cats A, van de Velde CJ, Coebergh JW, Lemmens VE. Gastric cancer: decreasing incidence but stable survival in the Netherlands, 2014. Acta Oncol;53:138-142.
3. Nashimoto A, Akazawa K, Isobe Y, Miyashiro I, Katai H, Kodera Y, Tsujitani S, Seto Y, Furukawa H, Oda I, Ono H, Tanabe S, Kaminishi M. Gastric cancer treated in 2002 in Japan: 2009 annual report of the JGCA nationwide registry, 2013. Gastric Cancer;16:1-27.
4. Bernards N, Creemers GJ, Nieuwenhuijzen GA, Bosscha K, Pruijt JF, Lemmens VE. No improvement in median survival for patients with metastatic gastric cancer despite increased use of chemotherapy, 2013. Ann Oncol;24:3056-3060.
5. Hartgrink HH, Putter H, Klein Kranenbarg E, Bonenkamp JJ, van de Velde CJ. Value of palliative resection in gastric cancer, 2002. Br J Surg;89:1438-1443.
6. Bonenkamp JJ SM, Hermans J, Van de Velde CJ. Tumor load and surgical palliation in gastric cancer, 2001. Hepatogastroenterology;48.
7. Ouchi K, Sugawara T, Ono H, Fujiya T, Kamiyama Y, Kakugawa Y, Mikuni J, Yamanami H. Therapeutic significance of palliative operations for gastric cancer for survival and quality of life, 1998. J Surg Oncol;69:41-44.
8. van Gestel YR, Lemmens VE, de Hingh IH, Steevens J, Rutten HJ, Nieuwenhuijzen GA, van Dam RM, Siersema PD. Influence of comorbidity and age on 1-, 2-, and 3-month postoperative mortality rates in gastrointestinal cancer patients, 2013. Ann Surg Oncol;20:371-380.
9. Oncoline. Cancer Clinical Practice Guidelines: Gastric carcinoma, 2009. www.oncoline.nl, accessed 1 November 2016
10. Dassen AE, Dikken JL, van de Velde CJ, Wouters MW, Bosscha K, Lemmens VE. Changes in treatment patterns and their influence on long-term survival in patients with stages I-III gastric cancer in The Netherlands, 2013. Int J Cancer;133:1859-1866.
11. Coniglio A, Tiberio GA, Busti M, Gaverini G, Baiocchi L, Piardi T, Ronconi M, Giulini SM. Surgical treatment for gastric carcinoma in the elderly, 2004. J Surg Oncol;88:201-205.
12. Huang KH, Wu CW, Fang WL, Chen JH, Lo SS, Wang RF, Li AF. Palliative resection in noncurative gastric cancer patients, 2010. World J Surg;34:1015-1021.
13. Takeno A, Takiguchi S, Fujita J, Tamura S, Imamura H, Fujitani K, Matsuyama J, Mori M, Doki Y. Clinical outcome and indications for palliative gastrojejunostomy in unresectable advanced gastric cancer: multi-institutional retrospective analysis, 2013. Ann Surg Oncol;20:3527-3533.
14. Rickham PP. Human Experimentation. Code of Ethics of the World Medical Association. Declaration of Helsinki, 1964. Br Med J;2:177.
15. von Elm, Altman DG, Egger M, Pocock SJ, Gotzsche PC, vandenbroucke JP; STROBE Initiative. The strengthening the Reporting of Observational Studies in Epidemiology (STROBE) stagement: guidelines for reporting observational studies, 2007. Lancet; 370:1453-1457.
16. Fritz AG. International classification of diseases for oncology: ICD-O 2000. 3rd ed;Geneva: World Health Organization.
17. van der Geest LG, Lam-Boer J, Koopman M, Verhoef C, Elferink MA, de Wilt JH. Nationwide trends in incidence, treatment and survival of colorectal cancer patients with synchronous metastases, 2015. Clin Exp Metastasis;32:457-465.
18. Speelman AD, van Gestel YR, Rutten HJ, de Hingh IH, Lemmens VE. Changes in gastrointestinal cancer resection rates, 2015. Br J Surg;102:1114-1122.
19. t Lam-Boer J, Van der Geest LG, Verhoef C, Elferink ME, Koopman M, de Wilt JH. Palliative resection of the primary tumor is associated with improved overall survival in incurable stage IV colorectal cancer: A nationwide population-based propensity-score adjusted study in the Netherlands, 2016. Int J Cancer;139:2082-2094.

20. Gastinger I, Windisch J, Meyer F, Ptok H, Steinert R, Otto R, Bruns C, Lippert H. [Palliative treatment of advanced gastric cancer from surgical point of view], 2015. Chirurg;86:570-576.

21. Gastinger I, Ebeling U, Meyer L, Meyer F, Schmidt U, Wolff S, Ptok H, Lippert H. [Advanced gastric cancer. Are there still indications for palliative surgical interventions?], 2012. Chirurg;83:472-479.

22. Sun J, Song Y, Wang Z, Chen X, Gao P, Xu Y, Zhou B, Xu H. Clinical significance of palliative gastrectomy on the survival of patients with incurable advanced gastric cancer: a systematic review and meta-analysis, 2013. BMC Cancer;13:577.

23. Tarantino I, Warschkow R, Worni M, Cerny T, Ulrich A, Schmied BM, Guller U. Prognostic Relevance of Palliative Primary Tumor Removal in 37,793 Metastatic Colorectal Cancer Patients: A Population-Based, Propensity Score-Adjusted Trend Analysis, 2015. Ann Surg;262:112-120.

24. Heng DY, Wells JC, Rini BI, Beuselinck B, Lee JL, Knox JJ, Bjarnason GA, Pal SK, Kollmannsberger CK, Yuasa T, Srinivas S, Donskov F, Bamias A, Wood LA, Ernst DS, Agarwal N, Vaishampayan UN, Rha SY, Kim JJ, Choueiri TK. Cytoreductive nephrectomy in patients with synchronous metastases from renal cell carcinoma: results from the International Metastatic Renal Cell Carcinoma Database Consortium, 2014. Eur Urol;66:704-710.

25. Flanigan RC, Salmon SE, Blumenstein BA, Bearman SI, Roy V, McGrath PC, Caton JR, Jr., Munshi N, Crawford ED. Nephrectomy followed by interferon alfa-2b compared with interferon alfa-2b alone for metastatic renal-cell cancer, 2001. N Engl J Med;345:1655-1659.

26. Ruiterkamp J, Voogd AC, Bosscha K, Tjan-Heijnen VC, Ernst MF. Impact of breast surgery on survival in patients with distant metastases at initial presentation: a systematic review of the literature, 2010. Breast Cancer Res Treat;120:9-16.

27. de Mestier L, Manceau G, Neuzillet C, Bachet JB, Spano JP, Kianmanesh R, Vaillant JC, Bouche O, Hannoun L, Karoui M. Primary tumor resection in colorectal cancer with unresectable synchronous metastases: A review, 2014. World J Gastrointest Oncol;6:156-169.

28. Lam-Boer J, Van der Geest LG, Verhoef C, Elferink ME, Koopman M, de Wilt JH. Palliative resection of the primary tumor is associated with improved overall survival in incurable stage IV colorectal cancer: A nationwide population-based propensity-score adjusted study in The Netherlands, 2016. Int J Cancer.

29. Fujitani K, Yang HK, Mizusawa J, Kim YW, Terashima M, Han SU, Iwasaki Y, Hyung WJ, Takagane A, Park do J, Yoshikawa T, Hahn S, Nakamura K, Park CH, Kurokawa Y, Bang YJ, Park BJ, Sasako M, Tsujinaka T, investigators Rs. Gastrectomy plus chemotherapy versus chemotherapy alone for advanced gastric cancer with a single non-curable factor (REGATTA): a phase 3, randomised controlled trial, 2016. Lancet Oncol;17:309-318.

30. Izuishi K, Mori H. Recent Strategies for Treating Stage IV Gastric Cancer: Roles of Palliative Gastrectomy, Chemotherapy, and Radiotherapy, 2016. J Gastrointestin Liver Dis;25:87-94.

31. Thrumurthy SG, Chaudry MA, Chau I, Allum W. Does surgery have a role in managing incurable gastric cancer?, 2015. Nat Rev Clin Oncol;12:676-682.

32. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012, 2015. CA Cancer J Clin;65:87-108.

33. Bonenkamp JJ, Songun I, Hermans J, Sasako M, Welvaart K, Plukker JT, van Elk P, Obertop H, Gouma DJ, Taat CW, et al. Randomised comparison of morbidity after D1 and D2 dissection for gastric cancer in 996 Dutch patients, 1995. Lancet;345:745-748.

Appendix 1 Proportions of patients with non-cardia gastric cancer having a palliative disease (cT4(b) or cM1) according to age group and period of diagnosis.

	Younger patients (age < 70 years)			Older patients (≥ 70 years)			Total		
	All	Pall.	Percent	All	Pall.	Percent	All	Pall.	Percent
Period of diagnosis									
1989-1993	3825	1589	42%	5482	1929	35%	9307	3518	38%
1994-1998	3209	1400	44%	4881	1669	34%	8090	3069	38%
1999-2003	2916	1393	48%	4425	1528	35%	7341	2921	40%
2004-2008	2657	1268	48%	4038	1526	38%	6695	2794	42%
2009-2013	2676	1253	47%	3895	1456	37%	6571	2709	41%
Total	15283	6903	45%	22721	8108	36%	38004	15011	39%

Appendix 2 Cox regression analysis of the influence of different clinicopathological factors on survival of younger and older patients who underwent palliative surgical resection.

	Younger patients (age < 70 years) n=1341		Older patients (≥ 70 years) n=1473	
	Hazard ratio	*P* value	Hazard ratio	*P* value
Period of diagnosis				
1989-1993	1.00 (reference)		1.00 (reference)	
1994-1998	0.81 (0.07, 0.94)	0.006	0.97 (0.85, 1.12)	0.710
1999-2003	0.81 (0.69, 0.95)	0.010	0.90 (0.77, 1.05)	0.193
2004-2008	0.81 (0.67, 0.97)	0.026	0.92 (0.78, 1.10)	0.353
2009-2013	0.71 (0.54, 0.93)	0.013	0.86 (0.67, 1.11)	0.245

Values in parentheses are 95 per cent confidence intervals.

* Adjusted for age, sex, tumor location, tumor morphology, tumor grade, cTNM-stage and type of diagnosing hospital.

Chapter 11

Long-term survival improvement in oesophageal cancer in the Netherlands

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Abstract

Background
Treatment for oesophageal cancer has evolved due to developments including the centralisation of surgery and introduction of neoadjuvant treatment. Therefore, this study evaluated trends in stage distribution, treatment and survival of oesophageal cancer patients in the last 26 years in the Netherlands.

Patients and methods
Patients with oesophageal cancer diagnosed in the period 1989-2014 were selected from the Netherlands Cancer Registry. Patients were divided into two groups: non-metastatic (M0) and metastatic (M1). Trends in stage distribution, treatment and relative survival rates were evaluated according to histology.

Results
Among all 35,760 patients the percentage of an unknown tumour stage decreased from 34% to 10% during the study period, while the percentage of patients with metastatic disease increased from 21% to 34%. Among surgically treated patients 32% underwent a resection in a high-volume hospital in 2005 which increased to 92% in 2014. Use of neoadjuvant chemoradiotherapy increased in non-metastatic oesophageal adenocarcinoma (OAC) and squamous cell carcinoma (OSCC) patients from respectively 4% and 2% in 2000-2004 to 43% and 26% in 2010-2014. Five-year relative survival increased from 8% to 22% for all patients; from 12% to 36% for non-metastatic OAC and from 9% to 27% for non-metastatic OSCC over 26 years. Median overall survival of metastatic patients improved from 18 to 22 weeks.

Conclusion
In the Netherlands, survival for oesophageal cancer patients improved significantly, especially in the period 2005-2014 which might be the result of better treatment related to the centralisation of surgery and introduction of neoadjuvant chemoradiotherapy.

Introduction

Oesophageal cancer is the sixth leading cause of cancer-related mortality and eight most common cancer worldwide.[1,2] It affects 456,000 people worldwide annually and the incidence is increasing rapidly.[1] There are two major histological types, oesophageal adenocarcinoma (OAC) and oesophageal squamous cell carcinoma (OSCC) each with a distinct aetiology and specific risk factors.[3] Although OSCC accounts for approximately 90% of all cases of oesophageal cancer worldwide, OAC has become the predominant type of oesophageal cancer in Europe and Northern America during the past decades.[1,4]

Treatment of oesophageal cancer has been subjected to paradigm shifts in the last two decades. Long term results from the CROSS trial confirmed the clinical value of multimodality treatment for oesophageal cancer with a 5-year overall survival difference of 14% in favour of patients who underwent neoadjuvant chemoradiotherapy followed by surgery compared to surgery alone.[5,6] Furthermore, endoscopic treatment was introduced for treatment of early stage tumours and definitive chemoradiotherapy is increasingly considered as a well-tolerated alternative for surgery in inoperable patients and especially in squamous cell oesophageal cancer.[7-10] Besides these major changes in treatment, improved diagnostic procedures facilitated a better patient selection.[11-14]

Oesophageal cancer surgery has been increasingly centralised in the Netherlands. As of 2006, surgical treatment for oesophageal cancer was centralised in hospitals performing a minimum of 10 resections per year and since 2011 a minimum of 20. Concentration of oesophageal cancer surgery has been shown to be associated with improved long-term overall survival for surgically and non-surgically treated patients.[15, 16] As treatment for oesophageal cancer has evolved over the last few decades due to several developments such as centralisation of surgery and new treatment approaches, the aim of this study was to evaluate trends in treatment and survival of patients with oesophageal cancer in the Netherlands.

Methods

Netherlands Cancer Registry

Data were obtained from the Netherlands Cancer Registry (NCR). This registry serves the total Dutch population of 16.9 million inhabitants. The NCR is based on the inclusion of all newly diagnosed malignancies in the Netherlands by the national automated pathological archive (PALGA). Additional sources are the national registry of hospital discharge and radiotherapy institutions. Specially trained data managers of the NCR routinely extract information on diagnosis, tumour stage and treatment from the medical records. Information on vital status is obtained through annual linkage with the Municipal Administrative Database, in which all deceased and emigrated persons in the Netherlands are registered.

Patients with oesophageal cancer (C15.0-C15.9) diagnosed in the period 1989-2014 were selected. Topography and morphology were coded according to the International Classification of Diseases for Oncology (ICD-O).[17] ICD-O morphology codes were used to classify tumours as adenocarcinoma, squamous cell carcinoma and other or unknown histology. Subsite distribution was divided as: cervical (C15.0), proximal 1/3 (C15.3), middle 1/3 (C15.4), distal 1/3 (C15.5) and overlapping or not otherwise specified (C15.8, C15.9).

Tumour staging was performed according to the Union for International Cancer Control (UICC) TNM classification that was valid at the time of diagnosis. As tumour stage classification was comparable from TNM-4 to -6, but changed with the introduction of TNM-7, all patients were recoded (stage I to IV and unknown) according to TNM-6 in this study. Furthermore, M1a tumours according to TNM-5 and 6 were categorised as N+ as most patients with a M1a tumour had a distal tumour with coeliac lymph nodes which can be considered N+ according to TNM-7. Pathologic tumour stage was assessed for stage distribution, or if not available, clinical tumour stage was noted. Patients with a cM1 or pM1 stage were classified as metastatic and all other patients as non-metastatic.

Treatment

For non-metastatic patients, neoadjuvant chemoradiotherapy was defined as chemoradiotherapy followed by surgery. Definitive chemoradiotherapy was defined as chemoradiotherapy without a surgical resection as the intention of chemoradiotherapy was not registered during the study period. An endoscopic resection was defined as a local tumour excision, endoscopic mucosal resection or an endoscopic submucosal dissection.

For metastatic patients, a distinction was made between chemoradiotherapy, systemic treatment or radiotherapy as single modality. Systemic treatment included chemotherapy and targeted therapy. Symptom-related treatment was classified as no treatment. All other treatments were grouped as 'other' therapy and were described below figure 3 and 4.

Statistical analysis

Differences in characteristics between patients were described according to period of diagnosis. Incidence and mortality rates were calculated as the number of new patients per 100,000 inhabitants per year, and age-standardized to European Standardised Rates (ESR). Survival time was defined as time from diagnosis to death or until February 1st 2017 for patients who were still alive. The median overall survival was estimated by using the Kaplan Meier method for metastatic patients. Relative survival was estimated by using life tables of the general population to correct for age- and gender specific background mortality. The Ederer II method with age standardisation to the most recent time period was used to compare relative survival between time periods.[18, 19] STATA version 14.1 was used for the survival analyses and all other analyses were conducted using SAS version 9.4. *P* values of <0.05 were considered statistically significant.

Results

Between January 1989 and December 2014, 35,760 patients were diagnosed with oesophageal cancer in the Netherlands. Age-standardised incidence rates increased from 5 per 100,000 inhabitants in 1989 to 9 in 2014, while mortality rates increased to a lesser extent from 5 to 7 (Figure 1). The incidence of OAC increased especially in males, from 3 per 100,000 inhabitants in 1989 to 10 in 2014. Corresponding to the increase of OAC, the number of patients with a distal tumour increased. The median age was 69 (interquartile range 60-77) in 1989-1994 and remained similar over time (Table 1).

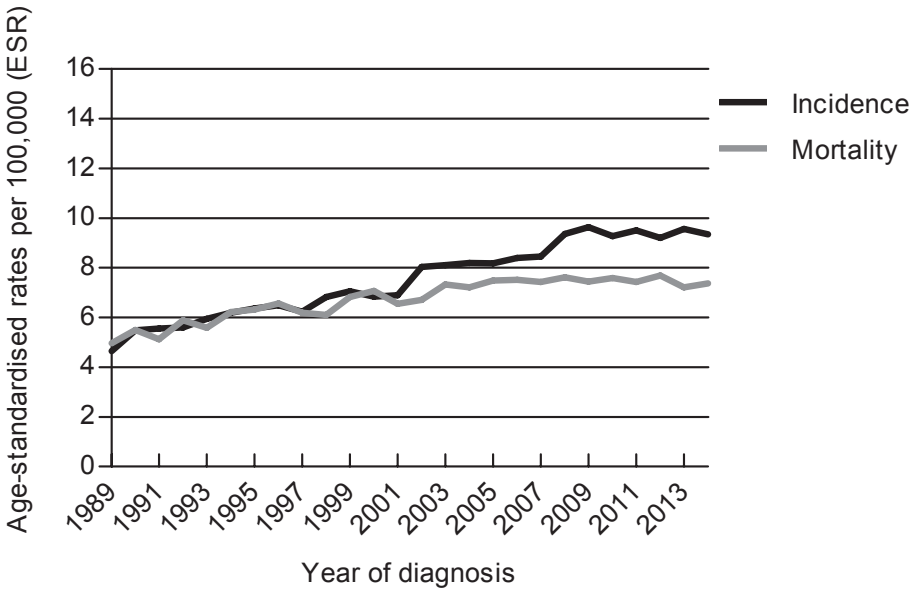


Figure 1 Incidence and mortality of oesophageal cancer in the Netherlands, 1989-2014.

Table 1 Characteristics of patients with oesophageal cancer in the Netherlands 1989-2014 (n=35 670).

	1989-1994		1995-1999		2000-2004		2005-2009		2010-2014	
	n	%	n	%	n	%	n	%	n	%
All patients	4999	100%	5299	100%	6722	100%	8554	100%	10096	100%
Gender										
Male	3312	66%	3633	69%	4790	71%	6256	73%	7484	74%
Female	1687	34%	1666	31%	1932	29%	2298	27%	2612	26%
Age (median yrs., IQR)	69	60-77	68	59-77	68	58-77	68	60-76	68	61-76
Age (yrs.)										
< 60	1233	25%	1386	26%	1860	28%	2115	25%	2171	22%
60-74	2201	44%	2296	43%	2783	41%	3804	44%	4941	49%
≥ 75	1565	31%	1617	31%	2079	31%	2635	31%	2984	30%
Tumour location										
Cervical	135	3%	138	3%	154	2%	125	1%	92	<1%
Upper thoracic	338	7%	353	7%	396	6%	447	5%	559	6%
Mid-thoracic	1147	23%	1189	22%	1241	18%	1382	16%	1512	15%
Lower thoracic	2769	55%	3146	59%	4443	66%	6043	71%	7243	72%
Overlapping, unknown	610	12%	473	9%	488	7%	557	7%	690	7%
Morphology										
Squamous cell carcinoma	2614	52%	2358	44%	2479	37%	2750	32%	3101	31%
Adenocarcinoma	2097	42%	2593	49%	3837	57%	5377	63%	6696	66%
Other/unknown	288	6%	348	7%	406	6%	427	5%	299	3%

IQR=interquartile range

The proportion of patients with an unknown tumour stage decreased from 34% to 10% in 1989-1994 and 2010-2014, with a corresponding decrease in the proportion of patients with a metastatic disease from 21% to 34% (Figure 2). Furthermore, the percentage of patients with a stage 0 tumour (pathologic or if not available clinical stage T0,N0,M0 or T0,NX,M0) increased from 0% in 2000-2004 to 6% in 2010-2014.

Trends in treatment

Among all patients, resection rates remained relatively stable with approximately 25% between 1989-2004 and 29% between 2010-2014. Among non-metastatic OAC the use of neoadjuvant chemoradiotherapy and surgery increased significantly from 4% in 2000-2004 to 43% in 2010-2014 and from 2% to 26% for non-metastatic OSCC (Figure 3a and 3b). During the same period the use of definitive chemoradiotherapy increased as well from 8% in 2000-2004 to 31% in 2010-2014 for non-metastatic OSCC, while this increase was less prominent for non-metastatic OAC (3% to 14%). The use of endoscopic resection hardly increased for non-metastatic OSCC but increased for non-metastatic OAC from 2% in 2000-2004 to 10% in 2010-2014. Furthermore, in 2005 32% of all resected patients underwent a resection in a high-volume hospital (performing ≥20 procedures per year) which increased to 92% in 2014 (Appendix 1).

The proportion of patients with metastatic OAC who received systemic treatment as a single modality increased from 11% in 1989-1994 to 28% in 2010-2014 and the use of chemoradiotherapy increased from 1% to 15% in these time periods (Figure 4a). In contrast, the increase in chemoradiotherapy was more prominent among patients with metastatic OSCC (3% in 1989-1994 and 21% in 2010-2014), while the use of chemotherapy remained stable (approximately 11%); Figure 4b).

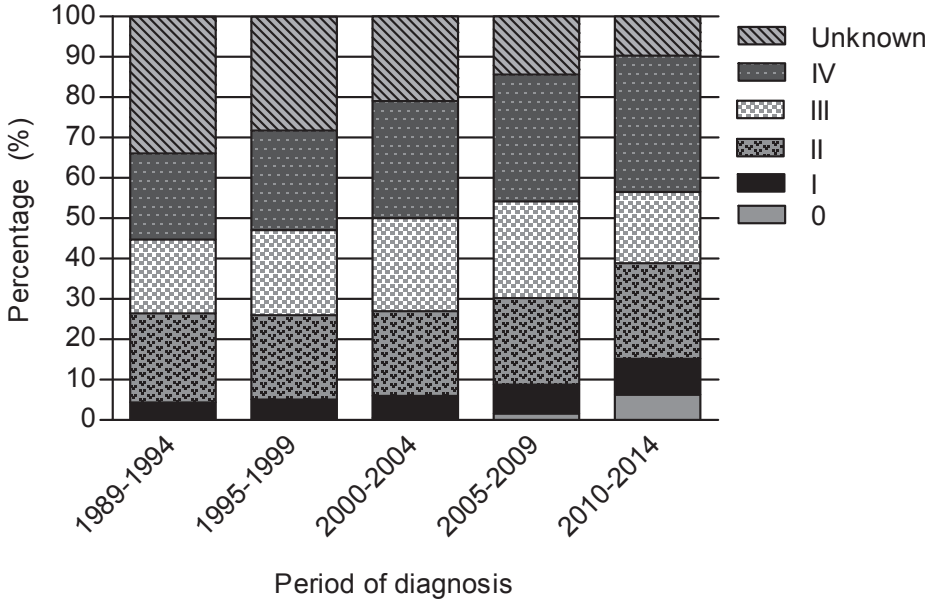


Figure 2 Stage distribution of all patients with oesophageal cancer according to period of diagnosis (n=35 670). Pathological tumour stage was assessed, or if not available, clinical tumour stage was noted.

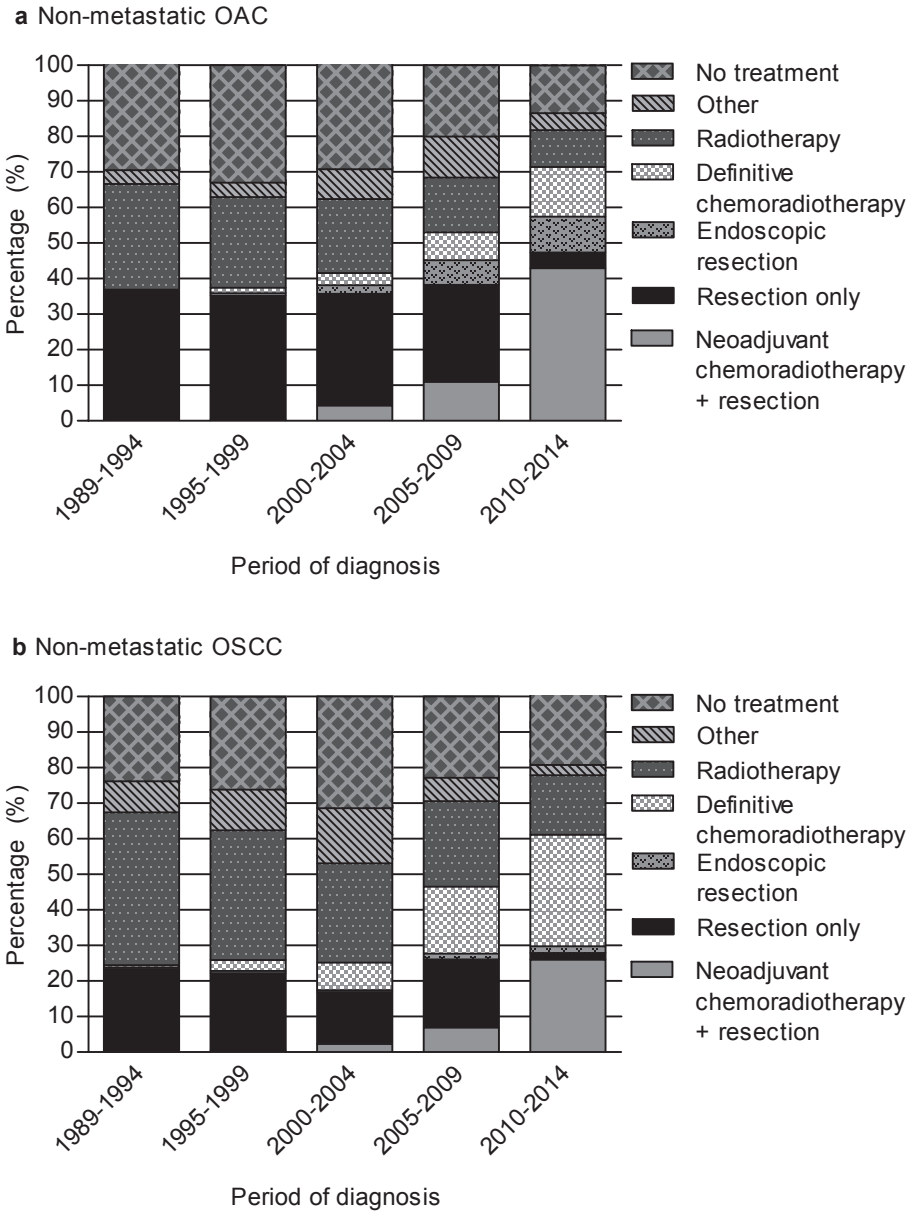


Figure 3 Treatment of patients with non-metastatic (M0) oesophageal cancer in the Netherlands, according to histology and period of diagnosis,1989-2014 (a; n=13 854, b; n=10 125).
OAC= oesophageal adenocarcinoma OSCC= oesophageal squamous cell carcinoma.
Other treatment mainly included: systemic treatment as a single modality, and chemotherapy combined with surgery.

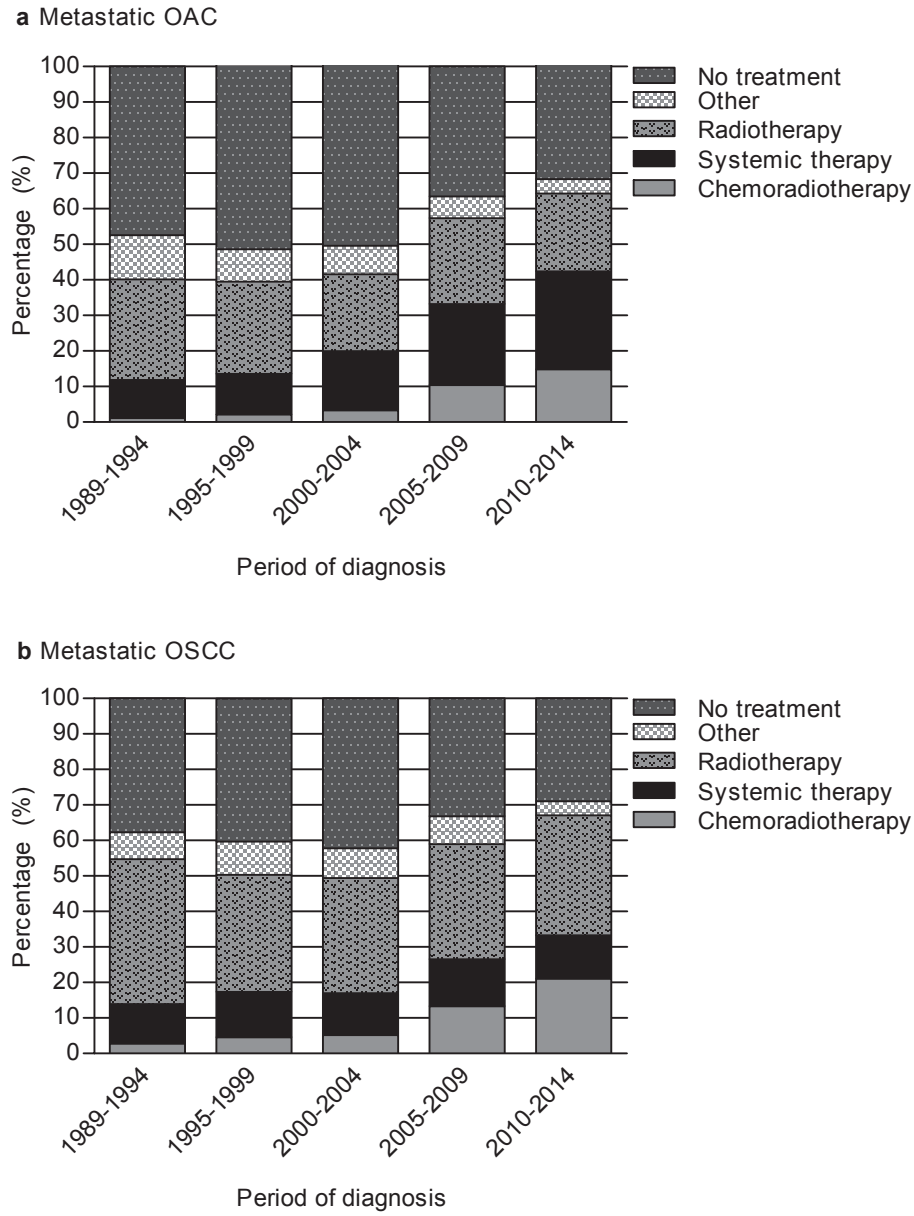


Figure 4 Treatment of patients with metastatic (M1) oesophageal cancer in the Netherlands, according to histology and period of diagnosis,1989-2014 (a; n=6746, b; n=3177).
OAC= oesophageal adenocarcinoma OSCC= oesophageal squamous cell carcinoma.
Other treatment mainly included: radiotherapy for metastases, metastasectomy and surgery alone, the latter especially in the earlier periods.

Survival

The 5-year relative survival for all patients with oesophageal cancer increased from 8% to 22% in 1989-2014 (Figure 5; Table 2a). The largest increases were observed in the last two periods. During these periods survival improved by 7% and 9% compared to the period before. Five-year relative survival tripled for both patients with non-metastatic OAC and OSCC, from 12% to 36% and 9% to 27% in 1989-1994 and 2010-2014, respectively (Figure 6a and 6b and Table 2b).

One-year relative survival for all patients with metastatic oesophageal cancer increased from 15% to 22% in 1989-2014 (Table 2c). The one-year relative survival increased with 3% in 2000-2004 for patients with metastatic OSCC and with 5% in 2005-2009 for metastatic OAC. After these periods relative survival remained stable (Figure 6c and 6d and Table 2c). Median overall survival for all metastatic patients increased with 4 weeks from 18 weeks in 1989-1994 to 22 weeks in 2010-2014.

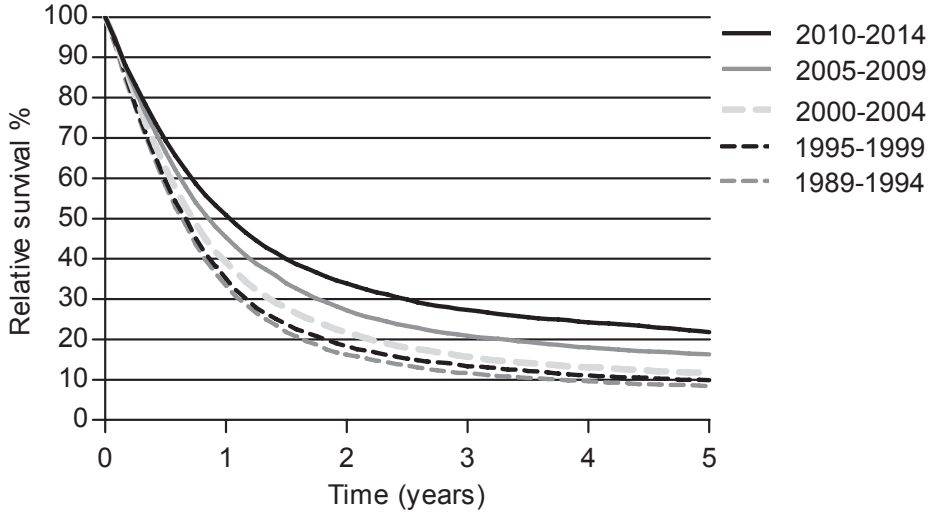


Figure 5 Relative survival of all patients with oesophageal cancer (n=35 670).

Table 2a Five-year relative survival for all patients with oesophageal carcinoma.

	All oesophageal cancer n=35 670		All OAC n=20 600		All OSCC n=13 302	
	Point estimate (%)	SE	Point estimate (%)	SE	Point estimate (%)	SE
Period of diagnosis						
1989-1994	8	0.4	9	0.7	8	0.6
1995-1999	10	0.5	11	0.7	10	0.7
2000-2004	12	0.4	13	0.6	11	0.7
2005-2009	16	0.4	18	0.6	15	0.7
2010-2014	22	0.5	23	0.6	20	0.9

SE= standard error.
OAC= oesophageal adenocarcinoma OSCC= oesophageal squamous cell carcinoma.

Table 2b Five-year relative survival for patients with non-metastatic (M0) oesophageal carcinoma.

	M0 oesophageal cancer n=25 214		M0 OAC n=13 854		M0 OSCC n=10 125	
	Point estimate (%)	SE	Point estimate (%)	SE	Point estimate (%)	SE
Period of diagnosis						
1989-1994	10	0.5	12	0.9	9	0.7
1995-1999	13	0.6	15	1.0	12	0.9
2000-2004	16	0.6	18	0.8	14	0.9
2005-2009	23	0.6	27	0.8	19	1.0
2010-2014	32	0.7	36	0.9	27	1.2

SE= standard error.
OAC= oesophageal adenocarcinoma OSCC= oesophageal squamous cell carcinoma.

Table 2c One-year relative survival for patients with metastatic (M1) oesophageal carcinoma.

	M1 oesophageal cancer n=10 456		M1 OAC n=6746		M1 OSCC n=3177	
	Point estimate (%)	SE	Point estimate (%)	SE	Point estimate (%)	SE
Period of diagnosis						
1989-1994	15	1.1	14	1.5	16	1.7
1995-1999	14	1.0	14	1.3	17	1.9
2000-2004	17	0.9	16	1.1	22	1.8
2005-2009	21	0.8	22	1.0	22	1.5
2010-2014	22	0.7	22	0.8	23	1.4

SE= standard error.
OAC= oesophageal adenocarcinoma OSCC= oesophageal squamous cell carcinoma.

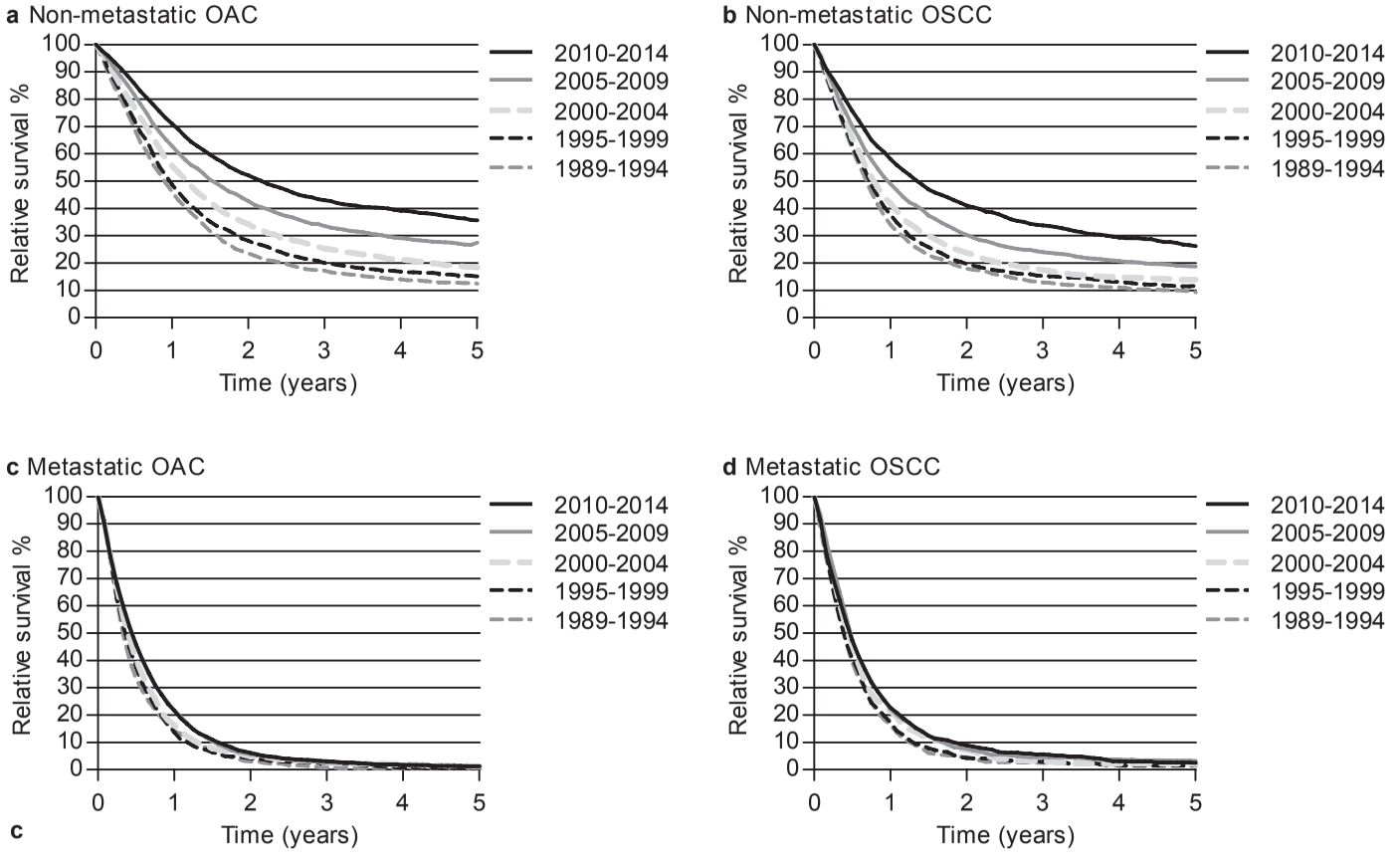


Figure 6 Relative survival of patients with oesophageal adenocarcinoma (OAC) and oesophageal squamous cell carcinoma (OSCC) in the Netherlands, 1989-2014 (n=20 600 and n=13 302).

Discussion

This large population-based nationwide study observed progress against oesophageal cancer in the last 26 years in the Netherlands, as the incidence increased and mortality decreased, suggesting an improvement in survival. Relative survival rates more than doubled for all patients and tripled for non-metastatic patients, particularly in the last two study periods. Moreover, an improvement in survival of metastatic patients was also observed.

The rising incidence in oesophageal cancer can be attributed to a rise in OAC, especially among males. OAC and OSCC have a distinct aetiology and specific risk factors. OSCC has been associated with tobacco smoking, overconsumption of alcohol and low intake of fruit and vegetables, whereas OAC has been associated with obesity, gastro-oesophageal reflux disease and Barrett's oesophagus.[2, 20] The increase in OAC among males may be attributed to the increase in obesity and especially abdominal (visceral) fat, which is more common among males and the strongest risk factor for Barrett's oesophagus and OAC.[2] Globally, the incidence of OAC is highest in Western industrialised countries, while the incidence of OSCC is highest in Asia, East Africa and South America.[4]

The widening gap between incidence and mortality for oesophageal cancer suggesting an improvement in survival.[21] There are several reasons why survival may artificially increase, such as improved detection (i.e. screening) and changes in incidence and underlying proportional changes in age, morphology and stage distribution. As screening programs are not the case for oesophageal cancer in the Netherlands and survival improved for non-metastatic and metastatic patients as well as for both morphology subgroups, changes in survival may reflect improved staging and treatment.

During the study period, relative survival also increased for patients with gastric cardia cancer, which is related to distal OAC, from 11% in 1989-1994 to 17% in 2010-2014. Survival especially improved in the last two periods. However, survival for gastric cardia cancer increased to a lesser extent compared to oesophageal cancer. An explanation may be that multimodality treatment has been administered less frequently in gastric cardia cancer as compared to oesophageal cancer.[22] Moreover, gastric cardia cancer patients can be treated with an oesophagectomy or gastrectomy which latter procedure is centralised more recently. Therefore, it is expected that survival will further increase in the next decade.

There are several possible explanations for the improvement in survival of patients with non-metastatic oesophageal cancer. First, the introduction of neoadjuvant chemoradiotherapy in a multimodality treatment for oesophageal cancer has contributed to better survival rates for resected patients by downstaging of the tumour and an improved locoregional and distant disease control.[5, 6] The results from the CROSS trial have led to a successful implementation of neoadjuvant chemoradiotherapy as preferred treatment for resectable patients with oesophageal cancer in the Netherlands. Nowadays, nearly all Dutch patients that undergo surgery receive neoadjuvant chemoradiotherapy. The downstaging effect of chemoradiotherapy possibly resulted in an increasing number of patients with a pathological complete response (stage 0) or stage I and II as shown in Figure 2.

Second, centralisation of oesophageal cancer surgery may have further contributed to the improved survival in the most recent periods for non-metastatic patients. Many population-based

studies have shown that centralisation improves surgical experience, decreases postoperative complications and mortality.[15, 23-26] Furthermore, centralisation also seems to improve patient selection as survival also improved for non-surgically treated patients.[15, 27]

Third, survival may have improved due to better diagnostic procedures, resulting in improved patient selection. With the introduction of high-quality computed tomography (CT) scanners, endoscopic ultrasonography (EUS), endobronchial ultrasonography (EBUS) and Positron Emission Tomography-Computed Tomography (PET-CT), staging has become more accurate.[13, 14, 28, 29] The higher proportion of patients diagnosed with an advanced tumour stage over time – instead of unknown - in the present study indicates stage migration due to improved diagnostic techniques. However, since the survival of all patients increased the influence of stage migration can only partly explain the increased survival.

Finally, the increased use of definitive chemoradiotherapy might have improved survival especially for patients with OSCC. Compared with neoadjuvant chemoradiotherapy followed by surgery, definitive chemoradiotherapy has been associated with an equivalent survival of patients with OSCC but higher rates of local relapse in two RCTs.[10, 30] As not each patient is fit for surgery, definitive chemoradiotherapy can be a well-tolerated alternative, especially in OSCC patients.[31]

The median overall survival of metastatic oesophageal cancer patients improved from 18 to 22 weeks (22%) during the last 26 years. Similar findings have been reported by two other Dutch studies.[32, 33] The prolonged survival in metastatic patients may be the result of major changes in treatment but also of stage migration due to improved diagnostic techniques, which facilitates detection of metastases at an earlier stage.[12]

Survival of patients with oesophageal cancer also improved in countries outside the Netherlands. The EUROCARE-5 study showed that the largest improvements in 5-year relative survival were observed in Ireland, the UK and Central Europe in the period 2005-2007 compared to 1999-2001 ranging from 4 to 5%.[34] The changes in survival between Belgium and the Netherlands are comparable. [35] Limited improvements were observed in Eastern and Southern Europe.[34] The average European 5-year relative survival of 12% in 2000-2007 was somewhat lower compared to the 5-year relative survival of 16% in 2005-2009 in the Netherlands. Furthermore, the improvement in five-year relative survival rates in the Netherlands was comparable to the improvement seen in the United states.[36]

This study has some limitations. First, information about the intention of chemoradiotherapy (curative or palliative) was not available. Therefore, among non-metastatic oesophageal cancer patients it was assumed that patients underwent chemoradiotherapy with curative intention (neoadjuvant or definitive). Second, the group of M0 patients who underwent definitive chemoradiotherapy may be heterogeneous, consisting of patients who indeed underwent definitive chemoradiotherapy, patients not fit enough to undergo surgery after neoadjuvant chemoradiotherapy and some patients with a complete clinical response after neoadjuvant chemoradiotherapy who may have refused surgery. Third, possible incompleteness of registration of endoscopic resections in the earlier period could have led to an underestimation of endoscopically treated patients. The strength of this study is its unique nationwide population-based design resulting in a large and representative study population with real world data about treatment patterns and survival in the past 26 years in the Netherlands.

In conclusion, the significant improvement in survival of oesophageal cancer patients especially after 2005 reflects the possibly improved staging, better patient selection and evolving therapeutic options including neoadjuvant treatment and centralisation of oesophageal cancer surgery. Further improvement may be achieved by earlier detection and treatment of (pre) malignant lesions and by use of more effective personalised systemic treatment.[37]

References

1. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012, 2015. Int J Cancer;136:E359-386.
2. Smyth EC, Lagergren J, Fitzgerald RC, Lordick F, Shah MA, Lagergren P, Cunningham D. Oesophageal cancer, 2017. Nat Rev Dis Primers;3:17048.
3. Pennathur A, Gibson MK, Jobe BA, Luketich JD. Oesophageal carcinoma, 2013. Lancet;381:400-412.
4. Arnold M, Soerjomataram I, Ferlay J, Forman D. Global incidence of oesophageal cancer by histological subtype in 2012, 2015. Gut;64:381-387.
5. van Hagen P, Hulshof MC, van Lanschot JJ, Steyerberg EW, van Berge Henegouwen MI, Wijnhoven BP, Richel DJ, Nieuwenhuijzen GA, Hospers GA, Bonenkamp JJ, Cuesta MA, Blaisse RJ, Busch OR, ten Kate FJ, Creemers GJ, Punt CJ, Plukker JT, Verheul HM, Spillenaar Bilgen EJ, van Dekken H, van der Sangen MJ, Rozema T, Biermann K, Beukema JC, Piet AH, van Rij CM, Reinders JG, Tilanus HW, van der Gaast A, Group C. Preoperative chemoradiotherapy for esophageal or junctional cancer, 2012. N Engl J Med;366:2074-2084.
6. Shapiro J, van Lanschot JJ, Hulshof MC, van Hagen P, van Berge Henegouwen MI, Wijnhoven BP, van Laarhoven HW, Nieuwenhuijzen GA, Hospers GA, Bonenkamp JJ, Cuesta MA, Blaisse RJ, Busch OR, Ten Kate FJ, Creemers GJ, Punt CJ, Plukker JT, Verheul HM, Bilgen EJ, van Dekken H, van der Sangen MJ, Rozema T, Biermann K, Beukema JC, Piet AH, van Rij CM, Reinders JG, Tilanus HW, Steyerberg EW, van der Gaast A, group Cs. Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): long-term results of a randomised controlled trial, 2015. Lancet Oncol;16:1090-1098.
7. Crosby TD, Brewster AE, Borley A, Perschky L, Kehagioglou P, Court J, Maughan TS. Definitive chemoradiation in patients with inoperable oesophageal carcinoma, 2004. Br J Cancer;90:70-75.
8. Wong R, Malthaner R. Combined chemotherapy and radiotherapy (without surgery) compared with radiotherapy alone in localized carcinoma of the esophagus, 2006. Cochrane Database Syst Rev:Cd002092.
9. Allum WH, Blazeby JM, Griffin SM, Cunningham D, Jankowski JA, Wong R, Association of Upper Gastrointestinal Surgeons of Great B, Ireland tBSoG, the British Association of Surgical O. Guidelines for the management of oesophageal and gastric cancer, 2011. Gut;60:1449-1472.
10. Stahl M, Stuschke M, Lehmann N, Meyer HJ, Walz MK, Seeber S, Klump B, Budach W, Teichmann R, Schmitt M, Schmitt G, Franke C, Wilke H. Chemoradiation with and without surgery in patients with locally advanced squamous cell carcinoma of the esophagus, 2005. J Clin Oncol;23:2310-2317.
11. Blom RL, Schreurs WM, Belgers HJ, Oostenbrug LE, Vliegen RF, Sosef MN. The value of post-neoadjuvant therapy PET-CT in the detection of interval metastases in esophageal carcinoma, 2011. Eur J Surg Oncol;37:774-778.
12. Rustgi A, El-Serag HB. Esophageal carcinoma, 2015. N Engl J Med;372:1472-1473.
13. Findlay JM, Bradley KM, Maile EJ, Braden B, Maw J, Phillips-Hughes J, Gillies RS, Maynard ND, Middleton MR. Pragmatic staging of oesophageal cancer using decision theory involving selective endoscopic ultrasonography, PET and laparoscopy, 2015. Br J Surg;102:1488-1499.
14. Puli SR, Reddy JB, Bechtold ML, Antillon D, Ibdah JA, Antillon MR. Staging accuracy of esophageal cancer by endoscopic ultrasound: a meta-analysis and systematic review, 2008. World J Gastroenterol;14:1479-1490.
15. van de Poll-Franse LV, Lemmens VE, Roukema JA, Coebergh JW, Nieuwenhuijzen GA. Impact of concentration of oesophageal and gastric cardia cancer surgery on long-term population-based survival, 2011. Br J Surg;98:956-963.

16. Dikken JL, Dassen AE, Lemmens VE, Putter H, Krijnen P, van der Geest L, Bosscha K, Verheij M, van de Velde CJ, Wouters MW. Effect of hospital volume on postoperative mortality and survival after oesophageal and gastric cancer surgery in the Netherlands between 1989 and 2009, 2012. Eur J Cancer;48:1004-1013.

17. Fritz A, Percy C, Jack A, Shanmugaratnam K, Sobin L, Parkin DM, Whelan S, editors. International Classification of Diseases for Oncology, third edition., 2000ed. Geneva: World Health Organization.

18. Lambert PC, Dickman PW, Rutherford MJ. Comparison of different approaches to estimating age standardized net survival, 2015. BMC Med Res Methodol;15:64.

19. Hakulinen T, Seppa K, Lambert PC. Choosing the relative survival method for cancer survival estimation, 2011. Eur J Cancer;47:2202-2210.

20. Lepage C, Remontet L, Launoy G, Tretarre B, Grosclaude P, Colonna M, Velten M, Buemi A, Danzon A, Molinie F, Maarouf N, Bossard N, Bouvier AM, Faivre J, French network of cancer r. Trends in incidence of digestive cancers in France, 2008. Eur J Cancer Prev;17:13-17.

21. Cho H, Mariotto AB, Schwartz LM, Luo J, Woloshin S. When do changes in cancer survival mean progress? The insight from population incidence and mortality, 2014. J Natl Cancer Inst Monogr;2014:187-197.

22. Koeter M, Parry K, Verhoeven RH, Luyer MD, Ruurda JP, van Hillegersberg R, Lemmens VE, Nieuwenhuijzen GA. Perioperative Treatment, Not Surgical Approach, Influences Overall Survival in Patients with Gastroesophageal Junction Tumors: A Nationwide, Population-Based Study in The Netherlands, 2016. Ann Surg Oncol;23:1632-1638.

23. Anderson O, Ni Z, Moller H, Coupland VH, Davies EA, Allum WH, Hanna GB. Hospital volume and survival in oesophagectomy and gastrectomy for cancer, 2011. Eur J Cancer;47:2408-2414.

24. Pasquer A, Renaud F, Hec F, Gandon A, Vanderbeken M, Drubay V, Caranhac G, Piessen G, Mariette C, GroupFRENCH FW. Is Centralization Needed for Esophageal and Gastric Cancer Patients With Low Operative Risk?: A Nationwide Study, 2016. Ann Surg;264:823-830.

25. Henneman D, Dikken JL, Putter H, Lemmens VE, Van der Geest LG, van Hillegersberg R, Verheij M, van de Velde CJ, Wouters MW. Centralization of esophagectomy: how far should we go?, 2014. Ann Surg Oncol;21:4068-4074.

26. Derogar M, Sadr-Azodi O, Johar A, Lagergren P, Lagergren J. Hospital and surgeon volume in relation to survival after esophageal cancer surgery in a population-based study, 2013. J Clin Oncol;31:551-557.

27. Lemmens VE, Bosscha K, van der Schelling G, Brenninkmeijer S, Coebergh JW, de Hingh IH. Improving outcome for patients with pancreatic cancer through centralization, 2011. Br J Surg;98:1455-1462.

28. van Vliet EP, Heijenbrok-Kal MH, Hunink MG, Kuipers EJ, Siersema PD. Staging investigations for oesophageal cancer: a meta-analysis, 2008. Br J Cancer;98:547-557.

29. Kim TJ, Kim HY, Lee KW, Kim MS. Multimodality assessment of esophageal cancer: preoperative staging and monitoring of response to therapy, 2009. Radiographics;29:403-421.

30. Bedenne L, Michel P, Bouche O, Milan C, Mariette C, Conroy T, Pezet D, Roullet B, Seitz JF, Herr JP, Paillot B, Arveux P, Bonnetain F, Binquet C. Chemoradiation followed by surgery compared with chemoradiation alone in squamous cancer of the esophagus: FFCD 9102, 2007. J Clin Oncol;25:1160-1168.

31. Lordick F, Mariette C, Haustermans K, Obermannova R, Arnold D, Committee EG. Oesophageal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up, 2016. Ann Oncol;27:v50-v57.

32. Bernards N, Haj Mohammad N, Creemers GJ, Rozema T, Roukema JA, Nieuwenhuijzen GA, van Laarhoven HW, van der Sangen M, Lemmens VE. Improvement in survival for patients with synchronous metastatic esophageal cancer in the south of the Netherlands from 1994 to 2013, 2016. Acta Oncol;55:1161-1167.

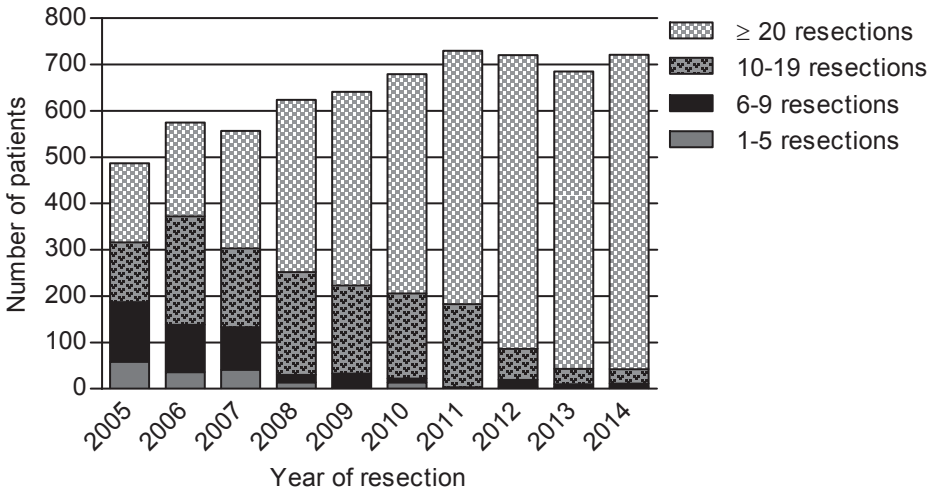
33. Dikken JL, Lemmens VE, Wouters MW, Wijnhoven BP, Siersema PD, Nieuwenhuijzen GA, van Sandick JW, Cats A, Verheij M, Coebergh JW, van de Velde CJ. Increased incidence and survival for oesophageal cancer but not for gastric cardia cancer in the Netherlands, 2012. Eur J Cancer;48:1624-1632.

34. Anderson LA, Tavilla A, Brenner H, Luttmann S, Navarro C, Gavin AT, Holleczek B, Johnston BT, Cook MB, Bannon F, Sant M, Group E-W. Survival for oesophageal, stomach and small intestine cancers in Europe 1999-2007: Results from EUROCARE-5, 2015. Eur J Cancer;51:2144-2157.

35. Stordeur S, Vlayen J, Vrijens F, Camberlin C, De Gendt C, Van Eycken E, Lerut T. Quality indicators for oesophageal and gastric cancer: a population-based study in Belgium, 2004-2008, 2015. Eur J Cancer Care (Engl);24:376-386.

36. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016, 2016. CA Cancer J Clin;66:7-30.

37. Oppedijk V, van der Gaast A, van Lanschot JJ, van Hagen P, van Os R, van Rij CM, van der Sangen MJ, Beukema JC, Rutten H, Spruit PH, Reinders JG, Richel DJ, van Berge Henegouwen MI, Hulshof MC. Patterns of recurrence after surgery alone versus preoperative chemoradiotherapy and surgery in the CROSS trials, 2014. J Clin Oncol;32:385-391.



Appendix 1 Number of oesophageal cancer resections per hospital volume category in the period 2005-2014.

Chapter 12

Discussion and future perspectives

Discussion

In this chapter the results observed in this thesis will be discussed in a broader context.

Centralisation of surgery

Improving quality of care for patients with oesophageal and gastric cancer is a major challenge as the incidence is relatively low and most patients have an advanced disease at time of diagnosis. Therefore, like in many other European countries, surgery is centralised in the Netherlands and now mainly performed in high-volume hospitals.[1] In the Netherlands, since 2006, hospitals should perform a minimum of 10 oesophagectomies per year and since 2012 a minimum of 10 gastrectomies per year which increased to 20 in 2011 and 2013 for oesophageal and gastric cancer, respectively. Currently, a large number of studies has been published on the impact of centralisation on outcomes after oesophagectomy and gastrectomy, showing short-term improved perioperative and oncologic results.[2-5] This thesis confirmed the reduction of postoperative mortality and showed also an improved long-term survival for surgically treated patients and all patients with gastric cancer in the period after centralisation.

An explanation for improved survival after centralisation could be the 'practice makes perfect' concept. This suggests that more experience is gained in hospitals that treat a greater number of patients, which could lead to improvements in the management of patients across the whole treatment pathway.[6] For example, specialisation of a surgeon should increase their experience and technical abilities. Moreover, the greater exposure of medical specialists and nurses to patients after Upper GI cancer surgery increases their ability to timely recognise and treat complications at an earlier stage and by doing so decreases postoperative mortality and failure to rescue.[7,8] Furthermore, a better patient selection by appropriate preoperative staging using endoscopic ultrasound and PET performed by experienced radiation oncologists and gastroenterologists is likely to play a significant role in improving overall survival.[9,10] In addition, medical oncologists and radiotherapists may be more aware of the possibilities of chemotherapy and radiotherapy when treating more patients. Finally, several studies have observed that pathological examination improves with growing experience, resulting in better staging.[11]

Many previous studies only included surgically treated patients to assess the influence of centralisation on the outcome of patients with upper gastrointestinal tumours.[12-15] However, improvement in survival after surgery observed by these studies may be explained by patient selection rather than by better care. Medical specialists may perform a more critical pre-operative selection withholding the less fit patients from surgical treatment. As a result, overall survival may be worse for all patients as improvement in survival is only the case in the selected group of patients.[6] Therefore, it is important to evaluate the impact of centralising treatment for all patients, irrespective of treatment, in a population-based setting as performed in this thesis.

Centralisation of surgery has enforced regionalisation of oncological care for oesophageal and gastric cancer within the Netherlands. Centralisation of surgery imposed by the Health Care Inspectorate and the Association of Surgeons in the Netherlands by defining a minimum number of procedures per year, resulted in an increasing number of hospitals starting to create regional agreements on referral of oesophageal and gastric cancer patients for surgery. Within these regions patients can be referred to high volume hospitals for surgery or discussed within

a multidisciplinary team (MDT's) meeting. Moreover, it avoids that low volume hospitals are confronted with complex patients and poor outcomes.[16] Currently multiple collaborative regions exists in the Netherlands. Sharing knowledge and experiences and making formal agreements on their specific role in the clinical pathway within these regional collaborations is of paramount importance as oncological care, like for oesophageal and gastric cancer, is increasingly complex.

Hospital of diagnosis and impact on treatment selection

Surgical treatment of both oesophageal and gastric cancer is nowadays centralised in the Netherlands, but the initial decision which treatment modality to perform, including the decision whether or not to refer patients for a curative treatment option is made in all hospitals, sometimes by consulting medical specialists from other hospitals. This thesis showed a large inter-hospital variation in the use of curative treatment options for patients with oesophageal and gastric cancer. Large differences between hospitals of diagnosis existed varying from 50% to 82% and from 48% to 78% for patients with oesophageal and gastric cancer, respectively. Moreover, patients diagnosed in hospitals with a low probability of undergoing curative treatment had a worse overall survival, even after adjustment for case-mix factors.

The variation between hospitals indicates that decision-making in oesophageal and gastric cancer can be improved. Due to centralisation of complex surgery an increasing number of patients are referred to another hospital for treatment by the hospital of diagnosis. Centralisation of surgery may have led to a "brain drain" of knowledge and experience of treatment options for these tumours among hospitals which do not perform these procedures (anymore). This possible downside of centralisation could have influenced the selection of patients for curative treatment and subsequently referral and overall survival.

Differences in the composition of a MDT meeting may explain variation in curative treatment between hospitals of diagnosis. According to the guidelines, all oesophageal and gastric cancer patients should be discussed in a MDT meeting for a consensus-based treatment decision before starting treatment in the Netherlands. Previous studies have found that MDTs improve diagnostic work-up and significantly influenced treatment decisions in oesophageal and gastric cancer.[17-19] However, no information is available as to which expertise in treatment of oesophageal and gastric cancer is present in this MDT. Differences in the presence of experienced specialists in these MDT meetings might explain differences between hospitals in the proportion of patients undergoing treatment with curative intent. Therefore, regional expert MDT meetings with involvement of experienced specialists in this field, for example by means of video conferencing, may improve treatment selection for patients with oesophageal and gastric cancer.

Early diagnosis of oesophageal cancer

Survival for patients with oesophageal cancer improved the last decades, probably related to the introduction of neoadjuvant chemoradiotherapy and centralisation of surgery. Further improvement may be achieved by earlier detection and treatment of premalignant and malignant lesions like Barrett's oesophagus.

This thesis showed that oesophageal adenocarcinoma and high-grade dysplasia was 'missed' at index Barrett's oesophagus endoscopy in up to 13% of the Barrett's oesophagus patients in Northern Ireland, who were subsequently diagnosed with one of these (pre)malignant diseases.

This percentage was significant but substantially lower than previously reported estimates by a systematic review (25%). However, this systematic review was severely lacking inclusion of robust, population-based data. Moreover, this review defined 'missed' as being diagnosed with oesophageal malignant or premalignant lesion within one year after Barrett's oesophagus diagnosis. However, a diagnosis less than three months after diagnosis of Barrett's oesophagus may be part of the diagnostic work-up.[20]

There could be two overarching explanations for the 'missed' (pre)malignant lesions. First, the missed cancers may be truly missed, which means that the cancer or premalignant lesions were already present at index endoscopy but not detected.[21] It is possible that cancer or premalignant lesions were not detected due to features that make them less likely to be seen by the endoscopist such as oesophagitis, oesophageal stricture and ulceration.[21] Methods to increase detection of cancer and premalignant lesions such as advanced endoscopic imaging techniques[22], greater time examining Barrett's oesophagus segments[23] and greater number of targeted biopsies[21] may decrease the burden of missed (pre)malignant lesions.[24] Second, it is plausible that the missed cancers may be more aggressive cancers which have no visible evidence at time of index Barrett's oesophagus endoscopy but develop rapidly afterward. Therefore, biomarkers could assist in determining the risk of progression at Barrett's oesophagus diagnosis and guide the targeting of endoscopic surveillance.[25-27] Nevertheless, it is important to put the 'missed' oesophageal (pre)malignant rate of 13%, into context of the total Barrett's oesophagus population. This figure represents only 0.26% of all Barrett's oesophagus patients diagnosed in Northern Ireland in the period 1993-2000, and so the ever-important question of identifying the very small proportion of high-risk patients remains a considerable challenge.

Perioperative treatment for gastric cancer

While survival of the total group of patients with oesophageal cancer showed major improvement during the last two decades as shown by this thesis, survival of patients with gastric cancer only improved for patients with a potentially curable disease.[28] As of 2006, perioperative chemotherapy for gastric cancer patients is recommended in several European countries based on results of the UK MAGIC trial.[29] However, a study in this thesis, based on real-world data, highlights that a more than expected proportion of the patients did not receive perioperative treatment in daily clinical practice.

In the MAGIC-trial, the French FNCLCC/FFCD, the CRITICS I trial and a study in this thesis, discontinuation of perioperative chemotherapy was mostly observed after surgery.[29-31] Therefore, research is necessary to elucidate the importance of the individual components of perioperative treatment. Although there is evidence that the omission of postoperative chemotherapy impairs oncologic outcomes in patients that did not receive neoadjuvant chemotherapy,[32] there is limited evidence for omission of postoperative chemotherapy in patients who received neoadjuvant chemotherapy.

There are several reasons that may explain why resectable gastric cancer patients do not receive perioperative treatment. Many patients with gastric cancer have an older age, comorbidities and suffer from malnutrition and weight loss which could preclude them from starting with the perioperative treatment regimen.[33] After preoperative chemotherapy there could be several reasons for not undergoing surgery such as disease progression, toxicity from

chemotherapy, patient request and death.[29,34] Moreover, gastric cancer surgery is associated with substantial morbidity and postoperative complications which could interfere with receiving postoperative treatment.[29,35-37] As only a minority of the patients is actually capable of receiving the full regimen, one could argue about the appropriateness of the current perioperative chemotherapy as a reference regime for patients with resectable gastric cancer.

If gastric cancer patients are able to undergo perioperative chemotherapy the optimal timing of chemotherapy after surgery seems equivocal. On one hand, it seems rational to start with postoperative chemotherapy as early as possible to eradicate microscopic disease that may exist after neoadjuvant treatment and gastrectomy. For colon and breast cancer, early timing of postoperative chemotherapy has indeed proven to benefit oncological outcomes.[38-41] However, these tumours have a relatively higher response rate to chemotherapy than gastric cancer, which may increase the importance for early timing of postoperative chemotherapy.[42-44] On the other hand, a gastrectomy is considered as a major surgical procedure, and patients need time to recover from surgery, which may take up to several months depending on the postoperative course.[45] Moreover, a study in this thesis showed that timing of the adjuvant component of perioperative treatment in gastric cancer was not associated with overall survival indicating that the early postoperative period may be safely used for recovery and optimising patients for the start of adjuvant chemotherapy

Nevertheless, results from a recent randomised controlled trial investigating different perioperative treatment regimens seem promising at first sight. This trial, the FLOT4-AIO trial, investigated whether perioperative chemotherapy with 5-Fluorouracil (5-FU), Leucovorin, Oxaliplatin and Docetaxel (FLOT regime) leads to improved survival compared with Epirubicin, Cisplatin and 5-FU/Capecitabine (ECF/ECX; MAGIC regime).[46] In the ECF/ECX arm, 37% of patients completed the planned postoperative treatment, whereas 46% of the patients allocated to the FLOT arm completed postoperative treatment. Three-year overall survival was 48% for ECF/ECX and 57% for FLOT (P=0.01). Perioperative complications were similar across the 2 arms of the FLOT. The FLOT seems superior to ECF/ECX and may be the new standard of care in perioperative treatment of patients with adenocarcinomas of the stomach or gastro-oesophageal junction. However, it should be noted that the patients included in the aforementioned trials which are relatively healthy, may not represent all gastric cancer patients seen in daily clinical practice.[47]

Age and treatment

Elderly patients represent a substantial proportion of the patients with oesophageal and gastric cancer. However, most treatment strategies and guidelines are based on clinical trials in which elderly patients are largely excluded.[48] Population-based studies are therefore needed to bridge the gap of knowledge between clinical trials in selected patients and unselected patients in daily clinical practice.[47,49]

Population-based studies in this thesis showed that the proportion of patients that received treatment declined with age. For example, as shown by this thesis, elderly patients with potentially curable oesophageal cancer underwent less often curative treatment compared to their younger counterparts. Reasons to withhold patients from treatment with curative intent could be comorbidity, bad general health condition of the patients, short life expectancy and refusal by the patients and/or family.[33,50] Nevertheless, cancer within the elderly is subject to

ageist stereotypes, with elderly cancer patients considered as frail and by some not as likely to recover as younger patients with cancer.[51] However, elderly patients may be very heterogeneous with respect to their underlying health status. Therefore, the use of biological age as opposed to chronological age is desirable in deciding on treatment.[52]

Medical specialists have to deal with elderly patients who are very heterogeneous with respect to their underlying health status. The variation in treatment between hospitals after adjustment for case-mix in this thesis shows the complexity of adequate selection of patients that will benefit from a specific treatment. Also shown by this thesis, older metastatic gastric cancer patients derived the same benefits from chemotherapy compared to their younger counterparts with regard to survival, but received chemotherapy far less often. Another study in this thesis demonstrated that elderly patients with oesophageal squamous cell carcinoma derived the same benefits, regarding survival, from definitive chemoradiotherapy as compared to chemoradiotherapy followed by surgery. Two randomised controlled trials support these findings. Results showed that patients with oesophageal cancer, especially squamous cell carcinoma, who are not fit enough to undergo surgery may benefit from definitive chemoradiotherapy which is regarded as a well-tolerated alternative.[53-55] However, treatment efficacy and toxicity should be balanced especially when selecting treatment in older patients. The inclusion of geriatrics and geriatric assessment may provide additional opportunities for refinement of treatment selection in older patients.[56-58]

Methodological considerations

Study design

The studies in this thesis are of an observational design and based on real-world data. While randomised clinical trials are considered the gold standard in evaluating the efficacy of treatments, observational studies based on real-world data have the ability to provide a broader insight of how treatment may be applied in daily clinical practice. Especially for subsets of patients who do not meet the eligibility criteria from randomised controlled trials, like relatively unhealthy patients, observational studies are of paramount importance because it provide an unique insight into the use and effectiveness of treatment in daily practice. Nevertheless, bias due to confounding factors is an important issue in population-based observational studies and should be carefully considered when interpreting the results of the studies in this thesis.

Selection bias

Selection bias was present in many studies included in this thesis. In these studies, baseline characteristics were different between groups as patients were grouped according to treatment based on clinical decisions. For example, patients treated with perioperative chemotherapy, preoperative chemotherapy or surgery alone differed for several patient and tumour characteristics such as age, cT stage and cN stage (chapter 6). We used propensity score matching to adjust for imbalances between treatment groups based on known and observed patients and tumour characteristics. However, even after propensity score matching, patients groups may still not be completely comparable and confounding due to non-randomised assignment may still exists. Moreover, one should consider the use of propensity score matching if variables that

affected treatment assignment were imbalanced between treated and untreated subjects. In that case propensity score matching may increase imbalance and bias.[59]

Immortal time bias

Some studies in this thesis have been exposed to immortal time bias (chapter 6 and 7). Immortal time bias arises when determination of a patient's treatment status involves a delay or wait period during which follow-up time is accrued. In this period death can not occur as patients must have been alive to receive the treatment. This kind of bias can generate an illusion of treatment effectiveness and often occurs when studies compare against patients who did not underwent treatment. To minimise the immortal time bias we defined survival time as of a certain starting point. For example, overall survival was defined as of four months after surgery for all patients irrespective of adjuvant treatment (chapter 6).

Stage migration

Stage migration should be taken into account when interpreting treatment and survival trends. Improved diagnostic techniques have led to the detection of smaller metastases that would have been missed in the earlier time period. Patients who previously might have been classified with non-metastasised disease may now have been classified with metastasised disease. Because of the migration of these patients, survival rates improve in each group even though no actual improvement has taken place. In chapter 11 survival improved for oesophageal cancer patients with and without metastasis. However, since survival of all patients combined also increased, stage migration can only partly explain the improved survival. Interestingly, in chapter 10 survival remained stable for patients with metastatic gastric cancer despite improved diagnostic techniques and an increased use of systemic therapy. An explanation may be that the proportion of the more aggressive diffuse tumour type increased and the proportion of the more indolent intestinal tumour type decreased.

Residual confounding

The studies that are described in this thesis are based on data from the Netherlands Cancer Registry. The data for studies in this thesis were collected independent of the research question. As a result, some information was lacking. For example, no information was available on performance status and nutritional status. So, we were only able to adjust for known and registered characteristics in our statistical analyses. However, even if we had all the information about known characteristics, there could still be unknown characteristics resulting in residual confounding.

What does the future hold?

Since the last two decades, survival improved for patients with oesophageal cancer in the Netherlands, probably due to the introduction of neoadjuvant chemoradiotherapy and centralisation of surgery. With the increasing incidence of oesophageal adenocarcinoma, combined with improvements in survival, more patients will be subjected to long-term follow-up and quality of life issues will become more important. Moreover, treatment for oesophageal adenocarcinoma and oesophageal squamous cell carcinoma will further diverge. The distinction of these two subtypes by TNM-8 for tumour staging may support this expectation together with a different treatment response to neoadjuvant chemoradiotherapy, a different aetiology, pathogenesis and different molecular characters.

Neoadjuvant chemoradiotherapy followed by surgery is the preferred treatment for resectable oesophageal cancer in the Netherlands. Chemoradiotherapy appears to be an effective preoperative treatment especially for oesophageal squamous cell carcinoma as these patients show excellent histological responses associated with radiotherapy.[60] Moreover, results from the CROSS trial showed that 49% of the patients with oesophageal squamous cell carcinoma compared to 23% of the patients with oesophageal adenocarcinoma had a pathological complete response after chemoradiotherapy.[61] These findings raise the question whether or not an oesophagectomy following chemoradiotherapy should be performed for these patients as an oesophagectomy is associated with severe postoperative morbidity and a substantial impact on the quality of life.[62-64] Therefore, the SANO trial, which is a phase III trial, will investigate neoadjuvant chemoradiotherapy plus surgery versus active surveillance after chemoradiotherapy for clinically complete responders with oesophageal cancer.

Trends in survival of gastric cancer may be explained by the differential response to treatment according to the Laurén classification and changes in the distribution of subgroups within this classification over time. According to the Laurén classification gastric adenocarcinoma can be subdivided in two major histological subtypes; the intestinal and diffuse tumour type.[65] The diffuse type is considered as more aggressive with a worse prognosis compared to the intestinal type. The studies in this thesis did not incorporate the Laurén classification as this information was not available in the Netherlands Cancer Registry at time of performing these studies. The Laurén classification is one of the factors that may support individualised treatment for gastric cancer, which is increasingly gaining attention in the scientific field. Moreover, trends in survival of gastric cancer may be explained by changes in the distribution of subgroups within the Laurén classification. Future studies should investigate trends and the effect of treatment among patients with gastric cancer according to the Laurén classification.

Survival for oesophageal and gastric cancer may further improve by minimising variation in curative treatment between hospitals for patients with oesophageal and gastric cancer. Therefore, regional expert MDT meetings with involvement of experienced specialists may improve treatment selection for patients with oesophageal and gastric cancer, for example by using video conferencing. However, studies that directly link the organisation of MDTs to variation between hospitals are lacking. Moreover, there is a lack of knowledge on amendable factors, such as behavioural and other organisational aspects, that influence variation in treatment decision. Therefore, a recently started project, funded by the Dutch Cancer Society,

will attempt to identify these factors. This project will use qualitative and quantitative methods to in-depth assess which factors influence the probability that a patient is treated with curative intent. In addition, the effect of reducing variation in treatment on survival, health-related quality of life and health economics will be assessed. More understanding and insight in these factors will aid patients and physicians in their treatment decision.

Many gastric cancer patients that are eligible for perioperative treatment do not receive the adjuvant component of perioperative treatment or they do not receive chemotherapy at all in addition to surgery. Future population-based studies should investigate why patients do not undergo chemotherapy at all or why they fail to undergo adjuvant treatment in clinical practice. These information may aid to assess the feasibility and importance of the individual components of perioperative chemotherapy. The CRITICS-II trial will hopefully evaluate three different neoadjuvant strategies: chemotherapy, chemoradiotherapy and combination chemotherapy and chemoradiotherapy. Furthermore, as of 2015 more information is registered in the Netherlands Cancer Registry for patients with oesophageal and gastric cancer, for example the type of systemic treatment, number of cycles received, response on chemotherapy, and reasons for not undergoing surgery or chemotherapy. This information will shed some more light on the use, feasibility and importance of the individual components of perioperative treatment for patients with gastric cancer.

Palliative treatment of oesophageal and gastric cancer remains a challenge for clinicians. The optimal therapeutic approach for patients with metastatic oesophageal and gastric cancer is not well defined. Moreover, about 40% of the patients have a metastatic disease at time of diagnosis. Therefore, a project started aiming to investigate the currently used palliative care modalities and the association with survival and toxicity in a population-based setting among patients with metastasised oesophageal and gastric cancer.

Concluding remarks

The studies in this thesis aimed to give more insight in the provided care and outcomes for patients with oesophageal and gastric cancer in daily clinical practice. Survival improved for patients with oesophageal cancer the last 26 years, probably due to the introduction of neoadjuvant chemoradiotherapy and centralisation of surgery. Survival of patients with gastric cancer improved as well in the period after centralisation of surgery. Nevertheless, still a more than expected proportion of patients with resectable gastric cancer do not receive perioperative chemotherapy. The large variation between hospitals of diagnosis in curative treatment rates suggest that there is room for further improvement in survival. Moreover, it is highly desirable to move from a 'one-size-fits all' approach to a more tailored MDT based treatment approach for the individual patient with maximisation of treatment efficacy and minimisation of treatment-related morbidity and mortality.

References

1. Strong VE. Gastric Cancer: Principles and Practice, 2015ed.: Springer International Publishing.
2. Anderson O, Ni Z, Moller H, Coupland VH, Davies EA, Allum WH, Hanna GB. Hospital volume and survival in oesophagectomy and gastrectomy for cancer, 2011. Eur J Cancer;47:2408-2414.
3. Jensen LS, Nielsen H, Mortensen PB, Pilegaard HK, Johnsen SP. Enforcing centralization for gastric cancer in Denmark, 2010. Eur J Surg Oncol;36 Suppl 1:S50-54.
4. Lemmens VE, Bosscha K, van der Schelling G, Brenninkmeijer S, Coebergh JW, de Hingh IH. Improving outcome for patients with pancreatic cancer through centralization, 2011. Br J Surg;98:1455-1462.
5. van de Poll-Franse LV, Lemmens VE, Roukema JA, Coebergh JW, Nieuwenhuijzen GA. Impact of concentration of oesophageal and gastric cardia cancer surgery on long-term population-based survival, 2011. Br J Surg;98:956-963.
6. Luft HS, Hunt SS, Maerki SC. The volume-outcome relationship: practice-makes-perfect or selective-referral patterns?, 1987. Health Serv Res;22:157-182.
7. Ghaferi AA, Birkmeyer JD, Dimick JB. Hospital volume and failure to rescue with high-risk surgery, 2011. Med Care;49:1076-1081.
8. Needleman J, Buerhaus P, Mattke S, Stewart M, Zelevinsky K. Nurse-staffing levels and the quality of care in hospitals, 2002. N Engl J Med;346:1715-1722.
9. Birkmeyer JD, Sun Y, Goldfaden A, Birkmeyer NJ, Stukel TA. Volume and process of care in high-risk cancer surgery, 2006. Cancer;106:2476-2481.
10. van Vliet EP, Hermans JJ, De Wever W, Eijkemans MJ, Steyerberg EW, Faasse C, van Helmond EP, de Leeuw AM, Sikkenk AC, de Vries AR, de Vries EH, Kuipers EJ, Siersema PD. Radiologist experience and CT examination quality determine metastasis detection in patients with esophageal or gastric cardia cancer, 2008. Eur Radiol;18:2475-2484.
11. Bilimoria KY, Talamonti MS, Wayne JD, Tomlinson JS, Stewart AK, Winchester DP, Ko CY, Bentrem DJ. Effect of hospital type and volume on lymph node evaluation for gastric and pancreatic cancer, 2008. Arch Surg;143:671-678; discussion 678.
12. Coupland VH, Lagergren J, Luchtenborg M, Jack RH, Allum W, Holmberg L, Hanna GB, Pearce N, Moller H. Hospital volume, proportion resected and mortality from oesophageal and gastric cancer: a population-based study in England, 2004-2008, 2013. Gut;62:961-966.
13. Wouters MW, Karim-Kos HE, le Cessie S, Wijnhoven BP, Stassen LP, Steup WH, Tilanus HW, Tollenaar RA. Centralization of esophageal cancer surgery: does it improve clinical outcome?, 2009. Ann Surg Oncol;16:1789-1798.
14. Boddy AP, Williamson JM, Vipond MN. The effect of centralisation on the outcomes of oesophagogastric surgery--a fifteen year audit, 2012. Int J Surg;10:360-363.
15. Gooiker GA, Lemmens VE, Besselink MG, Busch OR, Bonsing BA, Molenaar IQ, Tollenaar RA, de Hingh IH, Wouters MW. Impact of centralization of pancreatic cancer surgery on resection rates and survival, 2014. Br J Surg;101:1000-1005.
16. van Erning FN, van Steenbergen LN, van den Broek WT, Rutten HJ, Lemmens VE. No difference between lowest and highest volume hospitals in outcome after colorectal cancer surgery in the southern Netherlands, 2013. Eur J Surg Oncol;39:1199-1206.
17. Davies AR, Deans DA, Penman I, Plevris JN, Fletcher J, Wall L, Phillips H, Gilmour H, Patel D, de Beaux A, Paterson-Brown S. The multidisciplinary team meeting improves staging accuracy and treatment selection for gastro-esophageal cancer, 2006. Dis Esophagus;19:496-503.
18. Du CZ, Li J, Cai Y, Sun YS, Xue WC, Gu J. Effect of multidisciplinary team treatment on outcomes of patients with gastrointestinal malignancy, 2011. World J Gastroenterol;17:2013-2018.
19. van Hagen P, Spaander MC, van der Gaast A, van Rij CM, Tilanus HW, van Lanschot JJ, Wijnhoven BP. Impact of a multidisciplinary tumour board meeting for upper-GI malignancies on clinical decision making: a prospective cohort study, 2013. Int J Clin Oncol;18:214-219.
20. Chadwick G, Groene O, Hoare J, Hardwick RH, Riley S, Crosby TD, Hanna GB, Cromwell DA. A population-based, retrospective, cohort study of esophageal cancer missed at endoscopy, 2014. Endoscopy;46:553-560.

21. Yalamarthi S, Witherspoon P, McCole D, Auld CD. Missed diagnoses in patients with upper gastrointestinal cancers, 2004. Endoscopy;36:874-879.

22. Fitzgerald RC, di Pietro M, Ragunath K, Ang Y, Kang JY, Watson P, Trudgill N, Patel P, Kaye PV, Sanders S, O'Donovan M, Bird-Lieberman E, Bhandari P, Jankowski JA, Attwood S, Parsons SL, Loft D, Lagergren J, Moayyedi P, Lyratzopoulos G, de Caestecker J. British Society of Gastroenterology guidelines on the diagnosis and management of Barrett's oesophagus, 2014. Gut;63:7-42.

23. Gupta N, Gaddam S, Wani SB, Bansal A, Rastogi A, Sharma P. Longer inspection time is associated with increased detection of high-grade dysplasia and esophageal adenocarcinoma in Barrett's esophagus, 2012. Gastrointest Endosc;76:531-538.

24. Bhat SK, McManus DT, Coleman HG, Johnston BT, Cardwell CR, McMenamin U, Bannon F, Hicks B, Kennedy G, Gavin AT, Murray LJ. Oesophageal adenocarcinoma and prior diagnosis of Barrett's oesophagus: a population-based study, 2015. Gut;64:20-25.

25. Bird-Lieberman EL, Dunn JM, Coleman HG, Lao-Sirieix P, Oukrif D, Moore CE, Varghese S, Johnston BT, Arthur K, McManus DT, Novelli MR, O'Donovan M, Cardwell CR, Lovat LB, Murray LJ, Fitzgerald RC. Population-based study reveals new risk-stratification biomarker panel for Barrett's esophagus, 2012. Gastroenterology;143:927-935.e923.

26. Martinez P, Timmer MR, Lau CT, Calpe S, Sancho-Serra Mdel C, Straub D, Baker AM, Meijer SL, Kate FJ, Mallant-Hent RC, Naber AH, van Oijen AH, Baak LC, Scholten P, Bohmer CJ, Fockens P, Bergman JJ, Maley CC, Graham TA, Krishnadath KK. Dynamic clonal equilibrium and predetermined cancer risk in Barrett's oesophagus, 2016. Nat Commun;7:12158.

27. Stachler MD, Taylor-Weiner A, Peng S, McKenna A, Agoston AT, Odze RD, Davison JM, Nason KS, Loda M, Leshchiner I, Stewart C, Stojanov P, Seepo S, Lawrence MS, Ferrer-Torres D, Lin J, Chang AC, Gabriel SB, Lander ES, Beer DG. Paired exome analysis of Barrett's esophagus and adenocarcinoma, 2015;47:1047-1055.

28. Nelen SD, Verhoeven RH, Lemmens VE, de Wilt JH, Bosscha K. Increasing survival gap between young and elderly gastric cancer patients, 2017. Gastric Cancer.

29. Cunningham D, Allum WH, Stenning SP, Thompson JN, Van de Velde CJ, Nicolson M, Scarffe JH, Lofts FJ, Falk SJ, Iveson TJ, Smith DB, Langley RE, Verma M, Weeden S, Chua YJ, Participants MT. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer, 2006. N Engl J Med;355:11-20.

30. Verheij M, Jansen E, Cats A. A multicenter randomized phase III trial of neo-adjuvant chemotherapy followed by surgery and chemotherapy or by surgery and chemoradiotherapy in resectable gastric cancer: First results from the CRITICS study., 2016, ed. Oral presentation at ASCO 2016 Annual Meeting; June 3-7, 2016; Chicago. Abstract no. 4000.

31. Ychou M, Boige V, Pignon JP, Conroy T, Bouche O, Lebreton G, Ducourtieux M, Bedenne L, Fabre JM, Saint-Aubert B, Geneve J, Lasser P, Rougier P. Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCD multicenter phase III trial, 2011. J Clin Oncol;29:1715-1721.

32. Jin LX, Sanford DE, Squires MH, 3rd, Moses LE, Yan Y, Poultsides GA, Votanopoulos KI, Weber SM, Bloomston M, Pawlik TM, Hawkins WG, Linehan DC, Schmidt C, Worhunsky DJ, Acher AW, Cardona K, Cho CS, Kooby DA, Levine EA, Winslow E, Saunders N, Spolverato G, Colditz GA, Maithel SK, Fields RC. Interaction of Postoperative Morbidity and Receipt of Adjuvant Therapy on Long-Term Survival After Resection for Gastric Adenocarcinoma: Results From the U.S. Gastric Cancer Collaborative, 2016. Ann Surg Oncol;23:2398-2408.

33. Deans DA, Tan BH, Wigmore SJ, Ross JA, de Beaux AC, Paterson-Brown S, Fearon KC. The influence of systemic inflammation, dietary intake and stage of disease on rate of weight loss in patients with gastro-oesophageal cancer, 2009. Br J Cancer;100:63-69.

34. Reece-Smith AM, Saha S, Cunnell ML, Hameed K, Bessell EM, Duffy JP, Madhusudan S, Parsons SL. MAGIC in practice: experience of peri-operative ECF/X chemotherapy in gastro-esophageal adenocarcinomas, 2012. J Surg Oncol;106:748-752.

35. Luc G, Gersen-Cherdieu H, Degrandi O, Terrebonne E, Chiche L, Collet D. Impact of postoperative chemotherapy in patients with locally advanced gastroesophageal adenocarcinoma treated with perioperative chemotherapy strategy, 2015. Am J Surg;210:15-23.

36. Bartlett EK, Roses RE, Kelz RR, Drebin JA, Fraker DL, Karakousis GC. Morbidity and mortality after total gastrectomy for gastric malignancy using the American College of Surgeons National Surgical Quality Improvement Program database, 2014. Surgery;156:298-304.

37. Luc G, Durand M, Chiche L, Collet D. Major post-operative complications predict long-term survival after esophagectomy in patients with adenocarcinoma of the esophagus, 2015. World J Surg;39:216-222.

38. Czaykowski PM, Gill S, Kennecke HF, Gordon VL, Turner D. Adjuvant chemotherapy for stage III colon cancer: does timing matter?, 2011. Dis Colon Rectum;54:1082-1089.

39. Hershman D, Hall MJ, Wang X, Jacobson JS, McBride R, Grann VR, Neugut AI. Timing of adjuvant chemotherapy initiation after surgery for stage III colon cancer, 2006. Cancer;107:2581-2588.

40. Lohrisch C, Paltiel C, Gelmon K, Speers C, Taylor S, Barnett J, Olivotto IA. Impact on survival of time from definitive surgery to initiation of adjuvant chemotherapy for early-stage breast cancer, 2006. J Clin Oncol;24:4888-4894.

41. Bos AC, van Erning FN, van Gestel YR, Creemers GJ, Punt CJ, van Oijen MG, Lemmens VE. Timing of adjuvant chemotherapy and its relation to survival among patients with stage III colon cancer, 2015. Eur J Cancer;51:2553-2561.

42. Adlard JW, Richman SD, Seymour MT, Quirke P. Prediction of the response of colorectal cancer to systemic therapy, 2002. Lancet Oncol;3:75-82.

43. Fisher B, Gunduz N, Saffer EA. Influence of the interval between primary tumor removal and chemotherapy on kinetics and growth of metastases, 1983. Cancer Res;43:1488-1492.

44. Mansour JC, Tang L, Shah M, Bentrem D, Klimstra DS, Gonen M, Kelsen DP, Brennan MF, Coit DG. Does graded histologic response after neoadjuvant chemotherapy predict survival for completely resected gastric cancer?, 2007. Ann Surg Oncol;14:3412-3418.

45. Brenkman HJ, Ruurda JP, Verhoeven RH, van Hillegersberg R. Safety and feasibility of minimally invasive gastrectomy during the early introduction in the Netherlands: short-term oncological outcomes comparable to open gastrectomy, 2017. Gastric Cancer.

46. Al-Batran S, Homann N, Schmalemberg H. Perioperative chemotherapy with docetaxel, oxaliplatin, and fluorouracil/leucovorin (FLOT) versus epirubicin, cisplatin, and fluorouracil or capecitabine (ECF/ECX) for resectable gastric or gastroesophageal junction (GEJ) adenocarcinoma (FLOT4-AIO): a multicenter, randomized phase 3 trial, 2017, ed. ASCO 2017 Annual Meeting; June 2-6, 2017; Chicago. Abstract no. 4004.

47. Booth CM, Tannock IF. Randomised controlled trials and population-based observational research: partners in the evolution of medical evidence, 2014. Br J Cancer;110:551-555.

48. Rothwell PM. External validity of randomised controlled trials: "to whom do the results of this trial apply?", 2005. Lancet;365:82-93.

49. Booth CM, Mackillop WJ. Translating new medical therapies into societal benefit: the role of population-based outcome studies, 2008. JAMA;300:2177-2179.

50. van Erning FN, Janssen-Heijnen ML, Creemers GJ, Pruijt HF, Maas HA, Lemmens VE. Deciding on adjuvant chemotherapy for elderly patients with stage III colon cancer: a qualitative insight into the perspectives of surgeons and medical oncologists, 2015. J Geriatr Oncol;6:219-224.

51. Swaminathan D, Swaminathan V. Geriatric oncology: problems with under-treatment within this population, 2015. Cancer Biol Med;12:275-283.

52. Given B, Given CW. Older adults and cancer treatment, 2008. Cancer;113:3505-3511.

53. Lordick F, Mariette C, Haustermans K, Obermannova R, Arnold D, Committee EG. Oesophageal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up, 2016. Ann Oncol;27:v50-v57.

54. Bedenne L, Michel P, Bouche O, Milan C, Mariette C, Conroy T, Pezet D, Roullet B, Seitz JF, Herr JP, Paillot B, Arveux P, Bonnetain F, Binquet C. Chemoradiation followed by surgery compared with chemoradiation alone in squamous cancer of the esophagus: FFCD 9102, 2007. J Clin Oncol;25:1160-1168.

55. Stahl M, Stuschke M, Lehmann N, Meyer HJ, Walz MK, Seeber S, Klump B, Budach W, Teichmann R, Schmitt M, Schmitt G, Franke C, Wilke H. Chemoradiation with and without surgery in patients with locally advanced squamous cell carcinoma of the esophagus, 2005. J Clin Oncol;23:2310-2317.

56. Decoster L, Kenis C, Van Puyvelde K, Flamaing J, Conings G, De Greve J, Mets T, Milisen K, Lobelle JP, Wildiers H. The influence of clinical assessment (including age) and geriatric assessment on treatment decisions in older patients with cancer, 2013. J Geriatr Oncol;4:235-241.

57. Kenis C, Bron D, Libert Y, Decoster L, Van Puyvelde K, Scalliet P, Cornette P, Pepersack T, Luce S, Langenaeken C, Rasschaert M, Allepaerts S, Van Rijswijk R, Milisen K, Flamaing J, Lobelle JP, Wildiers H. Relevance of a systematic geriatric screening and assessment in older patients with cancer: results of a prospective multicentric study, 2013. Ann Oncol;24:1306-1312.

58. Papamichael D, Audisio RA, Glimelius B, de Gramont A, Glynne-Jones R, Haller D, Kohne CH, Rostoft S, Lemmens V, Mitry E, Rutten H, Sargent D, Sastre J, Seymour M, Starling N, Van Cutsem E, Aapro M. Treatment of colorectal cancer in older patients: International Society of Geriatric Oncology (SIOG) consensus recommendations 2013, 2015. Ann Oncol;26:463-476.

59. King G, Nielsen R. Why Propensity Scores Should Not Be Used for Matching, Working Paper, ed.

60. Lagergren J, Smyth E, Cunningham D, Lagergren P. Oesophageal cancer, 2017. Lancet.

61. Shapiro J, van Lanschot JJ, Hulshof MC, van Hagen P, van Berge Henegouwen MI, Wijnhoven BP, van Laarhoven HW, Nieuwenhuijzen GA, Hospers GA, Bonenkamp JJ, Cuesta MA, Blaisse RJ, Busch OR, Ten Kate FJ, Creemers GJ, Punt CJ, Plukker JT, Verheul HM, Bilgen EJ, van Dekken H, van der Sangen MJ, Rozema T, Biermann K, Beukema JC, Piet AH, van Rij CM, Reinders JG, Tilanus HW, Steyerberg EW, van der Gaast A, group Cs. Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): long-term results of a randomised controlled trial, 2015. Lancet Oncol;16:1090-1098.

62. Backemar L, Wikman A, Djarv T, Johar A, Lagergren P. Co-morbidity after oesophageal cancer surgery and recovery of health-related quality of life, 2016. Br J Surg;103:1665-1675.

63. Schandl A, Lagergren J, Johar A, Lagergren P. Health-related quality of life 10 years after oesophageal cancer surgery, 2016. Eur J Cancer;69:43-50.

64. Baba Y, Yoshida N, Shigaki H, Iwatsuki M, Miyamoto Y, Sakamoto Y, Watanabe M, Baba H. Prognostic Impact of Postoperative Complications in 502 Patients With Surgically Resected Esophageal Squamous Cell Carcinoma: A Retrospective Single-institution Study, 2016. Ann Surg;264:305-311.

65. Lauren P. The Two Histological Main Types of Gastric Carcinoma: Diffuse and So-Called Intestinal-Type Carcinoma. An Attempt at a Histo-Clinical Classification, 1965. Acta Pathol Microbiol Scand;64:31-49.

Summary

Summary

This thesis aims to optimise care and outcomes for patients with oesophageal and gastric cancer in daily clinical practice.

The thesis starts by assessing the magnitude of 'missed' cancers among patients with a Barrett's oesophagus who progress to oesophageal adenocarcinoma or high-grade dysplasia (**chapter 2**). For this study patients from the Northern Ireland Barrett's Oesophagus Register diagnosed between 1993 and 2010 were linked to the Northern Ireland Cancer Registry to identify patients who developed oesophageal adenocarcinoma or high-grade dysplasia. A 'missed' case was defined as a diagnosis within 3-12 months following Barrett's oesophagus diagnosis. Results demonstrate that oesophageal adenocarcinoma was 'missed' at index Barrett's oesophagus endoscopy in up to 13% of all Barrett's oesophagus patients and 9% of non-dysplastic Barrett's oesophagus patients who progressed, which was significant but substantially lower than previously reported estimates.

Although oesophageal and gastric cancer surgery is centralised in the Netherlands, the disease is often diagnosed in hospitals which do not perform these procedures. Therefore, the objective of the next two studies is to investigate the influence of hospital of diagnosis on the probability of receiving curative treatment and its impact on survival among patients with oesophageal and gastric cancer (**chapter 3 and 4**). For these studies patients with potentially curable oesophageal or gastric cancer tumours diagnosed between 2005 and 2013 were selected from the Netherlands Cancer Registry. Curative treatment was defined as receiving surgery with or without neoadjuvant chemoradiotherapy, definitive chemoradiotherapy or an endoscopic tumour resection for oesophageal cancer. For gastric cancer patients, surgery was considered as curative treatment. The probability to receive curative treatment was defined as the proportion of patients diagnosed in a hospital that eventually underwent curative treatment, regardless of the hospital in which those treatments were undertaken. After adjustment, the proportion of oesophageal cancer patients receiving curative treatment ranged from 50% to 82% and from 48% to 78% for patients with gastric cancer in 2010-2013, depending on hospital of diagnosis. Moreover, patients diagnosed in hospitals with a low probability of undergoing curative treatment had a worse overall survival in the period 2010-2013 (oesophageal cancer HR=1.15 95%CI 1.07-1.24; gastric cancer HR=1.21; 95%CI 1.04-1.41). These results indicates that treatment decision-making in oesophageal and gastric cancer patients may be improved.

The next study evaluates the impact of centralising gastric cancer surgery in the Netherlands for all gastric cancer patients (**chapter 5**). For this study all patients diagnosed in the Netherlands between 2009-2011 and 2013-2015 with gastric adenocarcinoma were included. Outcomes in the period before centralisation (2009-2011) were compared to the period after centralisation (2013-2015).Resection rates slightly increased from 38% pre-centralisation to 41% post-centralisation (P=0.026). Postoperative 90-day mortality rates dropped from 11% to 7% during the time periods (P<0.01). Two-year overall survival rates increased from 55% to 58% for patients who had surgery (P=0.03) and from 27% to 30% for all patients (P=0.01), whereas the median overall survival of non-surgically treated patients remained stable (P=0.46). Improvements remained after adjustment for case-mix however, adjustment for hospital volume attenuated

this association for surgically treated patients. Results demonstrated a reduced postoperative mortality for surgically treated patients and an improved survival for all gastric cancer patients in the period after centralisation. Although other mechanisms may play a role, the fact that survival improved for both surgically treated patients and for all patients irrespective of treatment, but not among patients who did not undergo surgery, suggests that advances in (peri-)operative treatment and factors closely related to surgical treatment have made an important contribution to these improvements. Moreover, period of resection was correlated with hospital volume for patients who underwent surgery.

In several European countries perioperative chemotherapy for resectable gastric cancer is recommended based on the results of the UK MAGIC trial. However, little is known about its use in daily clinical practice. Therefore, the aim of **chapter 6** is to examine the use of perioperative treatment and its impact on survival in the Netherlands. For this study patients diagnosed with potentially resectable gastric cancer between 2006 and 2014 were selected from the Netherlands Cancer Registry. Results revealed that still 74% of the patients was not treated with perioperative treatment in 2014. In addition, postoperative treatment was not administered to 43% of the patients who started with preoperative chemotherapy followed by surgery in 2014. Cox regression analysis showed a better overall survival for patients who underwent perioperative treatment compared to patients who underwent preoperative treatment only (HR=0.80 95%CI 0.70-0.93; propensity matched sample: HR=0.84 95%CI 0.71-0.99). However, even after propensity score matching, patient groups may not be completely comparable and confounding due to nonrandomised assignment still exists.

If gastric cancer patients are able to undergo perioperative chemotherapy the optimal timing of chemotherapy after surgery seems equivocal. Therefore, the next study assesses the influence of timing of adjuvant chemotherapy on overall survival in patients receiving perioperative chemotherapy for gastric cancer (**chapter 7**). Data from patients undergoing perioperative chemotherapy for gastric adenocarcinoma in the period 2010-2014 were extracted from the Netherlands Cancer Registry. Half of the patients started within 6 weeks after surgery with chemotherapy (Interquartile range 4.9 – 7.7 weeks). A delayed start of adjuvant chemotherapy was associated with a longer hospital stay. After adjustment for case-mix factors, survival was comparable between patients who started within 6 weeks after surgery and patients who started between 6-8 and >8 weeks after surgery. These results suggest that the early postoperative period may be safely used for recovery and optimizing patients for the start of adjuvant chemotherapy.

As stated previously in this thesis many patients with oesophageal and gastric cancer may be unfit for surgery because of severe fragility, comorbidity and a poor nutritional status. Definitive chemoradiotherapy is considered to be a good alternative in patients with oesophageal cancer not eligible for oesophagectomy. However, little is known about the impact of comorbidity on the choice of curative treatment, i.e. definitive chemoradiotherapy or neoadjuvant chemoradiotherapy followed by surgery. Therefore, the aim of **chapter 8** is to assess the effect of age and comorbidity on the type of curative treatment in patients with oesophageal cancer. All patients with potentially curable oesophageal cancer treated with definitive chemoradiotherapy or neoadjuvant chemoradiotherapy followed by surgery, diagnosed in the South East of the Netherlands between 2004 and 2014 were included. Having an older age

(≥ 75 years) and multiple comorbidities was associated with a higher probability to receive definitive chemoradiotherapy compared to neoadjuvant chemoradiotherapy and surgery. Survival was better for oesophageal adenocarcinoma patients who underwent neoadjuvant chemoradiotherapy followed by surgery instead of definitive chemoradiotherapy despite the number of comorbidities, whereas survival was comparable for patients with oesophageal squamous cell carcinoma having multiple comorbidities or being 75 years or older.

Elderly patients represent a substantial proportion of the patients with oesophageal and gastric cancer. However, most treatment strategies and guidelines are based on clinical trials in which elderly patients are largely excluded. Therefore, the next study investigates treatment patterns and the impact of treatment strategies on overall survival among elderly patients (≥ 75 years) with potentially curable oesophageal cancer (**chapter 9**). Results revealed an increased use of definitive chemoradiotherapy in elderly patients from 1.9% to 20% as well as in younger patients from 5.2% to 17% in the period 2003-2013. Approximately 16% of the elderly patients underwent surgery and this proportion remained stable over time, whereas the use of surgery increased from 60% to 67% for young patients. Due to the increase in definitive chemoradiotherapy, treatment with curative intent doubled among the elderly patients from 17% in 2003 to 37% in 2013. However, the proportion of younger patients receiving curative treatment was still significantly higher in 2013 (84%). After adjustment, survival was better for elderly patients with an adenocarcinoma who underwent neoadjuvant chemo(radio)therapy followed by surgery instead of definitive chemoradiotherapy, whereas survival was comparable for patients with a squamous cell carcinoma.

Many patients with oesophageal and gastric cancer have metastatic disease at time of diagnosis (approximately 40%). The study in **chapter 10** aims to assess trends in treatment and survival of young (< 70 years) and older (≥ 70 years) patients with metastasised gastric cancer diagnosed between 1989 and 2013. Palliative resection rates significantly decreased in young and older patients from 25% to 3% and from 26% to 5%, respectively, whereas the use of chemotherapy increased from 15% to 51% for young patients and from 2% to 21% of the older patients. Treatment among younger patients increased from 42% to 60% due to the increase in chemotherapy, while the proportion of older patients treated with chemotherapy, surgery or both remained stable (approximately 30%). Despite the changes in treatment, survival remained stable over time for all patients, even after adjustment for several clinicopathological factors.

Treatment for oesophageal cancer has evolved due to developments including the centralisation of surgery and introduction of neoadjuvant chemoradiotherapy. The last study (**chapter 11**) in this thesis evaluates trends in stage distribution, treatment and survival of oesophageal cancer patients between 1989 and 2014 in the Netherlands. Results demonstrated that 5-year overall survival rates more than doubled in the last 26 years from 8% to 22% for all patients particularly from 2005 onwards. Furthermore, the percentage of patients with an unknown tumour stage decreased from 34% to 10%, while the percentage of patients with a metastatic disease increased from 21% to 34%. Among the surgically treated patients 32% underwent a resection in a high-volume hospital (performing 20 or more procedures per year) in 2005 which increased to 92% in 2014. In addition, the use of neoadjuvant chemoradiotherapy increased for non-metastatic patients with an adenocarcinoma or squamous cell carcinoma from respectively 4.3% and 2.3% in 2000-2004 to 43% and 26% in 2010-2014.

Nederlandse samenvatting

(Dutch summary)

Inleiding

Kanker

Door de naoorlogse geboortegolf, stijgende levensverwachting en veranderingen in leefstijl neemt het aantal nieuwe patiënten met kanker toe in Nederland. Kanker, ook wel een kwaadaardige tumor genoemd, is een ongecontroleerde deling van lichaamscellen. Per dag vinden miljoenen celdelingen plaats in ons lichaam. Hierbij kunnen kleine foutjes optreden. Deze foutjes worden normaal gesproken gerepareerd of beschadigde cellen worden opgeruimd door het afweersysteem. Indien dit niet gebeurd kan de cel ongecontroleerd gaan delen en ingroeien in omliggende weefsels. Soms zaaien ze uit naar andere delen van het lichaam. We noemen dat uitzaaiingen van kanker.

In 2016 hebben ruim 108.000 mensen kanker gekregen in Nederland. Huidkanker is in 2016 de meest voorkomende vorm van kanker bij mannen en vrouwen samen. Borstkanker is de meest voorkomende vorm van kanker bij vrouwen en prostaatkanker de meest voorkomende vorm van kanker bij mannen. Gelukkig is het aantal mensen dat kanker overleeft de afgelopen jaren aanzienlijk toegenomen. Door het eerder ontdekken van de kanker en betere behandelingen genezen er steeds meer mensen van kanker.

Slokdarm- en maagkanker

Slokdarmkanker is momenteel de 8e meest voorkomende kankersoort onder mannen in Nederland. In 2016 kregen ruim 2.500 patiënten de diagnose slokdarmkanker, met name mannen in de leeftijdscategorie 60 tot 80 jaar. Het aantal mensen dat jaarlijks wordt gediagnosticeerd met slokdarmkanker neemt toe. De toename is vooral toe te schrijven aan een stijging van het adenocarcinoom, een vorm van slokdarmkanker die ontstaat als gevolg van overgewicht en reflux, oftewel het terugstromen van maagzuur in de slokdarm. In tegenstelling tot de stijging van het aantal patiënten met slokdarmkanker, is er een daling in het aantal patiënten dat jaarlijks gediagnosticeerd wordt met maagkanker. Deze daling heeft te maken met een lagere kans op besmetting met de Helicobacter pylori bacterie door verbeterde hygiëne en behandeling met antibiotica. De Helicobacter pylori bacterie kan in de maag overleven en leiden tot maagslijmvliesontsteking en maagkanker. Daarnaast wordt de afname in maagkanker gerelateerd aan de komst van de koelkast, waardoor minder gebruik wordt gemaakt van zout-gerelateerde conserveringsmethoden.

Een Barrett-slokdarm is het meest bekende voorstadium van slokdarmkanker. Bij mensen met een Barrett-slokdarm is het onderste deel van de slokdarm bekleed met ander weefsel dan normaal. Het weefsel is roze tot zalmkleurig vergelijkbaar met het weefsel van de maag. Ondanks dat de kans op slokdarmkanker hoger is voor patiënten met een Barrett-slokdarm, is de kans op het krijgen van deze ziekte klein. Minder dan vijf procent van de mensen met een Barrett-slokdarm krijgt uiteindelijk slokdarmkanker. Het is onduidelijk waarom sommige mensen met een Barrett-slokdarm wel slokdarmkanker krijgen en anderen niet. Daarom worden patiënten met een Barrett-slokdarm regelmatig gecontroleerd middels endoscopie. Dat is een onderzoek, waarmee de arts de slokdarm en de maag aan de binnenkant kan bekijken. Tevens kunnen er stukjes weefsel worden weggenomen om te controleren op aanwezigheid van afwijkende, onrustige cellen.

Bij diagnose zijn patiënten met slokdarm- of maagkanker gemiddeld 70 jaar oud. De behandeling gericht op genezing van slokdarm- en maagkanker bestaat doorgaans uit chemotherapie, radiotherapie (bestraling) of een operatie. Vaak wordt een combinatie van deze behandelingen gegeven. Bij patiënten met slokdarmkanker zonder uitzaaiingen wordt meestal gestart met een combinatie van chemotherapie en radiotherapie (chemoradiotherapie) gevolgd door een operatie. Patiënten met maagkanker krijgen doorgaans de aanbeveling om te starten met chemotherapie, gevolgd door een operatie en nogmaals chemotherapie. Helaas heeft ongeveer 40% van de patiënten al uitzaaiingen bij diagnose, waardoor genezing in veel gevallen niet meer mogelijk is. Deze patiënten kunnen vaak wel palliatief worden behandeld met chemotherapie, soms in combinatie met radiotherapie, om het leven te verlengen of om de kwaliteit van leven te optimaliseren. Zo'n palliatieve behandeling is afhankelijk van de conditie van de patiënt en de omvang van de ziekte. Indien patiënten niet meer in aanmerking komen voor palliatieve chemotherapie, kan er een stent worden geplaatst om de voedselpassage te waarborgen.

Chirurgie maakt een belangrijk deel uit van de behandeling gericht op genezing van slokdarm- of maagkanker. Het gaat hierbij om complexe operaties met risico's op complicaties en sterfte. Om met name de sterfte te verminderen en de overleving te verbeteren na deze complexe operaties, is men gestart met een proces van concentratie van deze chirurgische behandelingen. Dat wil zeggen dat alleen ziekenhuizen die minimaal twintig slokdarmkanker- of minimaal twintig maagkankeroperaties per jaar uitvoeren deze behandeling nog mogen uitvoeren. Dit betekent in de praktijk dat een deel van de patiënten met slokdarm- of maagkanker na het stellen van de diagnose doorverwezen moet worden naar een gespecialiseerd ziekenhuis voor een operatie.

Doel van dit proefschrift

Het onderzoek in dit proefschrift richt zich op verschillende veranderingen en uitdagingen in de diagnostisering en behandeling van patiënten met slokdarm- of maagkanker. De belangrijkste doelstellingen van dit proefschrift zijn als volgt:

- Evalueren van zorg aan patiënten met een Barrett-slokdarm, waarbij de nadruk ligt op de kwaliteit van de endoscopische controle op verdere ontwikkeling van weefsel tot een kwaadaardige tumor.
- Bepalen wat de invloed is van het ziekenhuis van diagnose op de kans om een behandeling te krijgen, gericht op genezing voor patiënten met slokdarm- of maagkanker.
- Bekijken wat het effect is van concentratie van chirurgie in gespecialiseerde ziekenhuizen op de overleving van patiënten met maagkanker.
- Bestuderen van trends in de behandeling en de invloed daarvan op de overleving voor specifieke groepen van patiënten met slokdarm- of maagkanker in de dagelijkse klinische praktijk.

Onderzoeksgegevens

Om deze onderzoeksvragen te beantwoorden, heb ik gebruik gemaakt van de Nederlandse Kankerregistratie (NKR). Dat is een database met betrouwbare en objectieve gegevens van alle gevallen van kanker. Vanaf 1989 zijn de gegevens op landelijk niveau beschikbaar. De NKR wordt gebruikt voor wetenschappelijk onderzoek, maar ook voor het evalueren van bevolkingsonderzoeken en naleving van richtlijnen voor de behandeling en het ontwikkelen van beleid door zorginstellingen en de overheid.

Belangrijkste bevindingen van dit proefschrift

Dit proefschrift start met een studie naar de kwaliteit van de endoscopische controle onder patiënten met een Barrett-slokdarm (**hoofdstuk 2**). Hiervoor is gebruik gemaakt van de Noord-Ierse kankerregistratie en een register met alle patiënten met een Barrett-slokdarm in Noord-Ierland. Deze twee datasets hebben we aan elkaar gekoppeld om te onderzoeken welke patiënten met een Barrett-slokdarm uiteindelijk slokdarmkanker hebben ontwikkeld. Vervolgens hebben we onderzocht hoeveel tijd er zat tussen de diagnose Barrett-slokdarm en de diagnose slokdarmkanker. Indien bij patiënten binnen drie tot twaalf maanden na de diagnose Barrett-slokdarm ook de diagnose slokdarmkanker werd gesteld, hebben we aangenomen dat de aanwezigheid van slokdarmkanker ten tijde van de diagnose Barrett-slokdarm is gemist.

Uit de resultaten van deze studie blijkt dat bij 13% van de patiënten met een Barrett-slokdarm die slokdarmkanker ontwikkelden de aanwezigheid van kwaadaardig tumorweefsel was gemist op het moment dat de diagnose Barrett-slokdarm werd gesteld. Dit percentage is relatief hoog, maar lager dan in eerdere studies is gevonden. Het is echter belangrijk om dit percentage te relativeren aangezien het hierbij gaat om 0,3% van alle patiënten die in Noord-Ierland met een Barrett slokdarm zijn gediagnosticeerd in de periode 1993-2000. Het blijft een uitdaging om patiënten met een Barrett-slokdarm te identificeren die een hogere kans hebben op het ontwikkelen van slokdarmkanker.

Door concentratie van slokdarm- en maagkankerchirurgie is het aantal ziekenhuizen waar een operatie wordt uitgevoerd gedaald, terwijl de diagnose in elk ziekenhuis kan worden gesteld. Dat betekent dat in de praktijk een toenemend aantal patiënten moet worden doorverwezen voor een operatie. In **hoofdstuk 3 en 4** beschrijven we de resultaten van twee studies naar de invloed van het ziekenhuis van diagnose op de kans om een behandeling te krijgen gericht op genezing van slokdarm- en maagkanker. Voor deze studies selecteerden we patiënten uit de Nederlandse Kankerregistratie die gediagnosticeerd waren met niet-uitgezaaide slokdarm- of maagkanker in de periode 2005 tot 2013. De resultaten van deze studies laten aanzienlijke verschillen zien tussen de ziekenhuizen van diagnose voor wat betreft de kans op een behandeling gericht op genezing voor slokdarm- of maagkanker, ongeacht in welk ziekenhuis de patiënt uiteindelijk werd behandeld na eventuele doorverwijzing. Zo varieerde de kans op een behandeling gericht op genezing van slokdarmkanker van 50% tot 82% tussen ziekenhuizen en van maagkanker van 48% tot 78%. Tevens werd een relatie gezien tussen de kans op het krijgen van een behandeling op basis van het ziekenhuis van diagnose en de overleving van patiënten met slokdarm- of maagkanker. Patiënten gediagnosticeerd in

een ziekenhuis met een hogere kans op een behandeling gericht op genezing hadden een betere overleving dan patiënten gediagnosticeerd in ziekenhuizen met een lagere kans op een dergelijke behandeling.

De conclusie van deze studies luidt dat de gevonden variatie tussen ziekenhuizen en het effect hiervan op de overleving suggereert dat de besluitvorming rondom de behandeling van slokdarm- en maagkanker in Nederland nog verder kan worden geoptimaliseerd. Verschillen in werkwijze en samenstelling van het multidisciplinair overleg (MDO) tussen ziekenhuizen kunnen een verklaring zijn voor de variatie in de kans op het krijgen van een behandeling. In Nederland vindt in alle ziekenhuizen op één of meerdere momenten in de week een MDO plaats om nieuwe patiënten met kanker te bespreken. Het zou kunnen dat niet alle benodigde, tumorspecifieke expertise binnen dit overleg vertegenwoordigd was of dat externe tumorspecifieke expertise niet (tijdig) bij de besluitvorming werd betrokken. Vooral bij complexe behandelingen, zoals bij slokdarm- en maagkanker, is het uitermate belangrijk dat de juiste kennis en ervaring beschikbaar is binnen het MDO. Regionale, tumorspecifieke MDO's in aanwezigheid van tumorspecifieke experts zouden de variatie tussen ziekenhuizen kunnen verminderen. Dit kan mogelijk bijdragen aan verbetering van de overlevingskansen van patiënten met slokdarm- en maagkanker. Vervolgonderzoek, gesubsidieerd door KWF Kankerbestrijding, zal uitwijzen welke factoren leiden tot variatie in behandeling en welke effecten dit heeft op de overleving van patiënten met slokdarm- of maagkanker.

Hoofdstuk 5 van dit proefschrift evalueert de invloed van de concentratie van chirurgie voor patiënten met maagkanker in Nederland. Vanaf 2012 moeten ziekenhuizen minimaal tien maagkankeroperaties per jaar uitvoeren en in 2013 is dit aantal verhoogd naar twintig per jaar. Deze regels zijn met name opgesteld om de sterfte na een maagkankeroperatie te verminderen en de overleving te verbeteren. Voor deze studie hebben we patiënten uit de NKR geselecteerd die gediagnosticeerd zijn met maagkanker in de periode 2009-2011 (voor concentratie van deze chirurgie) en 2013-2015 (na concentratie). De uitkomsten van patiënten gediagnosticeerd in deze twee periodes zijn met elkaar vergeleken. We zagen dat de sterfte binnen 90 dagen na de operatie daalde van 11% naar 7%. Ook nam het percentage patiënten dat nog in leven was binnen twee jaar na de diagnose toe van 27% naar 30%. Ook na correctie voor verschillen in patiëntkarakteristieken (onder andere leeftijd en tumorstadium) tussen beide periodes, was de overleving van alle patiënten met maagkanker beter in de periode na introductie van concentratie van deze chirurgie. Deze bevindingen suggereren dat de zorg aan patiënten met maagkanker verbetert indien men deze patiënten vaker behandelt. Hoe vaker een arts een operatie uitvoert, hoe beter hij of zij dit doet. Ook is het aannemelijk dat artsen en verpleegkundigen een complicatie na een maagoperatie eerder herkennen en kunnen behandelen, indien zij meer patiënten behandelen. Daarnaast is het mogelijk dat artsen de mogelijkheden van chemotherapie voor een patiënt beter kunnen inschatten indien zij vaker patiënten met maagkanker behandelen.

In verschillende Europese landen worden patiënten met maagkanker behandeld met chemotherapie, gevolgd door een operatie en daarna nogmaals chemotherapie. Deze combinatie wordt ook wel perioperatieve chemotherapie genoemd. Deze behandelkeuze is het gevolg van een klinische studie uit 2006 waarin is aangetoond dat toevoeging van chemotherapie voor en na een operatie bijdraagt aan aanzienlijke verbetering van de overleving van patiënten met

maagkanker. In deze studie werden echter patiënten geïncludeerd die voldeden aan strikte selectiecriteria die geen rekening houden met eigenschappen van patiënten die we zien in de dagelijkse klinische praktijk. Hierbij kan je denken aan de selectie van vitale patiënten met weinig andere ziektebeelden. Oudere patiënten worden hierdoor vaak geëxcludeerd. Door deze strikte selectiecriteria gelden de resultaten van dergelijke klinische studies niet zonder meer voor alle patiënten met maagkanker. Daarom beschrijven we in **hoofdstuk 6** de toepassing van perioperatieve chemotherapie en de invloed daarvan op de overleving voor patiënten met maagkanker in de dagelijkse klinische praktijk. In deze studie includeerden we patiënten met maagkanker die in aanmerking komen voor perioperatieve chemotherapie op basis van tumorstadium en zijn gediagnosticeerd in de periode 2006-2014. De uitkomsten van deze studie laten zien dat in 2014 bijna driekwart (74%) van de patiënten niet werd behandeld met perioperatieve chemotherapie, terwijl zij daar qua tumor stadium wel voor in aanmerking komen. Daarnaast krijgt bijna de helft van de patiënten die chemotherapie kregen vóór een operatie géén chemotherapie ná de operatie.

Er zijn verschillende redenen te noemen waarom patiënten geen perioperatieve chemotherapie kregen. Patiënten met maagkanker zijn gemiddeld 72 jaar oud, hebben vaak te maken met bijkomende ziekten, ondervoeding en gewichtsverlies. Indien deze patiënten starten met chemotherapie zijn er ook diverse oorzaken waarom zij daarna geen operatie krijgen, zoals bijwerkingen tijdens of na de chemotherapie of omdat de ziekte toch blijkt te zijn uitgezaaid naar andere plaatsen in het lichaam. Daarnaast kunnen patiënten te maken hebben met complicaties na de operatie, waardoor zij niet meer in staat zijn om chemotherapie te krijgen. Aangezien slechts een klein deel van de patiënten met maagkanker de huidige behandeling met perioperatieve chemotherapie wil volgen en daadwerkelijk kan afronden, is het de vraag of dit de beste behandeling is voor deze specifieke groep patiënten. Voor zover we nu weten lijkt dit de beste behandeling, maar de resultaten van deze studie suggereren dat we in de toekomst opzoek moeten naar een andere behandeling die beter wordt verdragen en minder bijwerkingen heeft.

Indien patiënten met maagkanker wel in staat zijn om chemotherapie te krijgen na de operatie, dan lijkt het momenteel onduidelijk wanneer zij daarmee moeten starten. In de Nederlandse richtlijn voor de behandeling van maagkanker wordt namelijk geen tijdsinterval vermeld. Daarom onderzoeken we in **hoofdstuk 7** het effect van de timing van chemotherapie na een behandeling met chemotherapie gevolgd door een operatie op de overleving van patiënten met maagkanker. Voor dit onderzoek selecteerden we patiënten met maagkanker die chemotherapie, een operatie en daarna nogmaals chemotherapie kregen in de periode 2010-2014. We zagen dat de helft van de patiënten binnen zes weken na de operatie startte met chemotherapie. Een langer herstel na de operatie, bijvoorbeeld door complicaties van de operatie, ging vaak gepaard met een latere start met chemotherapie. Nadat we hadden gecorrigeerd voor verschillen tussen patiënten die eerder dan wel later met chemotherapie waren gestart, zagen we dat patiënten die binnen zes weken waren gestart niet per se een betere overleving hadden dan patiënten die binnen zes tot twaalf weken na de operatie met chemotherapie waren gestart. Deze resultaten ondersteunen het beeld dat er ruimte is om de patiënten eerst te laten herstellen van de operatie.

Zoals al eerder is beschreven in deze samenvatting, kunnen patiënten met slokdarm- en maagkanker minder fit zijn voor een operatie vanwege andere aanwezige ziektebeelden, ondervoeding en gewichtsverlies. Definitieve chemoradiotherapie wordt in toenemende mate beschouwd als een goed alternatief voor patiënten met slokdarmkanker die minder geschikt zijn voor een operatie. Definitieve chemotherapie is het gelijktijdig volgen van chemotherapie en radiotherapie zonder een operatie. Deze behandeling is bedoeld om de patiënt te genezen. In **hoofdstuk 8** hebben we gekeken wat de invloed is van leeftijd en andere aanwezige ziektebeelden op de keuze van een behandeling gericht op genezing en op de overleving. Voor deze studie hebben we behandeling gedefinieerd als definitieve chemoradiotherapie of chemoradiotherapie gevolgd door een operatie. We hebben patiënten met slokdarmkanker geselecteerd uit de Nederlandse Kankerregistratie die deze behandelingen kregen in de periode 2004 tot 2014. Zoals verwacht hadden patiënten van 75 jaar en ouder of met twee of meer andere ziektebeelden een hogere kans om definitieve chemoradiotherapie te krijgen. Echter, de overleving van patiënten met een adenocarcinoom (een type slokdarmkanker) was beter wanneer zij chemoradiotherapie gevolgd door een operatie kregen, dit ongeacht leeftijd en het aantal andere ziektebeelden. Terwijl de overleving voor patiënten met een plaveiselcelcarcinoom, een ander type slokdarmkanker, gelijk was tussen beide behandelingen voor oudere patiënten en patiënten met twee of meer andere ziektebeelden. Dit suggereert dat definitieve chemoradiotherapie overwogen kan worden bij patiënten met slokdarmkanker (type plaveiselcelcarcinoom) die 75 jaar of ouder zijn of twee of meer andere ziektebeelden hebben.

Een aanzienlijk deel van de patiënten die gediagnosticeerd worden met slokdarm- of maagkanker is 70 jaar of ouder. De effectiviteit van medische behandelingen wordt vaak bepaald op basis van klinische studies, waarbij oudere patiënten grotendeels worden uitgesloten. In **hoofdstuk 9** evalueren we de behandeling en overleving van oudere patiënten met slokdarmkanker die op basis van de omvang van hun ziekte in aanmerking zouden kunnen komen voor een behandeling gericht op genezing. In de periode 2003 tot 2013 zagen we een flinke toename van het percentage patiënten dat definitieve chemoradiotherapie onderging bij zowel jongere als oudere patiënten met slokdarmkanker. Zo kreeg 2% van de oudere patiënten in 2003 definitieve chemoradiotherapie, terwijl in 2013 20% van de oudere patiënten deze behandeling kreeg. Het percentage oudere patiënten dat geopereerd werd bleef stabiel, ongeveer 16%. Door de toename van definitieve chemoradiotherapie onder oudere patiënten verdubbelde het aandeel op genezing gerichte behandelingen van 17% in 2003 tot 37% in 2013. Echter, 37% is laag vergeleken met jongere patiënten. In deze laatste leeftijdscategorie krijgt 84% een behandeling gericht op genezing. Vergelijkbaar met de resultaten uit hoofdstuk 8, was de overleving van oudere patiënten met een adenocarcinoom (een type slokdarmkanker) beter bij patiënten die chemoradiotherapie gevolgd door een operatie kregen vergeleken met patiënten die definitieve chemoradiotherapie kregen. De overleving na deze behandelingen was vergelijkbaar voor oudere patiënten met een plaveiselcelcarcinoom, een ander type slokdarmkanker.

Ongeveer 40% van de patiënten met slokdarm- en maagkanker heeft een uitgezaaide ziekte op het moment van diagnose. In **hoofdstuk 10** onderzoeken we de veranderingen in de behandeling en overleving van jongere en oudere patiënten met uitgezaaide of vergevorderde maagkanker die gediagnosticeerd zijn in de periode 1989 en 2013. Deze patiënten kunnen

in aanmerking komen voor een operatie ter verlenging van hun leven, hierna aangeduid als "palliatieve operatie". Uit de analyses die voor dit proefschrift zijn uitgevoerd, blijkt dat het aandeel palliatieve operaties tussen 1989 en 2013 aanzienlijk daalde, zowel bij jongere patiënten (van 25% naar 3%) als bij oudere patiënten (van 26% naar 5%). Tegelijkertijd is het percentage patiënten dat chemotherapie kreeg aanzienlijk gestegen van 15% naar 51% bij jongere patiënten en van 2% naar 21% bij oudere patiënten. Ondanks deze veranderingen in behandeling zien we geen verbetering in de overleving bij zowel jongere als oudere patiënten met uitgezaaide of vergevorderde maagkanker. De veranderingen in palliatieve, levensverlengende, behandelingen hangen mogelijk samen met een verbetering in diagnostiek en de beschikbaarheid van nieuwe systemische behandelingen (waaronder chemotherapie). Bovendien kan de daling in het aantal palliatieve operaties verklaard worden door een wijziging in de Nederlandse richtlijnen die vanaf 2009 is geïmplementeerd. Daarin wordt geadviseerd om palliatieve operaties uitsluitend te geven aan patiënten tot 70 jaar met een minimaal uitgezaaide of vergevorderde ziekte.

Verschillende ontwikkelingen hebben plaatsgevonden in de behandeling van slokdarmkanker. Vanaf 2008 worden patiënten steeds vaker behandeld met chemoradiotherapie voorafgaand aan de operatie om de tumor te verkleinen, zodat de operatie beter kan worden uitgevoerd. Een andere ontwikkeling betreft de concentratie van chirurgie voor patiënten met slokdarmkanker. Vanaf 2006 moeten ziekenhuizen minimaal tien slokdarmkankeroperaties per jaar uitvoeren en in 2011 is dit aantal verhoogd naar twintig per jaar. Deze regels zijn met name opgesteld om de sterfte na een slokdarmkankeroperatie te verminderen en de overleving te verbeteren. In **hoofdstuk 11** beschrijven we veranderingen in behandeling en overleving van patiënten met slokdarmkanker in de periode 1989 tot 2014. De uitkomsten laten zien dat de overleving van alle patiënten met slokdarmkanker de afgelopen 26 jaar meer dan verdubbeld is. De overleving van patiënten zonder uitzaaiingen is zelfs verdriedubbeld. In 2005 kreeg een derde van de geopereerde patiënten een operatie in een ziekenhuis dat meer dan twintig operaties per jaar uitvoerde, terwijl bijna alle geopereerde patiënten in 2014 een operatie kregen in een dergelijk ziekenhuis. De toename in de overleving van patiënten met slokdarmkanker kan worden toegeschreven aan de inzet van chemoradiotherapie voorafgaand aan de operatie en aan concentratie van slokdarmkankeroperaties. In de toekomst zou de overleving van deze patiënten mogelijk nog verder kunnen verbeteren door vroegere detectie van kwaadaardige tumoren, maar waarschijnlijk nog meer door de inzet van effectieve en gepersonaliseerde systemische behandelingen (waaronder chemotherapie).

Concluderende opmerkingen

De overleving van patiënten met slokdarmkanker is de afgelopen 26 jaar aanzienlijk toegenomen, waarschijnlijk door de inzet van chemoradiotherapie voorafgaand aan de operatie, maar ook door concentratie van slokdarmkankeroperaties in gespecialiseerde ziekenhuizen. De overleving voor patiënten met maagkanker lijkt eveneens te zijn toegenomen sinds de concentratie van maagkankeroperaties, die later is gestart dan de concentratie van slokdarmoperaties. Door deze complexe operaties te concentreren, is het waarschijnlijk dat de overleving van patiënten met maagkanker in de nabije toekomst nog verder verbetert. De gevonden variatie tussen ziekenhuizen wat betreft behandeling en het effect hiervan op de overleving van deze patiënten suggereert dat de besluitvorming rondom de zorg voor patiënten met slokdarm- en maagkanker

in Nederland nog verder kan worden geoptimaliseerd. Daarnaast is het belangrijk om de effecten van een behandeling te evalueren onder specifieke groepen patiënten. De onderzoeken in dit proefschrift dragen bij aan deze ontwikkeling, waarin steeds meer wordt gestreefd naar een behandeling op maat voor de individuele patiënt met slokdarm- of maagkanker.

List of publications

Publications included in this thesis

van Putten M, Johnston BT, Murray LJ, Gavin AT, McManus DT, Bhat S, Turkington RC, Coleman HG. 'Missed' oesophageal adenocarcinoma and high-grade dysplasia in Barrett's oesophagus patients: a large population-based study. United European Gastroenterology Journal 2017; Epub ahead of print.

van Putten M, Koëter M, van Laarhoven HWM, Lemmens VEPP, Siersema PD, Hulshof MCCM, Verhoeven RHA, Nieuwenhuijzen GAP. Hospital of diagnosis influences the probability of receiving curative treatment for esophageal cancer. Annals of Surgery 2018; 267(2): 303-310.

van Putten M, Verhoeven RHA, van Sandick JW, Plukker JTM, Lemmens VEPP, Wijnhoven BPL, Nieuwenhuijzen GAP. Hospital of diagnosis and probability of having surgical treatment for resectable gastric cancer. British Journal of Surgery 2016; 103(3): 233-241.

van Putten M, Nelen SD, Lemmens VEPP, Stoot JHMB, Hartgrink HH, Gisbertz SS, Spillenaar Bilgen EJ, Heisterkamp J, Verhoeven RHA, Nieuwenhuijzen GAP. Improved survival after centralisation of gastric cancer surgery in the Netherlands. Submitted.

van Putten M, Lemmens VEPP, Laarhoven HWM, Pruijt JFM, Nieuwenhuijzen GAP, Verhoeven RHA. Poor compliance with perioperative treatment in patients with resectable gastric cancer. Submitted.

Brenkman HJF, **van Putten M**, Visser E, Verhoeven RHA, Nieuwenhuijzen GAP, Slingerland M, van Hillegersberg R, Lemmens VEPP, Ruurda JP. Association between timing of adjuvant chemotherapy and overall survival in patients undergoing perioperative chemotherapy and gastrectomy for gastric cancer. Submitted.

Faiz Z, **van Putten M**, Verhoeven RHA, van Sandick JW, Nieuwenhuijzen GAP, van der Sangen MJC, Lemmens VEPP, Wijnhoven BPL, Plukker JTM. Impact of age and comorbidity on choice and outcome of two different treatment options for patients with potentially curable oesophageal cancer. Submitted.

Koëter M, **van Putten M**, Verhoeven RHA, Lemmens VEPP, Nieuwenhuijzen GAP. Definitive chemoradiation or surgery in elderly patients with potentially curable oesophageal cancer in the Netherlands: a nationwide population-based study on patterns of care and survival. Acta Oncologica 2018; Epub ahead of print.

Nelen SD, **van Putten M**, Lemmens VEPP, Bosscha K, de Wilt JHW, Verhoeven RHA. Effect of age on rates of palliative surgery and chemotherapy use in patients with locally advanced or metastatic gastric cancer. British Journal of Surgery 2017; 104(13): 1837-1846.

van Putten M, de Vos-Geelen J, Nieuwenhuijzen GAP, Siersema PD, Lemmens VEPP, Rosman C, van der Sangen MJC Verhoeven RHA. Long-term survival improvement in oesophageal cancer in the Netherlands. European Journal of Cancer 2018; Epub ahead of print.

Other publications

van Putten M, Verhoeven RHA, Koëter M, van Laarhoven HWM, van Sandick JW, Plukker JTM, Siersema PD, Hulshof MCCM, Wijnhoven BPL, Lemmens VEPP, Nieuwenhuijzen GAP. Ziekenhuis van diagnose beïnvloedt kans op curatieve behandeling voor slokdarm- en maagkanker. Nederlands Tijdschrift voor Geneeskunde 2018; in press.

Haj Mohammad N, Bernards N, **van Putten M**, Lemmens VEPP, van Oijen MGH, van Laarhoven HWM. Volume-outcome relation in palliative systemic treatment of metastatic oesophagogastric cancer. European Journal of Cancer 2017; 78: 28-36.

Bakens MJAM, van der Geest LGM, **van Putten M**, van Laarhoven HWM, Creemers GJ, Besselink MGH, Lemmens VEPP, de Hingh IHJT. The use of adjuvant chemotherapy for pancreatic cancer varies widely between hospitals: a nationwide population-based analysis. Cancer Medicine 2016; 5(10): 2825-2831.

van Putten M, Husson O, Mols F, Luyer MDP, van de Poll-Franse LV, Ezendam NPM. Correlates of physical activity among colorectal cancer survivors: results from the longitudinal population-based profiles registry. Journal of Supportive Care in Cancer 2016; 24(2): 573-583.

Mokadem I, **van Putten M**, Dijksterhuis W, Heuthorst L, Nieuwenhuijzen GAP, van Laarhoven HWM, Verhoeven RHA. Recurrence after preoperative chemotherapy and surgery for gastric adenocarcinoma: a multicenter study. To be submitted.

Dankwoord

(Acknowledgements)

Dankwoord

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Prof.dr. Lemmens, beste Valery, jij gaf mij de kans om dit promotieonderzoek uit te voeren. Bedankt voor jouw vertrouwen in mij als onderzoeker en voor alle keren dat je mij weer nieuwe energie gaf na afloop van een overleg. In jouw aanwezigheid startte ieder overleg met de broodnodige gesprekken over koetjes en kalfjes. Daarnaast heb ik veel bewondering voor jouw kennis van kankerepidemiologie en je altijd positieve instelling. Bedankt voor de fijne samenwerking!

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wilde zijn gedurende mijn master. Lonneke, ook jij wist mij vaak te inspireren door jouw passie voor kankeronderzoek. Erna, jij bent een hele zorgzame collega, iemand die zeker niet mocht ontbreken. Mieke, ik voelde me nooit bezwaard om vragen aan jou te stellen. Pauline, het was fijn om met jou over SAS te discussiëren. Felice, bedankt voor alle praktische tips in de eindfase van mijn promotieonderzoek. Gijs, waarom ben je niet eerder bij IKNL komen werken? Ik heb genoten van jouw aanwezigheid! En tot slot natuurlijk Amanda. We zijn tegelijk begonnen en tegelijk klaar met ons promotieonderzoek. Jij hebt echter enorme bergen moeten trotseren. Ik heb veel respect voor jou als collega, maar ook als mens. Bedankt dat je mijn paranimf wilt zijn!

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Margreet

Maart 2018

Curriculum Vitae

Curriculum Vitae

Margreet van Putten was born on the 14th of November 1989 in Deventer, the Netherlands. In 2008 she finished pre-university education at the Carmel College Salland in Raalte. Subsequently, she started to became a nurse at Windesheim University of Applied Sciences in Zwolle. During this study she worked in the Isala hospital, in care providing institutions and home care. Furthermore, she went to Surinam for a 3-month internship. After graduating from nursing school she started in 2012 with the premaster Health Sciences and in 2014 she completed the Master Health Sciences cum laude at the VU University Amsterdam. During her master she conducted scientific research at the Netherlands Comprehensive Cancer Organisation (IKNL). Subsequently, she started her PhD research at IKNL, location Eindhoven. Her research focused on the quality of care among patients with oesophageal or gastric cancer. As part of her PhD she performed a study at the Queen's University and Northern Ireland Cancer Registry in Belfast for a period of 3 months.
Margreet is living together with her boyfriend Jos in the rural area of Oirschot, the Netherlands.

PhD portfolio

PhD portfolio

Name PhD student:	Margreet van Putten
Erasmus MC Department:	Public Health / Netherlands Comprehensive Cancer Organisation (IKNL)
PhD period:	August 2014 – May 2018
Promotor:	Prof. dr. V.E.P.P. Lemmens
Copromotors:	Dr. G.A.P. Nieuwenhuijzen & Dr. R.H.A. Verhoeven

	Year	Workload Hours (ECTS)
Courses		
Basic course in Oncology, NVvO	2015	40 (1.4)
Multilevel analysis – EpidM, Vumc	2015	24 (0.9)
APC- analysis - from epidemiology to health promotion – NIHES	2015	8 (0.3)
Advanced course in epidemiologic methods – LUMC	2016	32 (1.1)
Internal course on survival analysis – by Paul Dickman from Karolinska Institute Sweden at IKNL	2016	24 (0.9)
Global Cancer Short Course – Queens University, Belfast, Northern Ireland	2016	32 (1.1)
Scientific integrity – Erasmus MC	2016	8 (0.3)
Oral presentations		
IKNL Symposium 'NKR in beweging'	2015	32 (1.1)
NVGE autumn meeting	2015	32 (1.1)
DUCG study evening	2015	32 (1.1)
10th National Barrett's symposium	2016	32 (1.1)
ESSO (2 presentations)	2016	64 (2.3)
IKNL symposium 'NKR naar buiten'	2017	32 (1.1)
Poster presentations		
2 posters ESMO GI	2017	32 (1.1)
1 poster IACR	2017	32 (1.1)
1 poster ESDE	2017	32 (1.1)
International conferences		
ESSO, Liverpool, United Kingdom	2014	32 (1.1)
10th National Barrett's symposium, London, United Kingdom	2016	8 (0.3)
ESSO, Krakow, Poland	2016	32 (1.1)
ECCO, Amsterdam, the Netherlands	2017	32 (1.1)
ESMO GI, Barcelona, Spain	2017	32 (1.1)
IACR, Utrecht, the Netherlands	2017	24 (0.9)
ESDE, Utrecht, the Netherlands	2017	24 (0.9)

	Year	Workload Hours (ECTS)
Dutch seminars and conferences		
NVGE autumn meeting	2015	16 (0.6)
IKNL symposium 'NKR in beweging'	2015	8 (0.3)
1th DUCG symposium	2015	8 (0.3)
2th 5D's congress	2016	8 (0.3)
Federaday 'Cancer and numbers'	2016	8 (0.3)
10th gastrointestinal symposium IKNL	2016	8 (0.3)
Satellite symposium translational research on oesophageal malignancies - EPGS	2016	8 (0.3)
Symposium, 'It is time to individualize multimodality treatment for oesophageal cancer'	2016	16 (0.6)
DICA congress	2017	16 (0.6)
2th DUCG symposium	2017	8 (0.3)
IKNL symposium 'NKR naar buiten'	2017	8 (0.3)
DUCG study evenings	2015-2018	32 (1.1)
Supervising Master's thesis		
Ibtissam Mokadem 'Recurrence after preoperative chemotherapy and surgery for gastric adenocarcinoma'	2016-2017	80 (3)
Vera Haagsman 'The impact of regional multidisciplinary team meetings on treatment decision making in patients with oesophageal and gastric cancer'	2017-2018	80 (3)
Teaching		
Lectures about cancer epidemiology for second-year medicine students, Erasmus MC	2016-2017	80 (3)
Other tasks		
3-month internship at Queens University Belfast, Northern Ireland	2016	240 (8.6)
Extending the registry and assessing the quality of the extended registry for oesophageal and gastric cancer	2015-2017	280 (10)
Provide training to registry clerks	2015-2017	40 (1.4)
Answering questions of registry clerks about the registry	2015-2018	40 (1.4)
Making regional reports about oesophageal and gastric cancer for hospitals	2015-2016	240 (8.6)
Total		**1896 (68)**