Hospital volume and outcome in locally advanced rectal cancer patients; results of a population-based study in The Netherlands

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Submitted

Abstract

Background

The treatment of rectal cancer mainly depends on the tumor stage. Clinically staged T1-3 rectal cancer (cT1-3) is treated by total mesorectal excision (TME) with or without neoadjuvant therapy, whereas cT4 rectal cancer requires a multimodality approach and often multivisceral surgery. The current study evaluates the outcome of cT1-3 and cT4 rectal cancer according to hospital volume.

Methods

This population-based study includes patients undergoing rectal cancer surgery between 2005 and 2013 in the Netherlands using data from the NCR. Cox-proportional hazards model was used for multivariable analysis of overall survival according to hospital volume. Hospitals were divided into low(1-20), medium(21-50) and high(>50 resections/year) volume for cT1-3 and into low(1-4), medium(5-9) and high(≥10 resections/year) volume for cT4 rectal cancer.

Results

A total of 14.050 confirmed cT1-3 patients and 2.104 cT4 patients underwent surgery. In cT1-3 rectal cancer, there was no significant difference in 5-year overall survival related to high, medium and low hospital volume (70% vs. 69% vs.69%). In cT4 rectal cancer, treatment in a high volume cT4 hospital was associated with a survival benefit compared to low volume cT4 hospitals (HR 0.81 95%CI 0.67-0.98) adjusted for non-treatment related confounders. There was increase in referral of cT4 rectal cancer to high volume hospitals, but the majority of patients was still treated in low volume hospitals.

Conclusion

Hospital volume was not associated with survival in cT1-3 rectal cancer. In cT4 rectal cancer, treatment in high volume cT4 hospitals was associated with an improved survival compared to low volume cT4 hospitals.

Introduction

Colorectal cancer is the third most common malignancy in the Western world and rectal cancer accounts for approximately one third of the colorectal cancer patients.[1] Outcome of rectal cancer has improved over the last two decades, mainly due to the introduction of improved imaging modalities, total mesorectal excision (TME) and neoadjuvant (chemo-)radiotherapy.[2-5]

Optimal treatment of rectal cancer is dependent on local tumor stage and the presence of distant metastases. Local tumor stage determines whether neoadjuvant (chemo-) radiotherapy should be administered to reduce local recurrence rate. In lower stages of rectal cancer, the effectiveness of neoadjuvant (chemo-)radiotherapy is limited, whereas in more advanced stages of rectal cancer (chemo-)radiotherapy is an essential part of the treatment.[6] It leads to tumor shrinkage, thereby facilitating complete resections and a decrease in local recurrence rate.[3,7]

Local tumor stage is also important to determine the optimal surgical treatment. Lower stages of rectal cancer can be treated by standard TME procedures or even rectal sparing surgery in selected patients.[8] Advanced stages of rectal cancer with tumors invading the mesorectal fascia often require a more radical surgical approach to achieve a complete resection. These procedures, such as extralevatory abdominoperineal resections and partial or total exenterations, require a surgical dissection beyond the standard TME plane.[9]

To improve the outcome of rectal cancer, the current Dutch standard indicates a minimum of 20 surgical resections of rectal cancer per year per hospital and the Dutch guideline advises centralization of care for patients with advanced stages of rectal cancer (i.e. clinically staged T4 and locally recurrent rectal cancer) in specialized colorectal cancer hospitals.[10] Due to the more complex treatment of the advanced stages of rectal cancer, a personalized 'tailor made' multimodality treatment is needed. Moreover, cT4 rectal cancer is relatively rare and exenterative surgery is technically demanding with higher amounts of blood loss, operation time and increased morbidity and mortality.[11] We hypothesize that hospital volumes may be more important in cT4 rectal cancer than in patients with cT1-3 rectal cancer. This study analyses the long-term results of cT1-3 and cT4 rectal cancer according to hospital volume in the Netherlands.

Patients and methods

Data collection

Data of all rectal cancer patients diagnosed between 2005 and 2013 in the Netherlands were retrieved from the nationwide population-based Netherlands Cancer Registry (NCR). Registration is mainly based on notification by the automated pathological archive

(PALGA) and the National Registry of Hospital Discharge Diagnosis. Trained registrars of the NCR collected data from the medical records of the different hospitals. The population based NCR database has a 95% completeness of cancer registrations.[12] Information concerning the cause of death was not available.

Study population

All patients undergoing surgery for rectal cancer were included. The following patient/tumour related variables were available: year of diagnosis, age, gender, clinical and pathological TNM stage, histopathology and the presence of synchronous distant metastases. Treatment related variables that were available were: neoadjuvant treatment, adjuvant treatment, hospital volume based on number of rectal cancer resections per year, type of surgical procedure (low anterior resection, abdominoperineal resection or proctocolectomy). Involvement of circumferential resection margin (CRM) was available from 2008 onwards.

Clinically staged T1-3 and T4 rectal cancer were analyzed separately. Patients with an unknown cT-stage were excluded from analysis, but were included in the determination of rectal cancer hospital volume. For cT1-3 rectal cancer, hospitals were divided into low volume hospitals (1-20 resections), medium volume hospitals (21-50 resections) and high volume hospitals (>50 resections), based on the total number of rectal cancer resections performed annually in one hospital. For cT4 rectal cancer, hospitals were divided into low (1-4 resections) medium (5-9 resections) and high (≥10 resections) volume based on cT4 rectal cancer resections performed annually in one hospital.

The TNM-classification was used according to the edition valid at the time of cancer diagnosis (6th edition for 2005-2009 and 7th edition for 2010-2013). The 7th edition included a distinction between cT4a (tumor penetrates the surface of the visceral peritoneum) and cT4b tumors (tumor invades or is adherent to surrounding organs or structures).

Endpoints

The primary endpoint was overall survival according to the total hospital volume for cT1-3 and cT4 rectal cancer.

Follow up

Vital status of patients was retrieved by linkage of the NCR to the nationwide municipal population registries network.

Statistical analysis

Data were reported as median (interquartile range) or mean (standard deviation) as appropriate. Categorical data were reported as count (percentage). The Chi-square was used for comparison of groups. For survival analysis, follow-up time was calculated from

date of diagnosis until date of death or end of follow-up. Patients who were alive at the end of follow-up were censored. Three and five-year survival rates were calculated by Kaplan-Meier analysis and comparisons between groups were made using log-rank tests. Multivariable Cox's proportional hazards analysis was performed to analyze differences in overall survival according to hospital volume. Variables with p-values <0.10 in the univariate analysis were included in the multivariable analysis. Only variables available for the whole study period were included in the multivariable analysis.

Results

16.154 patients underwent rectal cancer surgery and had a confirmed clinical T-stage, while in 6394 patients the cT-stage was unknown. Of those patients with a known cT-stage 14.050 patients (87%) had a cT1-3 tumor and 2.104 patients (13%) had a cT4 tumor.

cT1-3 rectal cancer

The baseline characteristics of the 14.050 patients with cT1-3 rectal cancer are outlined in *table I*. The majority of these patients underwent surgery in medium volume hospitals (62%), followed by high volume hospitals (21%) and low volume hospitals (17%). An increase was seen in patients treated in high volume hospitals (2005-2007: 13% vs. 2011-2013: 23%, p <0.001). Neoadjuvant chemoradiotherapy was administered more often to patients in high volume hospitals compared to medium volume and low volume hospitals (43% vs. 37% and 32%, p<0.001). High volume hospital hospitals performed less abdominoperineal resections (32% vs. 36% vs. 36%, p=0.002) and had a higher percentage of ypT0 stage (9% vs. 7% vs. 8%, P=0.01). There was no difference in nodal stage and CRM-involvement. Patients treated in low volume hospitals received adjuvant chemotherapy less often (11% in high and medium volume hospitals compared to 8% in low volume hospitals, p <0.001).

Outcomes

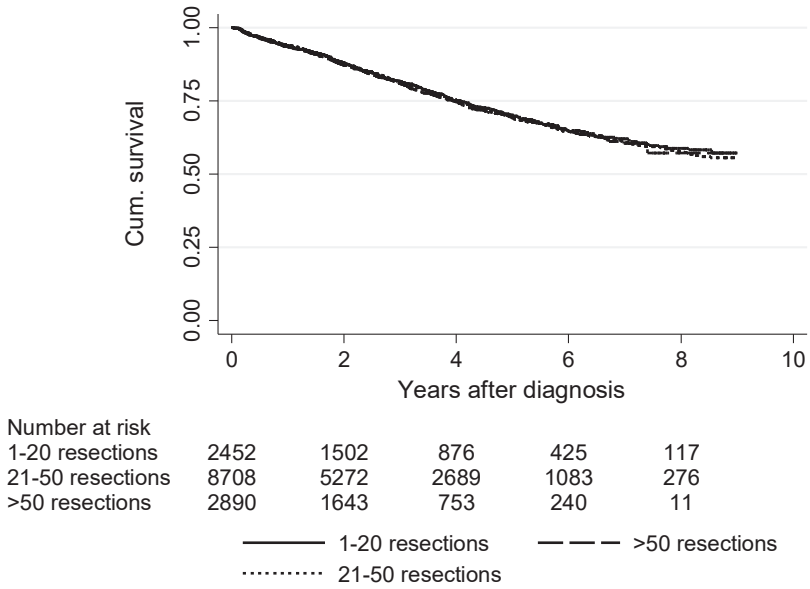
The median follow up was 31 months (IQR 15 – 54 months). The estimated 5-year survival rate of patients with cT1-3 rectal cancer who were treated in low, medium or high volume hospitals was similar (70%, 69%, 69% respectively; p=0.88). Survival curves are shown in *figure I*. Univariate Cox regression analysis showed no significant difference in survival between different hospital volumes. Univariate hazard ratios for survival of medium and high volume hospitals compared to low volume hospitals were 1.01 (95%CI: 0.92 – 1.11) and 1.03 (95%CI: 0.92 – 1.16) respectively.

Table I. Baseline characteristics cT1-3 rectal cancer patients

Total patients	Low volume hospitals 1-20/year 2452	Medium volume hospitals 20-50/year 8708	High volume hospitals ≥50/year 2890	P-value
Gender				
Male	1526 (62)	5573 (64)	1824 (63)	0.25
Female	926 (38)	3135 (36)	1066 (37)	
Median age	67	67	67	0.10
Year of diagnosis *				
2005-2007	685 (24)	1791 (63)	380 (13)	< 0.001
2008-2010	780 (16)	2985 (62)	1017 (21)	
2011-2013	987 (15)	3932 (61)	1493 (23)	
Neo-adjuvant treatment				
None	252 (10)	1007 (12)	280 (9)	< 0.001
Radiotherapy	1408 (57)	4448 (51)	1359 (47)	
Chemotherapy	7 (1)	48 (1)	16 (1)	
Chemoradiotherapy	785 (32)	3205 (37)	1235 (43)	
Type of surgery				
LAR/Hartmann	1569 (64)	5575 (64)	1952 (68)	0.002
APR	854 (35)	2980 (34)	892 (31)	
Proctocolectomy	12 (1)	65 (1)	27 (1)	
Not otherwise specified	17 (1)	88 (1)	19 (1)	
Pathological tumor stage				0.010
T0	190 (8)	648 (7)	269 (9)	
T1	183 (7)	627 (7)	209 (7)	
T2	824 (34)	2788 (32)	929 (32)	
T3	1174 (48)	4270 (49)	1384 (48)	
T4	50 (2)	191 (2)	57 (2)	
TX	31 (1)	184 (2)	42 (1)	
Pathological nodal stage				
N0	1592 (65)	5519 (63)	1863 (64)	0.17
N+	835 (34)	3087 (36)	993 (35)	
NX	25 (1)	102 (1)	34 (1)	
Pathological distant metastases				
M0	2381 (97)	8317 (96)	2767 (96)	0.002
M+	71 (3)	391 (4)	123 (4)	
Tumor grade				
Well differentiated	70 (3)	259 (3)	168 (2)	< 0.001
Moderately differentiated	1009 (41)	3466 (40)	1040 (36)	
Poorly differentiated/ undifferentiated	161 (7)	532 (6)	159 (6)	
Unknown	1212 (49)	4451 (51)	1623 (56)	
CRM-involvement #				
Involved	125 (7)	477 (7)	180 (7)	0.50
Not involved	1292 (73)	4967 (72)	1779 (71)	
Unknown	349 (20)	1470 (21)	551 (22)	
Adjuvant chemotherapy	201 (8)	980 (11)	326 (11)	< 0.001

*LAR; Low anterior resection, APR, Abdominal perineal resection, CRM; Circumferential resection margin, *, percentages are calculated within years of diagnosis. #, CRM was reported in the database starting from 2008*

Figure I. Overall survival in cT1-3 patients according to hospital volume.



cT4 rectal cancer

The baseline characteristics of 2.104 patients with cT4 rectal cancer are depicted in *table II.* The majority of patients (60%) underwent surgery in low volume cT4 hospitals, followed by high volume hospitals (25%) and medium volume hospitals (15%). Eight hospitals performed less than one surgical procedure for cT4 rectal cancer per year on average (2005-2013). There was an increase in referral of cT4 rectal cancer patients for resection to any other hospital from 23% in 2005 to 38% in 2013 (p=0.003) (*figure IIa)*. CT4 patients were most often referred by low volume hospitals, followed by medium and high volume hospitals *(figure IIb)* and most often referred to high volume hospitals, but also to medium volume hospitals and even to other low volume hospitals *(figure 2c).*

The percentage of patients who received neoadjuvant therapy was higher in high volume cT4 hospitals (98%) than in medium and low volume cT4 hospitals (respectively 91% and 88%, p<0.001). In high volume cT4 hospitals, 83% of the patients received chemoradiotherapy, compared to 70% in medium volume cT4 hospitals and 62% in low volume cT4 hospitals.

Figure IIa. Referral of cT4 rectal cancer patients for resection

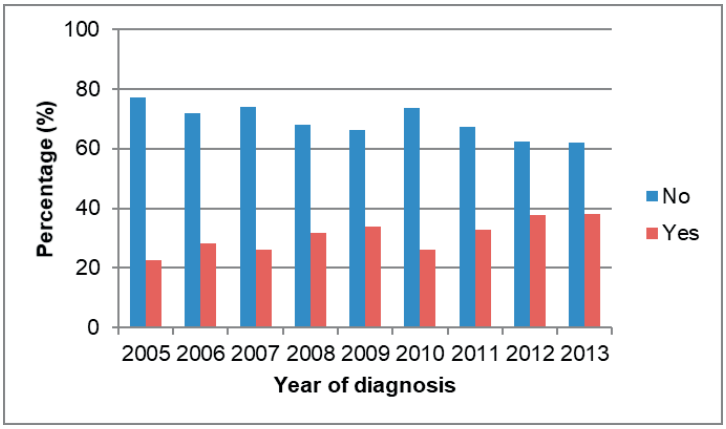


Figure IIb. Volume of hospital of diagnosis of the referred patients

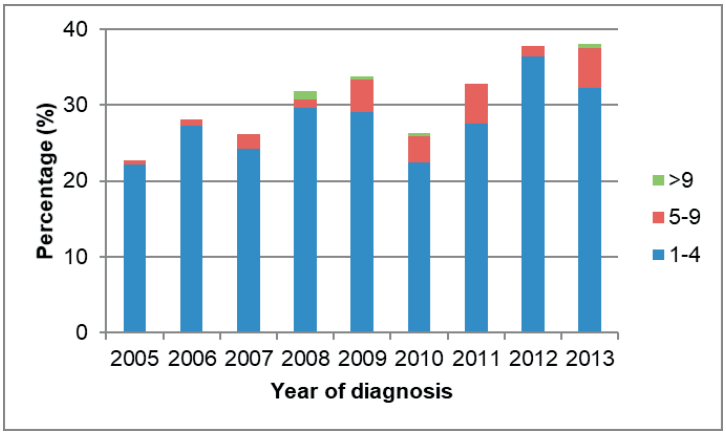


Figure IIc. Volume of hospital of resection of the referred patients

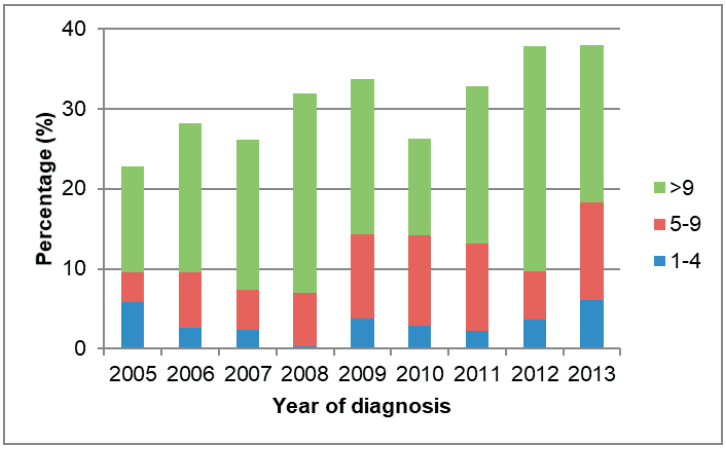


Table II. Baseline characteristics of cT4 rectal cancer patients

	Low volume hospitals 1-4/year	Medium volume hospitals 5-9/year	High volume hospitals ≥10/yea	P-value
Total patients	1.256	328	520	
Gender				
Male	622 (50)	175 (53)	294 (57)	0.02
Female	634 (50)	153 (47)	226 (43)	
Median age	67	65	63	<0.001
Year of diagnosis *				
2005-2007	433 (64)	102 (15)	142 (21)	0.03
2008-2010	442 (59)	120 (16)	188 (25)	
2011-2013	381 (56)	106 (16)	190 (28)	
Neo-adjuvant treatment				
None	156 (12)	29 (9)	13 (2)	<0.001
Radiotherapy	308 (25)	53 (16)	58 (11)	
Chemotherapy	10 (1)	16 (5)	15 (3)	
Chemoradiotherapy	782 (62)	230 (70)	434 (83)	
Type of surgery				<0.001
LAR/Hartmann	528 (42)	103 (31)	138 (27)	
APR	590 (47)	157 (48)	259 (50)	
Proctocolectomy	121 (10)	63 (19)	114 (22)	
Not otherwise specified	17 (1)	5 (2)	9 (2)	
Pathological tumor stage				
T0	87 (7)	23 (7)	47 (9)	0.02
T1	26 (2)	10 (3)	19 (4)	
T2	198 (16)	43 (13)	59 (11)	
T3	610 (49)	142 (43)	239 (46)	
T4	287 (23)	95 (29)	143 (28)	
TX	48 (4)	15 (5)	13 (3)	
Pathological nodal stage				
N0	710 (57)	204 (62)	330 (64)	0.04
N+	512 (41)	113 (34)	179 (34)	
NX	34 (3)	11 (3)	11 (2)	
Pathological distant metastases				
M0	1,174 (93)	294 (90)	461 (89)	0.001
M+	82 (7)	34 (10)	59 (11)	
Tumor grade				
Well differentiated	34 (3)	6 (2)	18 (3)	<0.001
Moderately differentiated	455 (36)	87 (27)	147 (28)	
Poorly differentiated/undifferentiated	116 (9)	25 (8)	38 (7)	
Unknown	651 (52)	210 (64)	317 (61)	
CRM-involvement #				
Involved	160 (19)	45 (20)	63 (17)	0.58
Not involved	466 (57)	131 (58)	213 (56)	
Unknown	197 (24)	50 (22)	102 (27)	
Adjuvant chemotherapy	172 (14)	52 (16)	54 (10)	0.05

*LAR; Low anterior resection, APR, Abdominal perineal resection, CRM; Circumferential resection margin, *, percentages are calculated within years of diagnosis. #, CRM was reported in the database starting from 2008*

The proportion of patients with a pathological T4-stage was higher in high volume hospitals compared to low volume hospitals (28 vs. 23%). In a subgroup analysis of the cT4 patients diagnosed between 2010 and 2013, more patients were staged cT4b in high volume hospitals compared to medium volume hospitals (82% vs. 70%, p=0.007) and low volume hospitals (82% vs. 68% p<0.001). Low volume hospitals had the highest proportion of node positive patients: 41% compared to 34% in both medium volume and high volume hospitals. The number of synchronously metastasized patients was significantly higher in high volume hospitals compared to low volume cT4 hospitals (11% vs. 7%, p=0.001) and was similar in medium cT4 hospitals (11% vs. 10%, p=0.66). In the period 2008-2013, there was no significant difference in CRM-involvement between high, medium and low volume cT4 hospitals (respectively 19%, 20%, 17%, p=0.58).

Outcomes

There was no difference in 30-days mortality and 90-days mortality according to hospital volume. Patients were followed with a median of 33 (IQR 16 - 60) months. The estimated overall survival of cT4 patients treated in high volume cT4 hospitals was significantly longer than in medium and low volume cT4 hospitals (p=0.001). The estimated 3-year survival rate was 76%, 71% and 67% respectively and the 5-year survival rate was 63%, 53% and 54% respectively (*Figure III).* Multivariable analysis demonstrated that resection in high volume cT4 hospitals was independently associated with a better overall survival compared to low volume cT4 hospitals (HR 0.81, 95%CI 0.67-0.98)), after adjusting for patient/tumour related confounders (age, pTNM-stage and tumor differentiation) *(table III).*

Figure III. Overall survival of cT4 rectal cancer according to the cT4 hospital volume

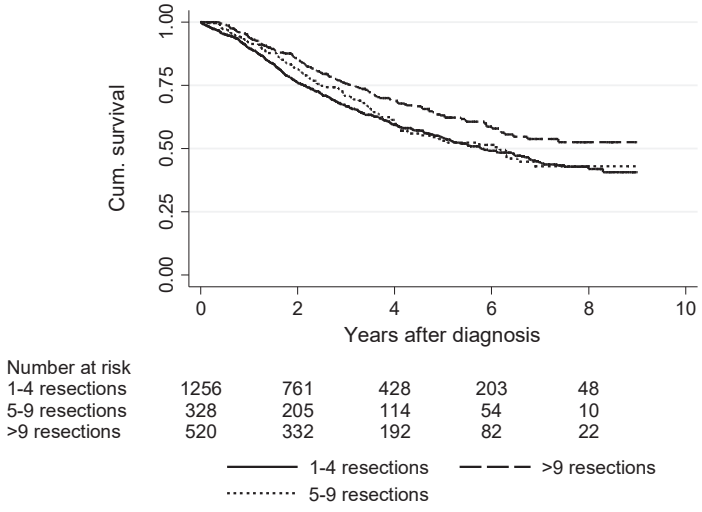


Table III. Univariate and multivariable survival analysis for overall survival of cT4 tumors with and without treatment related confounders

	Univariate Hazard ratio (95%CI)	p-value	Multivariable Hazard ratio (95%CI)	Multivariable Hazard ratio (95%CI)
Hospital volume (procedure per year)		<0.001		
1-4	1		1	1
5-9	0.93 (0.76-1.14)		0.97 (0.79-1.19)	0.99 (0.81-1.22)
≥10	0.71 (0.59-0.85)		0.81 (0.67-0.98)	0.87 (0.71-1.05)
Gender		0.98		
Male	1		-	-
Female	1.00 (0.87-1.15)		-	-
Age	1.03 (1.02-1.04)	<0.001	1.03 (1.03-1.04)	1.03 (1.02-1.04)
Year of diagnosis	0.98 (0.95-1.02)	0.32		
Neo-adjuvant therapy		<0.001		
None	1		-	
Radiotherapy	0.58 (0.46-0.73)		-	0.70 (0.54-0.88)
Chemotherapy	0.59 (0.35-0.97)		-	0.69 (0.41-1.17)
Chemoradiotherapy	0.32 (0.26-0.39)		-	0.53 (0.42-0.68)
Type of surgery		0.02		
LAR/Hartmann	1		-	1
APR	0.81 (0.69-0.95)		-	0.99 (0.84-1.17)
Proctocolectomy	0.95 (0.78-1.16)		-	0.95 (0.77-1.18)
Not otherwise specified	1.42 (0.83-2.43)		-	1.47 (0.85-2.53)
Pathological tumor stage				
T0	1	<0.001	1	1
T1	0.89 (0.35-2.24)		0.92 (0.37-2.32)	0.87 (0.35-2.21)
T2	2.02 (1.20-3.39)		1.84 (1.09-3.10)	1.75 (1.04-2.94)
T3	3.57 (2.22-5.72)		2.73 (1.69-4.41)	2.53 (1.56-4.09)
T4	5.89 (3.65-9.50)		4.30 (2.65-6.99)	3.89 (2.38 (6.37)
TX	2.64 (1.46-4.78)		2.50 (1.38-4.56)	2.42 (1.33-4.41)
Pathological nodal stage		<0.001		
N0	1		1	1
N1	1.64 (1.38-1.95)		1.34 (1.12-1.61)	1.32 (1.10-1.58)
N2	2.74 (2.29-3.28)		2.06 (1.71-2.49)	1.95 (1.61-2.36)
NX	2.31 (1.62=3.30)		2.06 (1.43-2.97)	2.11 (1.46-3.04)
Pathological distant metastases				
M0/X	1	<0.001	1	1
M+	2.14 (1.71-2.67)		2.12 (1.68-2.69)	1.99 (1.56-2.52)
Tumor grade		<0.001		
Well differentiated	0.93 (0.62-1.42)		1.04 (0.69-1.60)	1.11 (0.73-1.69)
Moderately differentiated	1		1	1
Poorly differentiated/undifferentiated	1.66 (1.32-2.09)		1.49 (1.18-1.88)	1.47 (1.16-1.86
Unknown	0.83 (0.71-0.97)		1.01 (0.86-1.19)	1.14 (0.96-1.35)
Adjuvante chemotherapy				
No	1		-	-
Yes	1.06 (0.87-1.30)	0.54	-	*

*LAR; Low anterior resection, APR, Abdominal perineal resection, CRM; Circumferential resection margin, *, percentages are calculated within years of diagnosis.* #, CRM was reported in the database starting from 2008

When treatment related confounders were included in the multivariate analysis, neoadjuvant chemoradiotherapy was associated with improved survival. Adjustment for neoadjuvant therapy resulted in the disappearance of a significant difference between high, medium and low volume hospitals.

Discussion

The current population-based study found an overall survival benefit of cT4 rectal cancer patients treated in high volume cT4 hospitals compared to low volume cT4 hospitals. In cT1-3 rectal cancer, we were not able to find an overall survival difference related to hospital volume. In the present study patients with locally advanced (cT4) rectal cancer treated in high volume hospitals (≥10 resections annually) had a significantly improved 5-year overall survival of 63% compared to 53% in low volume (1-4 resections). This contradicts a previous study executed in the Southern part of the Netherlands, which did not found an association between hospital volume and long term overall survival for both colon and rectal cancer patients.[13] However, that study did not analyze the long-term outcome of cT4 and cT1-3 separately. This may explain why we found a survival difference, while the other study did not. Although the referral of cT4 tumors to high volume hospitals has increased during the study period, the majority of patients (56%) were still treated in a low volume cT4 hospital in the period 2011-2013

Rectal cancer is a relatively common malignancy and the majority of patients can be treated by a standard TME procedure. The Dutch TME-trial, which included a teaching program for the TME technique, showed us that this technique can be taught and rolled out nationwide and results in low recurrence rates.[4] However, only patients with cT1-3 rectal cancer are suitable candidates for a standard TME procedure, because standard TME in patients with tumor invasion through the mesorectal fascia (cT4) leads to an involved mesorectal fascia and thus incomplete resections (R1/2-resections). Involved circumferential resection margins (CRM) are uncommon in cT1-3 rectal cancer patients and reported to be <10%, whereas in cT4 patients positive CRM is demonstrated in approximately 20%.[14] Incomplete resections are deleterious for oncological outcome and all efforts should be aimed at avoiding R1/2-resections.[15] This makes more radical procedures in patients with cT4 rectal cancer necessary to achieve R0-resections. These surgical procedures beyond the TME plane are less straightforward and more technically demanding than standard TME surgery.[9,16,17] Additionally, the advanced stages of rectal cancer have the greatest benefit of a multimodality treatment, including neoadjuvant chemoradiotherapy leading to more complete resections and reduces local recurrence rates.[3,7]

Accurate staging of the rectal tumor is essential in selecting patients who should be treated with neoadjuvant therapy and to differentiate between those who can be treated by a standard TME procedure and those who require more extended surgery. The quality of this assessment may be enhanced by multidisciplinary tumor board meetings (MDT), including dedicated radiologists, radiation oncologists, medical oncologists and surgeons. Nowadays, almost all rectal cancer patients in the Netherlands are staged by MR imaging and are discussed in an MDT.[2] In an experienced MDT, cT4 tumors are potentially more accurately assessed and a more appropriate surgical procedure may be selected. Furthermore, in experienced MDTs, standardized care for patients with advanced stages of rectal cancer may result in an improved long-term outcome.

Several studies have reported survival differences according to hospital volume in complex surgical procedures in other malignancies, such as esophagus, pancreas and bladder cancer.[18-20] The hypothesis of this survival benefit is that more exposure and experience in the multimodality treatment (staging, neo-adjuvant therapy and surgical expertise) of these relatively rare malignancies results in an improved long-term outcome. In line with the findings of studies in other malignancies, the current study showed a survival benefit in the treatment of cT4 rectal cancer in high volume cT4 hospitals, but not in the more common cT1-3 rectal tumors. In a previous study from data of the NCR no difference in survival was demonstrated between high and low volume centers for all colon or rectal patients.[13] However, the results from the present study, suggest that locally advanced (cT4) rectal cancer requires a minimal number of resections per hospital, irrespective of the number of resections performed for cT1-3 rectal cancer in that same hospital.

The reason for the overall survival benefit of cT4 tumors treated in high volume cT4 hospitals cannot be defined by this population-based study. Presumably, the overall survival benefit is caused by multiple factors. Optimal staging, neoadjuvant therapy, surgical treatment and experience of the MDT may lead to superior selection, treatment and results when optimally combined. Optimal staging may results in the selection of the appropriate neoadjuvant treatment. Experience with extensive rectal resections in high volume hospitals may contribute. However, this did not lead to a lower percentage of CRM-involvement in high volume cT4 hospital compared to medium and low volume cT4 hospital in the years evaluated. This may be explained by referral of patients with more advanced tumors to high volume cT4 hospitals, which explains the higher pathological stage (pT4a and p T4b) in high volume cT4 hospitals, regardless of the higher percentage of neoadjuvant therapy administered. Another factor that may have contributed to the survival benefit is the availability of intraoperative radiotherapy (IORT). High volume cT4 hospitals in The Netherlands have the ability to apply an extra radiation dose during surgery. IORT may eradicate remaining tumor cells and this may lead to a survival

benefit.[21,22] Unfortunately, IORT was not comprehensively registered in the Netherlands Cancer Registry making further evaluation of the role of IORT impossible.

Unfortunately, the data available on different aspects of treatment is limited. The type of procedure was registered, but is limited to ''low anterior resection', 'abdominoperineal resection' and 'proctocolectomy'. Especially in cT4 rectal cancer, data on resections outside the TME plane, the need for multivisceral surgery, urinary tract reconstructions and the admission of intra-operative radiotherapy may provide more insight into what type of tumours were treated in different hospitals. However, these data are not available; only the administration of neoadjuvant therapy was registered comprehensively and indeed was identified as an independent prognostic factor for survival. We argue that when the quality of a multidisciplinary/multimodality treatment of rectal cancer is assessed, the singling out of an individual aspect, because that variable happens to be available, is inappropriate. The administration of all contributors of the multimodality treatment, at the right time, to the right patient is what defines quality of care. When important treatment related variables are lacking, a valid multivariate analysis of treatment related variables is impossible. The fact that this study identifies neo-adjuvant chemoradiotherapy as a prognostic factor for survival when randomized clinical trials did not, adds to our skepticism towards the appropriateness of a multivariate analysis of treatment related confounders in this study[23].

Although referral of cT4 rectal cancer has increased during the study period, further centralization of cT4 rectal cancer seems warranted. Remarkably, some of the patients diagnosed in low volume hospitals were referred to other low volume cT4 hospitals for treatment. To improve care for rectal cancer patients in the Netherlands, it seems logical to refer cT4 rectal cancer patients to high volume hospitals only. The total number of cT4 rectal cancer diagnosed annually in the Netherlands (approximately 250 patients) is limited and the appointment of 4 or 5 cT4 rectal cancer centers would seem appropriate. Excluding cT4 rectal cancer from the required total number of rectal cancer procedures per hospital can eliminate the stimulus to treat these patients in hospitals without T4 rectal cancer experience.

As all retrospective studies do, this study has limitations. The younger age of patients treated in high volume cT4 hospitals may indicate that the patients referred to high volume centers for extensive surgery were the ones in a relatively good clinical condition and that may improve their survival significantly. On the other hand, the pathological T-stage and the number of metastasized patients was significantly higher in high volume cT4 hospitals, suggesting that advanced stages of disease were referred to high volume cT4 hospitals, which would decrease overall survival in these patients. This type of discussion on the profile of patient groups in different hospitals is often referred to as the 'case mix' discussion. Unfortunately, for reasons described earlier, we cannot

conclude whether case mix is the driver behind the differences that we did and did not find. We stress, however, that earlier studies that suggested improved outcome in high volume centers for complex surgery also relied on retrospective data and were flawed by the same confounders. The observation that in a cohort of more than 14.000 cT1-3 rectal cancer patients, no relationship between hospital volume and overall survival was present, stands. This makes it questionable whether such a relationship, should we have missed it in this study, could realistically be clinically relevant.

In conclusion, the treatment of cT4 rectal cancer in high volume cT4 hospitals was associated with an improved survival compared to low volume cT4 hospitals after adjustment for patient and tumour related confounders. Hospital volume in cT1-3 rectal cancer was not associated with overall survival in the present study. There was a small increase in referral of cT4 rectal cancer to high volume cT4 hospitals, but further centralization of cT4 rectal cancer seems warranted to further improve outcome for this difficult group of patients.

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