# Hospital volume and outcome in rectal cancer patients; results of a population-based study in the Netherlands

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*European Journal of Surgical Oncology. 2019 Apr;45(4):613-619. doi: 10.1016/j.ejso.2018.12.018. Epub 2018 Dec 26. PMID: 30600101*

# ABSTRACT

## Background

Clinically staged T1-3 rectal cancer (cT1-3) is generally treated by total mesorectal excision (TME) with or without neoadjuvant therapy and sometimes requires beyond TME-surgery, whereas cT4 rectal cancer often requires both. This study evaluates the outcome of cT1-3 and cT4 rectal cancer according to hospital volume.

## Methods

Patients undergoing rectal cancer surgery between 2005 and 2013 in the Netherlands were included from the National Cancer Registry. Hospitals were divided into low (1 - 20), medium (21 - 50) and high (> 50 resections/year) volume for cT1-3 and low (1- 4), medium (5- 9) and high (≥ 10 resections/year) volume for cT4 rectal cancer. Cox-proportional hazards model was used for multivariable analysis of overall survival (OS).

## 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 OS 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, but this was not significant after adjustment for neoadjuvant treatment. Patients with cT4-tumours treated in high volume hospitals had a significantly lower age, more synchronous metastases, more patients treated with neoadjuvant therapy and a higher pT-stage.

## Conclusions

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 improved survival compared to low volume cT4 hospitals, although this association lost statistical significance after correction for neoadjuvant treatment.

## 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.(2-6)

Optimal treatment of rectal cancer is dependent on local tumour stage and the presence of distant metastases. 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.(7) It leads to tumour shrinkage, thereby facilitating complete resections and a decrease in local recurrence rate.(3, 8)

Local tumour 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.(9) Advanced stages of rectal cancer with tumours 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.(10)

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 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.(11) 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 multivisceral surgery is technically demanding with higher amounts of blood loss, operation time and increased morbidity and mortality.(12) 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.(13) Information concerning the cause of death was not available. No ethical approval was required for this study.

## 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. Available treatment related variables 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 analysed 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 ($6^{th}$ edition for 2005-2009 and $7^{th}$ edition for 2010-2013). The $7^{th}$ edition included a distinction between cT4a (tumour penetrates the surface of the visceral peritoneum) and cT4b tumours (tumour 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 comparison of the proportion of patients treated per volume category over time the Chi-square test for linear trend was used. 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 analyse 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. Two sided p-values < 0.05 were considered statistically significant.

## RESULTS

16.154 patients underwent rectal cancer surgery and had a confirmed clinical T-stage, while in 6394 patients the cT-stage was unknown. The number of patients with an unknown cT-stage was especially high in the first years and this decreased over the study period (55% in 2005 and 7% in 2013). Of those patients with a known cT-stage, 14.050 patients (87%) had a cT1-3 tumour and 2.104 patients (13%) had a cT4 tumour.

### cT1-3 rectal cancer

The baseline characteristics of the 14.050 patients with cT1-3 rectal cancer are outlined in Table 1. 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 hospitals performed less abdominoperineal resections (31% vs. 34% vs. 35%, p = 0.002) and had a higher percentage of ypT0 stage (9% vs. 7% vs. 8%, P = 0.010). 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).

**Table 1.** Baseline characteristics cT1-3 rectal cancer patients

| | Low volume hospitals 1-20/year | Medium volume hospitals 20-50/year | High volume hospitals ≥50/year | P-value |
|---|---|---|---|---|
| **Total patients** | 2452 | 8708 | 2890 | |
| **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 tumour stage** | | | | 0.01 |
| 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) | |
| **Tumour grade** | | | | |
| Well differentiated | 70 (3) | 259 (3) | 168 (2) | < 0.001 |
| Moderately differentiated | 1009 (41) | 3466 (40) | 1040 (36) | |

**Table 1.** Baseline characteristics cT1-3 rectal cancer patients (continued)

| | Low volume hospitals 1-20/year | Medium volume hospitals 20-50/year | High volume hospitals ≥50/year | P-value |
|---|---|---|---|---|
| **Total patients** | 2452 | 8708 | 2890 | |
| 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*

### *Outcomes*

The median follow up was 31 months (IQR 15 – 54 months). The estimated 5-year survival rates of patients with cT1-3 rectal cancer who were treated in low, medium or high volume hospitals were similar (70%, 69%, 69% respectively; p = 0.88). Survival curves are shown in Figure 1. 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.

## cT4 rectal cancer

The baseline characteristics of 2.104 patients with cT4 rectal cancer are depicted in Table 2. The majority of patients (60%) underwent surgery in low volume cT4 hospitals (1 - 4 resections/year), followed by 25% in high volume hospitals (≥ 10 resections/year) and 15% in medium volume hospitals (5 - 9 resections/year). Eight hospitals performed less than one surgical procedure for cT4 rectal cancer per year on average (2005 - 2013). An increase was seen in patients treated in high volume hospitals (2005 - 2007: 21% vs. 2011 - 2013: 28%, p = 0.03). 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 2a). CT4 patients were most often referred by low volume hospitals, followed by medium and high

volume hospitals (Figure 2b) and most often referred to high volume hospitals, but also to medium volume hospitals and even to other low volume hospitals (Figure 2c).

Patients treated in high volume cT4 hospitals had a significantly lower age compared to medium and low volume hospitals ($p < 0.001$). 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%, $p = 0.66$). 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. The proportion of patients with a pathological T4-stage was higher in high volume hospitals compared to low volume hospitals (28% vs. 23%, $p = 0.02$). Low volume hospitals had the highest proportion of node positive patients: 41% compared to 34% in both medium volume and high volume hospitals ($p=0.04$).

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% $p < 0.001$). However, there was no significant difference between the proportion of patients with pT4b stage in high volume hospitals compared to medium volume (20% vs. 22%, $p = 0.86$) or low volume hospitals, (20% vs 26%, $p = 0.48$). In the period 2008 - 2013, there was no

**Table 2.** Baseline characteristics of cT4 rectal cancer patients

| | Low volume hospitals 1-4/year | Medium volume hospitals 5-9/year | High volume hospitals ≥10/year | 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 |

**Table 2.** Baseline characteristics of cT4 rectal cancer patients (continued)

| | Low volume hospitals 1-4/year | Medium volume hospitals 5-9/year | High volume hospitals ≥10/year | P-value |
|---|---|---|---|---|
| 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 tumour 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) | |
| **Tumour 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

significant difference in CRM-involvement between high, medium and low volume cT4 hospitals (respectively 19%, 20%, 17%, p = 0.58).

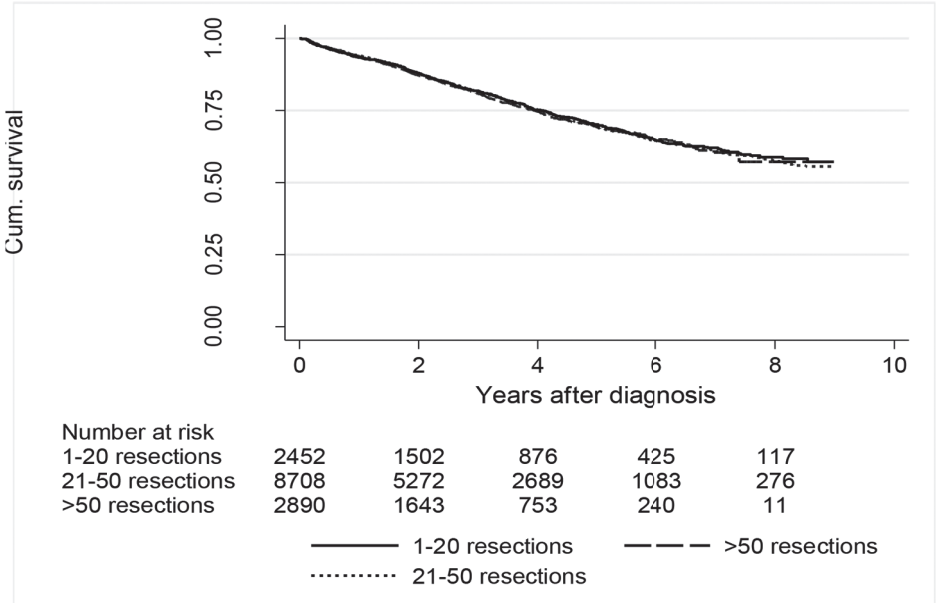


**Figure 1.** Overall survival in cT1-3 patients, according to hospital volume.

### *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 3). 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 tumour differentiation) (Table 3). 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.

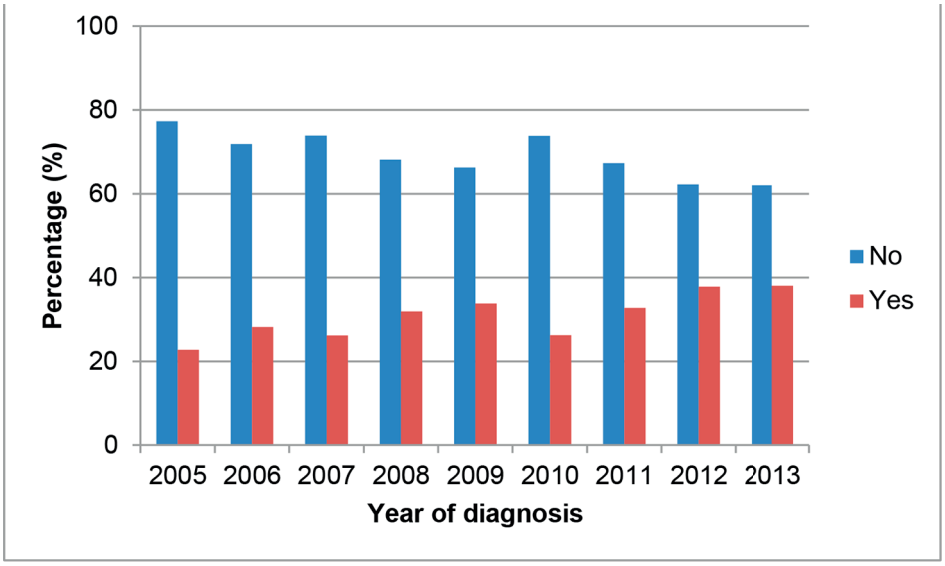


**Figure 2a.** Referral of cT4 rectal cancer patients for resection

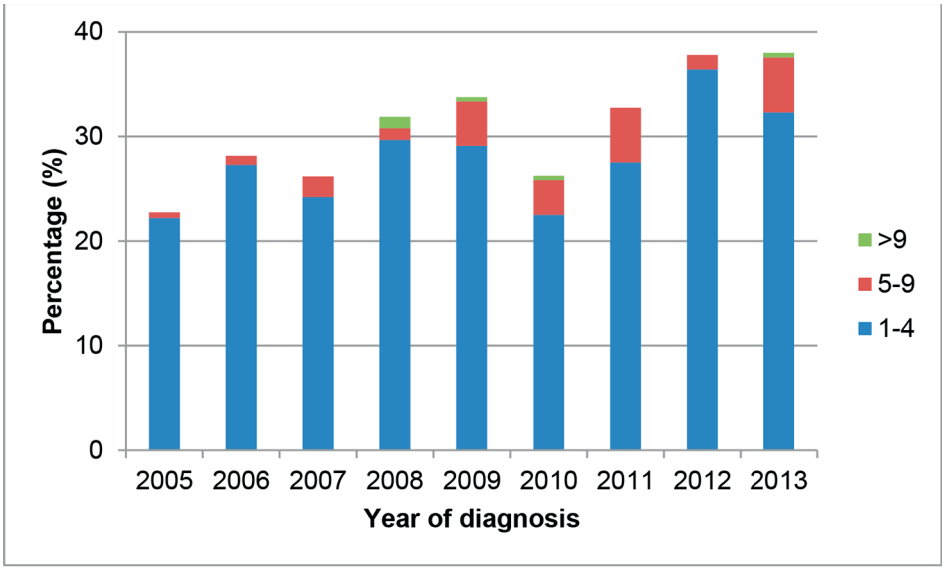


**Figure 2b.** Volume of hospital of diagnosis of the referred patients

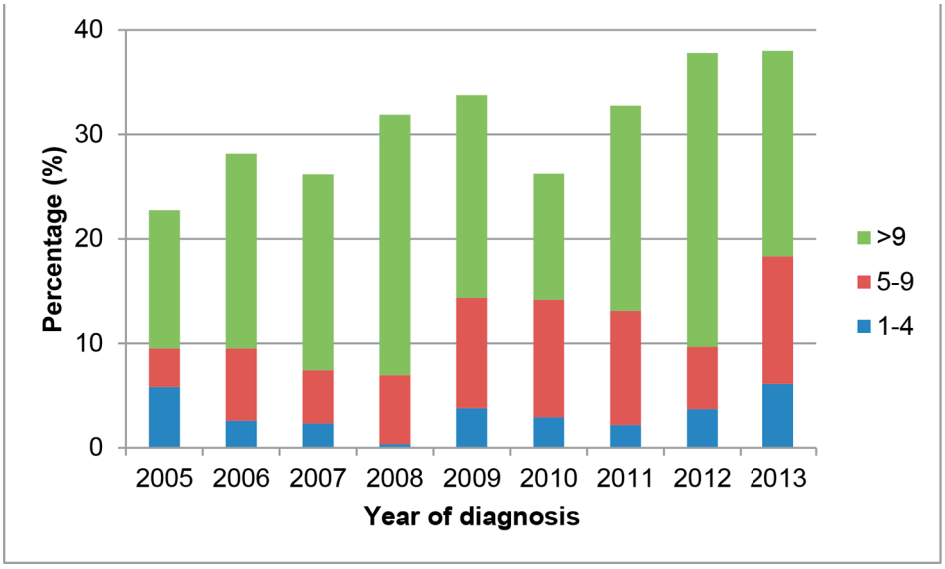


**Figure 2c.** Volume of hospital of resection of the referred patients

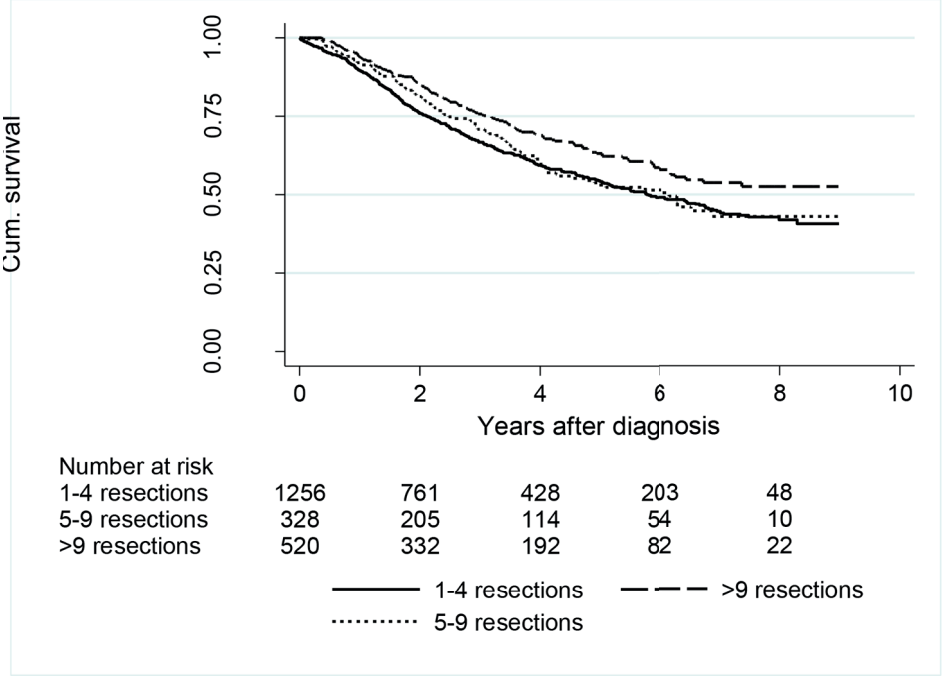


**Figure 3.** Overall survival of cT4 rectal cancer according to the cT4 hospital volume

**Table 3.** Univariate and multivariable survival analysis for overall survival of cT4 tumours with and without treatment related confounders

| | Univariate Hazard ratio (95%CI) | p-value | Multivariable Hazard ratio (95%CI) without treatment related confounders | Multivariable Hazard ratio (95%CI) with treatment related confounders |
|---|---|---|---|---|
| **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 tumour 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) |

**Table 3.** Univariate and multivariable survival analysis for overall survival of cT4 tumours with and without treatment related confounders (continued)

| | Univariate Hazard ratio (95%CI) | p-value | Multivariable Hazard ratio (95%CI) without treatment related confounders | Multivariable Hazard ratio (95%CI) with treatment related confounders |
|---|---|---|---|---|
| **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) |
| **Tumour 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) |
| Adjuvant chemotherapy | | | | |
| No | 1 | | - | - |
| Yes | 1.06 (0.87-1.30) | 0.54 | - | * |

*LAR; Low anterior resection, APR, Abdominal perineal resection.*

## DISCUSSION

The current population-based study found an overall survival benefit for cT4 rectal cancer patients treated in high volume cT4 hospitals compared to low volume cT4 hospitals. This overall survival difference related to hospital volume was not found in cT1-3 rectal cancer. Patients with locally advanced (cT4) rectal cancer treated in high volume hospitals (≥ 10 resections/year) had a significantly improved 5-year overall survival of 63% compared to 53% in low volume (1 - 4 resections) and 54% in medium volume cT4 hospitals (5 - 9 resections), when corrected for patient and tumour related confounders, but this difference disappeared after adjustment for neoadjuvant therapy. The referral of cT4 tumours to high volume hospitals has increased during the study period, but in the period 2011-2013, the majority of patients (56%) were still treated in a low volume cT4 hospital.

Patients with cT1-3 rectal cancer are suitable candidates for a standard TME procedure, although beyond TME surgery is sometimes required if the mesorectal fascia is involved. Standard TME in patients with close tumour contact to the mesorectal fascia (cT4 or cT3MRF+/) often leads to incomplete resections (R1/2-resections).(14) Incomplete resections are deleterious for oncological outcome and all efforts should be aimed at avoiding R1/2-resections.(15) The advanced stages of rectal cancer have the greatest benefit of

multimodality treatment, including neoadjuvant chemoradiotherapy, which potentially leads to tumour shrinkage, more complete resections and reduces local recurrence rates. (3, 8) Accurate staging of the rectal tumour 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 beyond TME surgery. The quality of this assessment may be enhanced by multidisciplinary tumour board meetings (MDT), including dedicated radiologists, radiation oncologists, medical oncologists and surgeons. Nowadays, almost all rectal cancer patients in the Netherlands undergo MRI staging of the primary tumour and are discussed in an MDT.(2) In an experienced MDT, cT4 tumours are potentially more accurately assessed and a more appropriate neoadjuvant and surgical strategy may be selected. This may explain why more patients in low volume hospitals did not receive chemoradiotherapy despite the clear indication for chemoradiotherapy. Furthermore, in experienced MDTs, standardized care for patients with advanced stages of rectal cancer may result in an improved long-term outcome. Other legitimate reasons for refraining from chemoradiotherapy in low or medium volume centres including patient factors, such as comorbidities, age or patient preference, cannot be retrieved form the NCR.

Several studies have reported survival differences according to hospital volume in complex surgical procedures in other malignancies, such as oesophagus, pancreas and bladder cancer.(16-18) The hypothesis of this survival benefit is that more exposure and experience in the multimodality treatment (staging, induction therapy and surgical expertise) of these relatively rare malignancies results in an improved long-term outcome.(16-18) 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 tumours. A previously published Dutch population based study in a smaller cohort described no differences in long-term oncological outcomes for rectal cancer (cT1-4) based on hospital volume, but no separate analysis for cT4 rectal cancers were performed.(19)

Presumably, the overall survival benefit of cT4 rectal cancer in high volume cT4 hospitals is caused by multiple factors. Optimal staging, neoadjuvant therapy, surgical treatment differences and experience of the MDT may lead to superior selection, treatment and results when optimally combined. Optimal staging may result in the selection of appropriate neoadjuvant treatment. Experience with extensive rectal resections in high volume hospitals may contribute, but 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 partly be explained by referral of patients with more advanced tumours to high volume cT4 hospitals, which explains the higher pathological stage (pT4)

in high volume cT4 hospitals compared to low volume hospitals, regardless of the higher percentage of neoadjuvant therapy administered. In a subgroup analysis the proportion of pT4b tumours was higher in high volume hospitals compared to medium and low volume hospitals (26% vs. 22% vs 20%), but not significantly so. Even in an experienced high volume hospital, radical resection of cT4b tumours is challenging and referral of these patients to high volume hospitals could offer an explanation for similar CRM involvement in different volume hospitals. Our data cannot prove this referral pattern. Moreover, a difficult resection does not automatically translate in a pT4b stage, especially since most patients undergo neoadjuvant chemoradiotherapy. The number of multivisceral resections per hospital may also provide an indication of the complexity and difficulty of the procedures performed in different volume hospitals. The NCR, however, started gathering data on multivisceral resections since 2010 only. Secondly, multivisceral resections were not registered as such in the Dutch registry of surgical procedures resulting in a large amount of missing data with regard to this variable. In addition, the availability of intraoperative radiotherapy (IORT) may have contributed to the survival benefit is. High volume cT4 hospitals in the Netherlands have the ability to apply an extra radiation dose during surgery. IORT may eradicate remaining tumour cells and this may lead to a survival benefit.(20, 21) Unfortunately, IORT was not comprehensively registered in the NCR making further evaluation of the role of IORT impossible.

The relatively high CRM-involvement (17%) in cT4 rectal cancer patients treated in high volume hospitals in our study suggests that even in high volume hospitals there is room for improvement. A more recent cohort by Jonker et al. (22) on perioperative outcomes for cT1-3 and cT4 rectal cancer by hospital volumes did find a significantly higher rate of irradical resections for cT4 rectal cancer in low volume hospitals compared to medium and high volume hospitals, and therefore advocates that centralization may be beneficial for cT4 patients. Further centralization leading to an increase in the number of patients treated in high volume hospitals could further improve treatment in these centres, and eventually result in a higher percentage of clear margins, a decrease in local recurrence rates and an increase in overall survival. The total number of cT4 rectal cancer diagnosed annually in the Netherlands (approximately 250) is limited. The appointment of 4 or 5 cT4 rectal cancer centres would seem appropriate and result in an adequate number of patients in specialized centres. Excluding cT4 rectal cancer from the required total number of rectal cancer procedures per hospital may eliminate the stimulus to treat these patients in hospitals without T4 rectal cancer experience.

Due to its retrospective nature, this study has limitations. Patients referred to high volume centres for extensive surgery were younger, and probably in a relatively good clinical condition. Both may improve their survival. On the other hand, the pathological T-stage and

the number of metastasized patients was 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.

In conclusion, hospital volume was not associated with overall survival after surgery for cT1-3 rectal cancer. The treatment of cT4 rectal cancer in high volume cT4 hospitals was associated with an improved survival compared to low volume cT4 hospitals when corrected for patient and tumour related confounders. This association was no longer statistically significant after correction for neoadjuvant treatment, but the omission of neoadjuvant treatment in cT4 rectal cancer may also reflect lower quality of care. 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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