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Predictors of undergoing multivisceral resection, margin status and survival in Dutch patients with locally advanced colorectal cancer

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ABSTRACT

Background: The aim of this nationwide observational study was to evaluate factors associated with multivisceral resection (MVR), margin status and overall survival in locally advanced colorectal cancer (CRC).

Material and methods: Patients with (y)pT4, cM0 CRC between 2006 and 2017 were selected from the Netherlands Cancer Registry. Cox-proportional hazards modelling was used for survival analysis, stratified for T4a and T4b. Annual hospital volume cut-off was 75 for colon and 40 for rectal resections.

Results: A total of 11.930 patients were included and 2410 patients (20.2%) underwent MVR. Factors associated with MVR for colon and rectal cancer besides cT4 category were more recent diagnosis (OR 3.61, CI 95% 3.06–4.25 (colon) and OR 2.72, CI 95% 1.82–4.08 (rectum)) and high hospital volume (OR 1.20, CI 95% 1.05–1.38 (colon) and OR 2.17, CI 95% 1.55–3.04 (rectum)). Patients ≥70 year were less likely to undergo MVR for colon cancer (OR 0.80, 95% CI 0.70–0.90). Risk factors for incomplete resection were cT4 (OR 3.08, CI 95% 2.35–4.04 (colon) and OR 1.82, CI 95% 1.13–2.94 (rectum)) and poor/undifferentiated tumors (OR 1.41, CI 95% 1.14–1.72 (colon) and OR 1.69, CI 95% 1.05–2.74 (rectum)). More recent diagnosis was independently associated with less incomplete resections in colon cancer (OR 0.58, CI 95% 0.40–0.76). Independent predictors of survival were age, resection margin, nodal status and adjuvant chemotherapy, but not MVR.

Conclusion: Treatment of locally advanced CRC with MVR at population level was influenced by year of diagnosis and hospital volume. Margin status in colon cancer improved substantially over time.

1. Introduction

Patients with locally advanced colorectal cancer (CRC) represent approximately 10–20% of all CRC patients [1]. The combination of limited incidence and the advanced stage of disease makes preoperative accurate radiologic staging and treatment of locally advanced CRC more demanding. Surgery with the purpose of a complete resection (R0 resection) is an important prognostic factor associated with enhanced local control and overall survival (OS) in all stages and especially in locally advanced CRC [2–4].

Colon and rectal cancer are two clinically distinct entities, based on differences in pathophysiology, molecular carcinogenesis, genetic mechanism, incidence, clinical staging and treatment related aspects. In locally advanced rectal cancer (LARC), neo-adjuvant therapy is standard of care for tumor downstaging and downsizing, in order to facilitate complete resection. The type of neo-adjuvant treatment is subject of many international studies and is also determined by underlying comorbidity, frailty, age and patients' preferences [5–7]. Generally long-course radiotherapy in combination with 5-FU is considered the standard treatment, but new strategies including total neoadjuvant treatment are emerging. The benefit of preoperative treatment in locally advanced colon cancer (LACC) has recently gained more attention because of promising data from studies demonstrating adequate

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Table 1
Patient characteristics of pT4M0 patients who underwent surgical resection.

	Colon			Rectum		
	MVR (n = 2004)	Standard resection (n = 8874)	p-value	MVR (n = 406)	Standard resection (n = 646)	p-value
Demographics						
Age, median (IQR)	71.0 (63.0–78.0)	73.0 (64.0–80.0)	<0.001	68.0 (59.0–76.0)	69.0 (60.0–76.0)	0.11
Age groups, years, n (%)						
- <65	585 (29.2)	2329 (26.2)	<0.001	159 (39.2)	232 (35.9)	0.06
- 65-79	998 (49.8)	4227 (47.6)	0.001	196 (48.3)	297 (46.0)	<0.001
- ≥80	421 (21.0)	2318 (26.1)		51 (12.6)	117 (18.1)	
Males, n (%)	874 (43.6)	4251 (47.9)		155 (38.2)	365 (56.6)	
Year of diagnosis, n (%)						
- 2006–2009	417 (20.8)	2921 (32.9)	<0.001	97 (23.9)	229 (35.4)	<0.001
- 2010–2013	704 (35.1)	2891 (32.6)		142 (35.0)	211 (32.7)	
- 2014-20017	883 (44.1)	3062 (34.5)		167 (41.1)	206 (31.9)	
Tumor characteristics and additional therapy						
Location, colon only						
- Left-sided (distal to splenic flexure)	1017 (50.7)	3619 (40.8)				
- Right-sided (proximal to splenic flexure)	920 (45.9)	4984 (56.2)				
- Missing	67 (3.3)	271 (3.1)	<0.001	–	–	–
Clinical TNM stage, n (%)						
- ≤ T2	15 (0.7)	361 (4.1)	<0.001	6 (1.5)	57 (8.8)	<0.001
- T3	82 (4.1)	1487 (17.9)	<0.001	44 (10.8)	276 (42.7)	<0.001
- T4	1722 (85.9)	2682 (30.2)		347 (85.5)	217 (33.6)	
- Tx	184 (9.2)	4243 (47.8)		9 (2.2)	96 (14.9)	
- N0	893 (44.6)	4161 (46.9)		114 (28.1)	227 (35.1)	
- N1	499 (24.9)	1900 (21.4)		122 (30.0)	201 (31.1)	
- N2	156 (7.8)	438 (4.9)		134 (33.0)	100 (15.5)	
- Nx	456 (22.8)	2375 (26.8)		36 (8.9)	118 (18.3)	
Morphology, n (%)						
- Adenocarcinoma	1560 (77.8)	7065 (79.6)	0.004	328 (80.8)	536 (83.0)	0.80
- Mucinous	371 (18.5)	1425 (16.1)		66 (16.3)	91 (14.1)	
- Signet ring cell	35 (1.7)	240 (2.7)		10 (2.5)	15 (2.3)	
- NOS	38 (1.9)	144 (1.6)		2 (0.5)	4 (0.6)	
Tumor grade, n (%)						
- Well differentiated	63 (3.1)	328 (3.7)	<0.001	9 (2.2)	19 (2.9)	0.01
- Moderately differentiated	1141 (56.9)	5412 (61.0)		180 (44.3)	316 (48.9)	
- Poorly differentiated	491 (24.5)	2177 (24.5)		39 (9.6)	92 (14.2)	
- Undifferentiated	12 (0.6)	27 (0.3)		0 (0.0)	0 (0.0)	
- Unknown	297 (14.8)	930 (10.5)		178 (43.8)	219 (33.9)	
Neoadjuvant therapy, n (%)						
- None	1820 (90.8)	8766 (98.8)	<0.001	48 (11.8)	197 (30.5)	<0.001
- Radiotherapy	8 (0.4)	33 (0.4)		66 (16.3)	235 (36.4)	
- Chemoradiation	71 (3.6)	25 (0.3)		287 (70.7)	214 (33.1)	
- Chemotherapy	105 (5.2)	50 (0.6)		5 (1.2)	0 (0.0)	
Adjuvant therapy, n (%)*						
- None	1190 (59.4)	5011 (56.5)	<0.001	364 (89.7)	521 (80.7)	<0.001
- Chemotherapy	789 (39.4)	3815 (43.0)		31 (7.6)	109 (16.9)	
- Chemoradiation	13 (0.6)	25 (0.3)		3 (0.7)	5 (0.8)	
- Radiation	12 (0.6)	23 (0.3)		8 (2.0)	11 (1.7)	
Surgical characteristics						
Type of surgery, n (%) [$]						
- Elective surgery	1541 (76.9)	6017 (67.8)	<0.001	95 (23.4)	120 (18.6)	0.02
- Emergency/non-elective surgery	245 (12.2)	1369 (15.4)		10 (2.4)	5 (0.7)	
- Unknown/missing	218 (10.9)	1488 (16.7)		301 (74.2)	521 (80.7)	
Extensiveness of additional resection						
- Limited[A]	717 (35.8)	–	–	185 (45.6)	–	–
- Extended[B]	1287 (64.2)			221 (54.4)		
Pathology (after resection)						
Pathological (some y-) T stage, n (%)						
- T4a	324 (16.2)	4699 (53.0)	<0.001	26 (6.4)	298 (46.1)	<0.001
- T4b	1263 (63.0)	1254 (14.1)		283 (69.7)	119 (18.4)	
- T4 NOS	417 (20.8)	2921 (32.9)		97 (23.9)	229 (35.4)	
Pathological (some y-) N stage, n (%)						
- N0	1056 (52.7)	3574 (40.3)	<0.001	243 (59.9)	264 (40.9)	<0.001
- N1	549 (27.4)	2896 (32.6)		107 (26.4)	200 (31.0)	
- N2	366 (18.3)	2333 (26.3)		49 (12.1)	175 (27.1)	
- Nx	33 (1.6)	71 (0.8)		7 (1.7)	7 (1.1)	
Resection margins, n (%) [#]						
- R0	1374 (86.1)	6390 (87.6)	0.06	261 (77.2)	380 (71.3)	0.27
- R1	140 (8.7)	638 (8.7)		67 (19.8)	136 (25.5)	
- R2	81 (5.2)	269 (3.7)		10 (3.0)	17 (3.2)	
30-days mortality, n (%)	94 (4.7)	526 (5.9)	0.03	8 (2.0)	18 (2.8)	0.41
Hospital characteristics						
Annual surgical volume, n (%)	579 (28.9)	3051 (34.4)	<0.001	–	–	–
Colon:	1418 (70.8)	5783 (65.1)		108 (26.6)	299 (46.3)	<0.001

(*continued on next page*)

Table 1 (*continued*)

	Colon			Rectum		
	MVR (n = 2004)	Standard resection (n = 8874)	p-value	MVR (n = 406)	Standard resection (n = 646)	p-value
- <75	7 (0.3)	40 (0.5)		297 (73.2)	345 (53.4)	
- ≥75 resections	–	–		1 (0.2)	2 (0.3)	
- Missing						
Rectum						
- <40 resections						
- ≥40 resections						
- Missing						

Abbreviations, MVR: multivisceral resection, SD: standard deviation. Gy: Gray (unit of ionizing radiation dose). Tis: in situ. NOS: not otherwise specified. RT: radiotherapy. AL: anastomotic leakage.
* Chemoradiation: combination of radiation therapy and 5-FU, chemotherapy: various 5-FU based therapies, according to the Dutch guidelines.
$ Data was collected and therefore presented from 2008 onwards.
A + B Multivisceral resections were specified as limited (resection of the abdominal wall, omentum, gallbladder, vagina or ovaries) or extended (pelvic exenteration, additional bowel resections, or resection of the sacrum, bladder, ureters, urethra, prostate, uterus, stomach, liver, hepatic ducts, pancreas, spleen, diaphragm, vesiculae or kidney.
R1: microscopic not radical. R2: macroscopic not radical.
Missing data was not used for analysis.

tumor downstaging, acceptable toxicity, low morbidity and mortality and preliminary better outcome [8–10].

Locally advanced CRC can be divided into T4a and T4b categories, in which the former represents ingrowth in the surface of the visceral peritoneum and the latter entails adjacent organ involvement [11]. To achieve R0 resection for patients with T4b cancers, multivisceral resection (MVR) is required [12,13]. MVR can be technically challenging depending on the extensiveness of ingrowth and the type of structures that are involved and is accompanied with higher morbidity and mortality rates, especially in a non-elective setting [4,14–18]. Regarding survival, the impact of MVR is difficult to determine related to comparative observational data with high risks of bias (i.e. selection, allocation). An improved 5-year OS after MVR for both T4b colon and rectal cancer patients was suggested based on the SEER database [19], but this could not be demonstrated in other studies [15,16,20,21].

This nationwide observational study aimed to determine factors independently associated with the chance of undergoing MVR, completeness of resection and OS in patients with pathologically proven T4 CRC. More specifically, the influence of year of diagnosis and hospital volume on these outcomes was evaluated.

2. Material and methods

An observational study was conducted with the use of the Netherlands Cancer Registry (NCR). All newly diagnosed malignancies are registered in the NCR by trained registry personnel, which gather data on patient, tumor and treatment characteristics directly from the medical records. Data on a patients' vital status was achieved by linking the dataset to the Municipal Personal Records Database.

From the NCR, adult patients who were diagnosed with (y)pT4 colorectal malignancy between 2006 and 2017 were selected. Only those who underwent surgical resection and showed no signs of distant metastasis were included for analysis. The anatomical site of a tumor was coded according to the International Classification of Diseases for Oncology [22], while the TNM-classification was used for staging the primary tumor according to the edition valid at the time of cancer diagnosis [23].

2.1. Subgroups, variables and definitions

Patient, tumor and treatment characteristics were stratified for colon and rectal cancer, as well as for standard resection (SR) and MVR. For survival analyses, patients were stratified for (y)pT4a and (y)pT4b category. Treatment characteristics included the use and type of (neo)adjuvant treatment, setting of surgery (elective, non-elective/emergency), type of resection (SR, limited MVR, extended MVR) and 30-day postoperative mortality. Limited MVR was defined as resection of the abdominal wall, omentum, gallbladder, vagina or ovaries and extended MVR as pelvic exenteration, additional bowel resections, or resection of the sacrum, bladder, ureters, urethra, prostate, uterus, stomach, liver, hepatic ducts, pancreas, spleen, diaphragm, vesiculae or kidney. Pathological variables were completeness of resection (R0, R1, R2), histology and number of (positive) lymph nodes. Vital status at end of follow-up was extracted to assess OS. Tumor location and histology were classified according to the ICD-0-3, see appendix 1 for details. To assess potential changes over time, three subsequent periods with year of diagnosis between 2006 and 2009, 2010–2013 and 2014–2017 were defined. Annual hospital volume was classified as low if less than 75 colonic resections or less than 40 rectal resections were performed and volumes above these cut-offs were classified as high.

2.2. Statistical analysis

Comparisons of patient, tumor and treatment characteristics were performed by X^2 test/Fisher's Exact test for categorical data and Man-Whitney U or unpaired *t*-test for continuous data depending on the distribution of data. Logistic regression analysis was used to determine predictive factors for multivisceral resection and R0 resection. Variables with p-values <0.1 in univariable analysis were included in multivariable analysis. Kaplan-Meier analysis was used to calculate median OS and 5-year OS from the date of surgery. Comparisons were made using a log-rank test. Patients were censored if they were lost to follow-up. Univariable and multivariable Cox regression analyses were used to determine predictive factors of OS. Outcomes were reported as hazard ratios (HRs) with 95% confidence intervals (CI), defining a survival benefit by HR < 1.0. The level of significance was set at $p < 0.05$. Statistical analyses were performed with SPSS version 25.

3. Results

Of 11.930 patients with the histological classification (y)pT4 CRC without distant metastases, 4968 patients (41.6%) were preoperatively staged as cT4 tumor. The majority of patients (n = 10.878, 91.2%) comprised LACC and 1052 patients (8.8%) had LARC. Table 1 shows the baseline characteristics of (y)pT4M0 colon and rectal cancer patients, who underwent MVR or SR. In the preoperatively staged cT4 patients MVR was conducted in 1722 colon patients

(39.1%) and in 347 rectal patients (61.6%, data not shown). As a result, a total of 2410 pT4 patients (20.2%) underwent MVR with an increasing proportion over time for both colon and rectal cancer. Appendix 2 depicts the involved organs in MVRs.

Patients who underwent MVR for LARC more often received neoadjuvant chemoradiotherapy compared to those whom underwent SR (70.7% versus 33.1%). LACC and LARC patients who underwent MVR had significantly more node positive disease ($p < 0.001$). In LARC patients, significantly more pT4b tumors were diagnosed after MVR (283 patients, 69.7%) than after SR (119 patients, 18.4%, $P < 0.001$). Adjuvant chemotherapy was given in 13% of LARC patients, which was not standard therapy during the study period in the Netherlands. Postoperative mortality rates were higher in LACC and there was a significant difference in 30-day mortality between MVR and SR for LACC (4.7% vs. 5.9%, $p = 0.03$), but not for LARC (2.0% vs. 2.8, $p = 0.41$).

3.1. Predictors of MVR

Univariable logistic regression analyses of variables for MVR are presented in appendix 3. Results of multivariable analysis to determine independent factors associated with the chance to undergo MVR are displayed in Table 2. For LACC patients, MVR was independently associated with younger age, recent year of diagnosis, cT4 stage, left-sided tumor location and high annual hospital volume. For LARC patients, these factors were female gender, more recent years of diagnosis, cT4 stage, neoadjuvant radiotherapy and high annual hospital volume.

Table 2
Multivariable logistic regression analysis of factors associated with multivisceral resection in patients with (y)pT4 colorectal cancer.

Variables	Colon multivariable analysis		Rectum multivariable analysis	
	Adjusted OR's (95% CI)	p-value	Adjusted OR's (95% CI)	p-value
Age				
<70 year	1.00 (referent)	–	1.00 (referent)	–
≥70 year	0.80 (0.70–0.90)	**<0.001**	–	–
Gender				
Male	1.00 (referent)	–	1.00 (referent)	–
Female	1.11 (0.98–1.26)	0.10	1.81 (1.32–2.47)	**<0.001**
Year of diagnosis				
2006–2009	1.00 (referent)	–	1.00 (referent)	–
2010–2013	1.95 (1.66–2.28)	**<0.001**	2.18 (1.47–3.24)	**<0.001**
2014–2017	3.61 (3.06–4.25)	**<0.001**	2.72 (1.82–4.08)	**<0.001**
T stage, clinically assessed				
cT1-2-3	1.00 (referent)	–	1.00 (referent)	–
cT4	18.76 (14.92–23.60)	**<0.001**	11.47 (7.93–16.60)	**<0.001**
Tumor location (colon only) #				
Left-sided[A]	1.00 (referent)	–	–	–
Right-sided[B]	0.57 (0.51–0.65)	**<0.001**	–	–
Neoadjuvant treatment (rectum only) #				
None	–	–	1.00 (referent)	–
Neoadjuvant RT or CRT	–	–	2.18 (1.42–3.34)	**<0.001**
Annual hospital volume #				
Low/moderate volume	1.00 (referent)	–	1.00 (referent)	–
High volume	1.20 (1.05–1.38)	**<0.001**	2.17 (1.55–3.04)	**<0.001**

[A + B]: Left-side tumors are located distal to the splenic flexure, right-side tumors are located proximal to the splenic flexure.
Low/moderate volume = < 75 colonic resections per year OR <40 rectum resections per year; High volume = >75 colons OR >40 rectal resections per year.
OR>1.0 are associated with multivisceral resections.

Table 3
Multivariable logistic regression analysis for predictors of incomplete resection in patients with (y)pT4 colorectal cancer.

Variables	Colon multivariable analysis		Rectum multivariable analysis	
	adjusted OR's (95% CI)	p-value	adjusted OR's (95% CI)	p-value
Year of diagnosis				
2006–2009	1.00 (referent)	–	–	–
2010–2013	0.80 (0.63–1.02)	**0.07**	–	–
2014–2017	0.64 (0.49–0.85)	**0.002**	–	–
T stage tumor, clinically assessed				
cT1-2-3	1.00 (referent)	–	1.00 (referent)	–
cT4	3.61 (2.72–4.79)	**<0.001**	1.82 (1.13–2.94)	**0.01**
Lymph node status, clinically assessed				
cN0	1.00 (referent)	–	–	–
cN+	1.45 (1.18–1.77)	**<0.001**	–	**-**
Morphology				
Well/moderately differentiated	1.00 (referent)	–	1.00 (referent)	–
Poor/undifferentiated	1.39 (1.13–1.71)	**0.002**	1.69 (1.05–2.74)	**0.03**
Hospital volume (colon only) #				
<75 colon resections per year	1.00 (referent)	–	–	–
≥75 colon resections per year	0.98 (0.79–1.21)	0.84	–	–
Surgical resection				
Standard resection	1.00 (referent)	–	1.00 (referent)	–
Multivisceral resection	0.62 (0.49–0.79)	**<0.001**	0.67 (0.42–1.08)	0.10

Abbreviations: OR: odds ratio. CI: confidence interval. # No analysis for rectum given the univariable analysis. OR>1.0 are associated with incomplete resections.

3.2. Predictors of incomplete resection

Univariable logistic regression analyses of variables for incomplete resection are presented in appendix 4. In multivariable analysis, a significant increase in the chance of R0 resection over time was seen for LACC, but not for LARC. Independent risk factors for incomplete resection of LACC were cT4, cN+ and poor/undifferentiated tumors, while MVR was associated with less incomplete resections.

In LARC patients, cT4 and poor/undifferentiated tumors were associated with a higher chance of incomplete resection. After correction for confounders, MVR was not an independent predictor for completeness of resection in LARC patients. The results are shown in Table 3.

3.3. Survival

Median follow-up time for LACC patients was 40.0 months (IQR 17.9–73.6) in the MVR group and 39.4 months (IQR 16.4–76.0, p = 0.80) in the SR group. For LARC patients, this was 38.0 months (IQR 19.4–67,3) in the MVR group and 39.2 months (IQR 18.4–72.2, p = 0.78) in the SR group. In (y)pT4b colon cancer, a significantly better 5-year OS after MVR was found than after SR (54% vs. 49%, p < 0.001) and corresponding 5-year OS rates were similar in (y)pT4a colon cancer (50% vs. 50%, p = 0.87; Fig. 1a and b). In (y)pT4a rectal cancer, MVR and SR resulted in 5-year OS rates of 39% and 45%, respectively (p = 0.34). Significantly better 5-year OS was found for MVR if compared to SR in (y)pT4b rectal cancer (44% vs. 28%, p = 0.004; Fig. 2a and b). Univariable Cox regression analyses are presented in appendix 5. In multivariable Cox regression analyses, no significant associations between MVR and OS remained after correction for confounders. Still, after conducting the multivariable analyses without completeness of resection no survival benefit of MVR was witnessed. In both T4 subcategories and in both LACC and LARC, older age, node positivity and incomplete resections were significantly associated with worse OS. Details of the multivariable Cox regression analysis are displayed in Table 4.

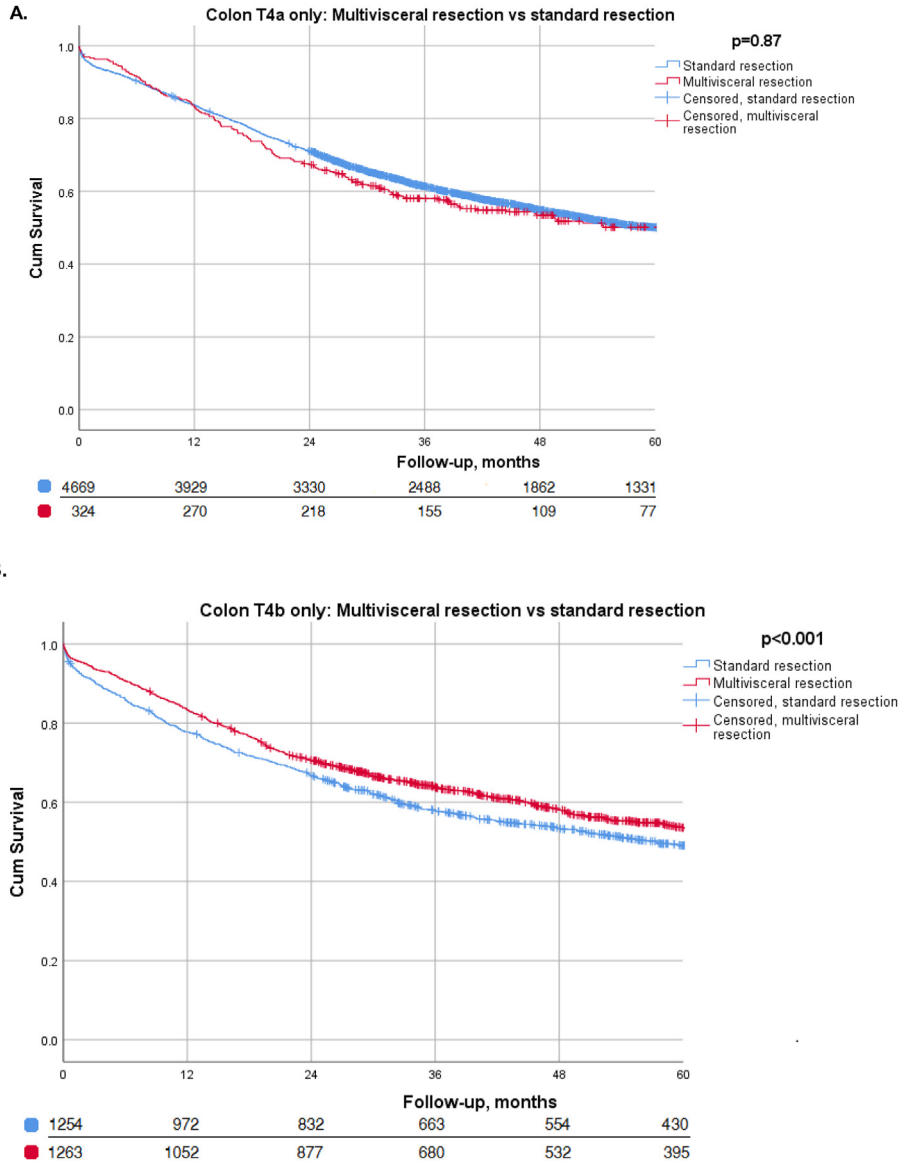

Fig. 1. Kaplan-Meier curve for 5-year overall survival in patients with colon cancer, according to multivisceral resection or standard resection. A. T4a colon tumor only. B. T4b colon tumor only. P-values (log rank test).

4. Discussion

In the present population-based study including patients who underwent resection of (y)pT4M0 CRC between 2006 and 2017, factors independently associated with the chance to undergo MVR for both colon and rectal cancer were more recent diagnosis and high annual hospital volume with the highest ORs for cT4 category. Age ≥70 year resulted in a lower chance of MVR for colon cancer, while male gender was associated with lower chance of undergoing MVR in rectal cancer. Independent risk factors for incomplete resection in both colon and rectal cancer were cT4 and poor/undifferentiated tumors. In LACC, MVR was independently associated with less incomplete resections. A significant improvement in completeness of resection over time was observed for colon cancer, but not for rectal cancer. MVR revealed better OS among (y)pT4b subcategory for both colon and rectal cancer in univariable analysis, but this did not remain significant after correction for confounding factors. Main independent prognostic factors for overall survival were resection margin, node positivity, receiving adjuvant chemotherapy and age.

Regarding national and international guideline compliance to perform MVR in case of cT4 colorectal cancer, 61.6% LARC and 39.1% LACC cT4 patients underwent MVR between 2009 and 2017 in the Netherlands [12,13]. Previous studies reported lower or similar MVR rates in locally advanced colorectal cancer patients [14,19,24,25]. Surgeon related factors, such as experience or willingness to undertake a long complicated surgical procedure play a role in observed MVR rates [26]. Other determinants are logistic barriers, the need for regularly scheduled multidisciplinary meetings and involvement of tertiary centers [26]. Additionally, surgeons potentially feel reluctant to MVR because of higher morbidity and associated mortality risk, including the assumption that a

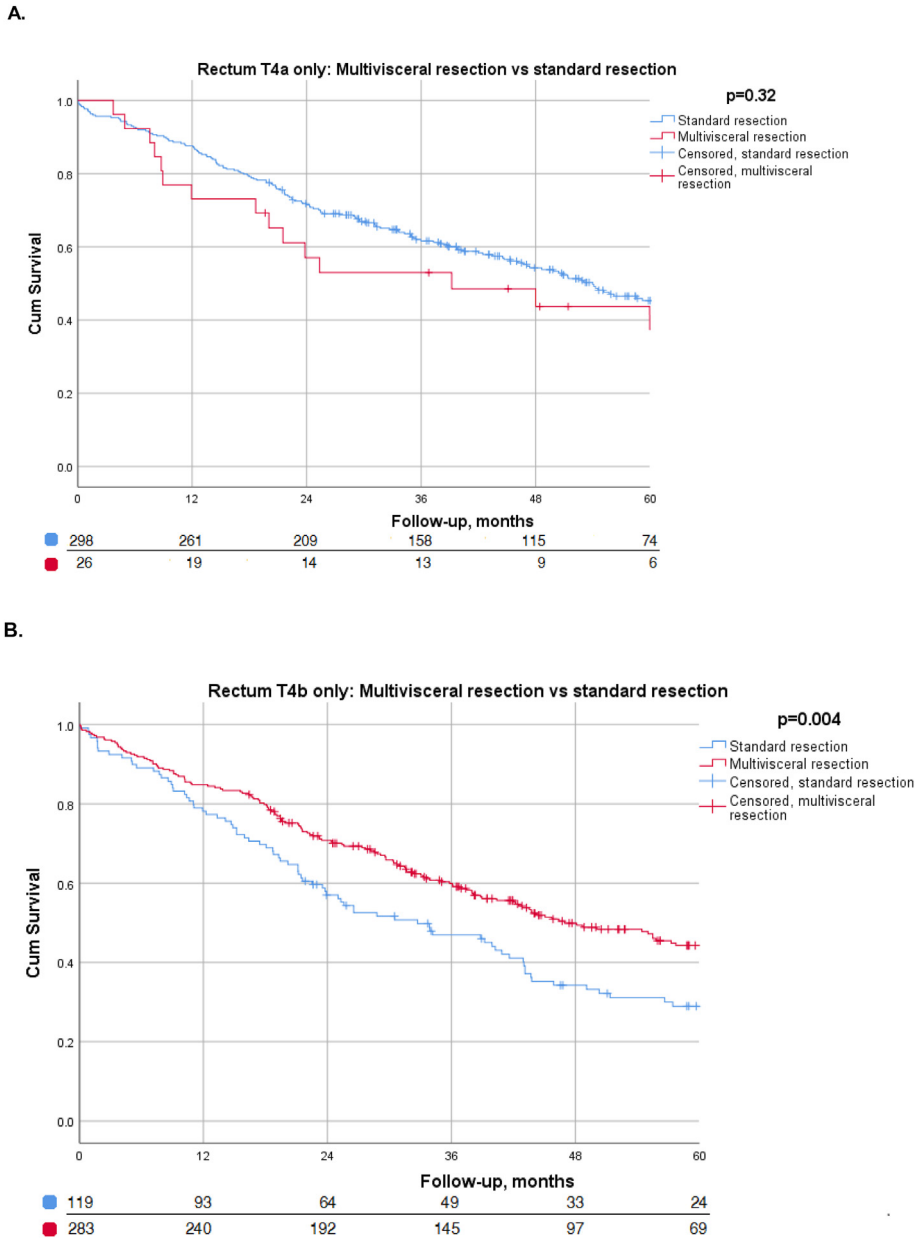

Fig. 2. Kaplan-Meier curve for 5-year overall survival in patients with rectal cancer, according to multivisceral resection or standard resection. A. T4a rectal tumor only. B. T4b rectal tumor only. P-values (log rank test).

patient lacks the ability to tolerate major surgery. Moreover, radiologic and intra-operative misinterpretation of true tumor invasion into surrounding organs or inflammatory response could have resulted in SRs, while there was actually an indication for MVR [18]. The significant increase in proportion of MVR over time in our study suggests more specialization with improvements in staging and multidisciplinary decision making, with better quality of surgery.

One could consider that surgery for locally advanced colorectal cancer needs to be centralized. The decision whether or not to perform MVR should be thoroughly made in each patient pre- and intra-operatively by dedicated specialists. More expertise in locally advanced CRC in high volume hospitals could probably lead to less positive resection margins and better short and long-term oncological outcomes.

Patient-related factors such as older age can also negatively influence the chance to undergo MVR, as suggested by the present study. Age bias in MVR for CRC might be explained by the fact that older patients often have more comorbidity affiliated with increased risk of morbidity and mortality following extensive surgery [19,24]. Age, however, should not be the only reason to omit additional treatment and extended resection. The finding that females were more likely to undergo MVR for LARC in the present study was in line with other studies [14,19]. Differences in MVR rate between women and men might be explained by more severe morbidity following resection of genitourinary organs in men [19], while females have a middle pelvic compartment that allows for en bloc hysterectomy or partial resection of the vagina without the need for total exenteration and urinary diversion.

In the present study we report less incomplete resection margins in LACC over the years. This might also indicate an improvement in quality of surgical care for colon cancer, similar to the observed increase in MVR rate over time. During the past decades, quality improvement in CRC care has mainly focused on rectal cancer, whereas colon cancer surgery only gained more attention in recent years. This might explain that such an improvement in resection margin status was not observed in rectal cancer during the study period. A recently published population-based study observed substantial circumferential margin positivity in rectal cancer, in which positive resection margins occurred significantly more often in MVR (21.2%) versus total mesorectal excision (TME; 13.9%) for LARC and 32% of pT4 rectal cancer patients had involved resection margins without significant difference over the years [27]. The PelvEx Collaborative demonstrated a R0 resection rate of 79.9% for LARC patients who underwent pelvic exenteration with significantly reduced 3-year survival in patients who underwent a R1 resection (29.6%) or R2 (8.1%) resection [28]. There is still room for improvement regarding completeness of resection in both LACC and LARC, especially given the fact that margin status is one of the most important prognostic factors for survival in the present study and previous papers [4,18,28,29].

For locally advanced CRC, several novel induction strategies have been studied to enhance tumor clearance [30–33]. For LACC, a recent study reported a potential benefit of neoadjuvant chemotherapy, because of the positive effect on tumor and lymph node stage and OS was comparable to adjuvant chemotherapy [34]. Results from the FOXTROT study demonstrated less involved margins in LACC patients who underwent neo-adjuvant chemotherapy, which resulted in 95% R0 resections versus 90% ($p = 0.001$) in those who underwent surgery with only adjuvant chemotherapy [30]. Downsizing LACC with radiotherapy might also be beneficial to improve both surgical as well as long-term oncological outcomes

Table 4
Multivariable Cox regression analysis for associations between study population characteristics and overall survival.

Variables	Colon T4a only		Colon T4b only		Rectum T4a only		Rectum T4b only	
	Adjusted HR (95% CI)	p-value	Adjusted HR (95% CI)	p-value	Adjusted HR (95% CI)	p-value	Adjusted HR (95% CI)	p-value
Age								
<70 year	1.00 (referent)	–	1.00 (referent)	–	1.00 (referent)	–	1.00 (referent)	–
≥70 year	1.40 (1.26–1.56)	**<0.001**	1.51 (1.28–1.77)	**<0.001**	1.46 (1.03–2.07)	**0.03**	1.66 (1.10–2.50)	**0.02**
Lymph node status								
pN0	1.00 (referent)	–	1.00 (referent)	–	1.00 (referent)	–	1.00 (referent)	–
pN1	1.69 (1.50–1.90)	**<0.001**	1.80 (1.53–2.11)	**<0.001**	1.77 (1.17–2.69)	**0.007**	1.09 (0.69–1.73)	0.71
pN2	3.30 (2.92–3.74)	**<0.001**	3.11 (2.62–3.69)	**<0.001**	2.55 (1.64–3.97)	**<0.001**	2.12 (1.25–3.58)	**0.01**
Surgical resection								
Standard resection	1.00 (referent)	–	1.00 (referent)	–	1.00 (referent)	–	1.00 (referent)	–
MVR	1.01 (0.83–1.23)	0.93	1.01 (0.88–1.15)	0.90	1.10 (0.57–2.11)	0.78	0.92 (0.58–1.46)	0.72
Morphology								
Well/moderately differentiated	1.00 (referent)	–	1.00 (referent)	–	–	–	1.00 (referent)	–
Poor/undifferentiated	1.18 (1.06–1.32)	**0.002**	1.30 (1.13–1.49)	**<0.001**	–	–	1.29 (0.79–2.11)	0.30
Neoadjuvant treatment								
None	–	-	–	-	–	–	1.00 (referent)	–
Neoadjuvant RT	–	-	–	-	–	–	1.28 (0.72–2.27)	0.40
Neoadjuvant CRT	–	-	–	-	–	–	0.84 (0.50–1.42)	0.52
Adjuvant treatment								
None	1.00 (referent)	–	1.00 (referent)	–	1.00 (referent)	–	–	–
Adjuvant chemotherapy	0.36 (0.32–0.40)	**<0.001**	0.40 (0.34–0.48)	**<0.001**	0.36 (0.21–0.62)	**<0.001**	–	–
Hospital volume								
<75 colon resection/year	1.00 (referent)	–	–	–	–	–	–	–
≥75 colon resection/year	0.95 (0.86–1.05)	0.32	–	–	–	–	–	–
Resection margins								
R0	1.00 (referent)	–	1.00 (referent)	–	1.00 (referent)	–	1.00 (referent)	–
R1	1.63 (1.38–1.93)	**<0.001**	2.13 (1.74–2.60)	**<0.001**	1.14 (0.76–1.71)	0.56	1.72 (1.11–2.67)	**0.02**
R2	3.39 (2.47–4.65)	**<0.001**	2.91 (2.32–3.65)	**<0.001**	7.78 (2.78–22.13)	**<0.001**	6.93 (2.91–16.52)	**<0.001**
Tumor location								
Left-sided[A]	1.00 (referent)	–	1.00 (referent)	–	–	–	–	–
Right-sided[B]	1.03 (0.94–1.13)	0.54	1.05 (0.92–1.21)	0.48	–	–	–	–

Abbreviations: HR: Hazard ratio. CI: confidence interval. MVR: multivisceral resection. RT: radiotherapy. CRT: chemoradiotherapy. R1: microscopic not radical. R2: macroscopic not radical. Significant p-values are printed in bold.
[A + B]: Left-side tumors are located distal to the splenic flexure, right-side tumors are located proximal to the splenic flexure. HR < 1.0 are associated with survival benefit.

[17]. In LARC neoadjuvant (chemo)radiation followed by surgery is generally applied, depending on patient's comorbidity and physical status [5–7]. For LARC, preoperative intensified strategies, i.e. total neoadjuvant therapy, could possibly improve oncological outcome [31]. Preoperative chemotherapy followed by chemoradiotherapy and subsequent TME showed promising results of tumor downstaging and a low rate of involved resection margins in a phase 2 trial with 105 high-risk rectal cancer patients [32]. Furthermore, the RAPIDO-trial determined the added value of preoperative short-course RT followed by chemotherapy as an intensified induction regimen for high-risk rectal cancer with high response rates, although no impact on OS could be demonstrated [33].

The 5-year survival rates after MVR and SR for both locally advanced colon and rectal cancer patients are in concordance with previous studies [14,16,24]. Two studies based on SEER data found better survival when patients underwent MVR in contrast to the present study [19,24], although this should be interpreted with caution as a result of high risk of bias. One American study reported data from 1988 to 2002 with overall substantial lower OS, however survival has significantly improved over the years [19,35].

Despite the fact that our study represents a large cohort of recently treated patients analysed on national level, there are several limitations. First of all, the data are retrospectively collected with inherent methodological short comings. Secondly, the observational design of the study limits the comparability between treatment strategies as a consequence of allocation bias. Factors leading to variation in guideline adherence, completion rate of neoadjuvant or systemic therapy and considerations to perform SR or MVR were missing.

In conclusion, year of diagnosis and hospital volume determined the chance of MVR in locally advanced colorectal cancer. MVR can be safely performed with acceptable postoperative mortality and provides the possibility to obtain a radical resection in locally advanced CRC, which is one of the key prognostic factors for overall survival. Completeness of resection margins has only improved in colon cancer over the years. Aside from margin status, other prognostic predictors identified for overall survival were node positivity, receiving adjuvant chemotherapy and age.

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Appendix A. Supplementary data

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