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Trends and outcome of neoadjuvant treatment for rectal cancer: a retrospective analysis and critical assessment of a 10-year prospective national registry

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Running head: trends of neoadjuvant treatment

ABSTRACT

Introduction: Preoperative treatment and adequate surgery increase local control in rectal cancer. However, modalities and indications for neoadjuvant treatment may be controversial. Aim of this study was to assess the trends of preoperative treatment and outcomes in patients with rectal cancer included in the Rectal Cancer Registry of the Spanish Associations of Surgeons

Method: This is a STROBE-compliant retrospective analysis of a prospective database. All patients operated on with curative intention included in the Rectal Cancer Registry were included. Analyses were performed to compare the use of neoadjuvant/adjuvant treatment in three timeframes: I)2006-2009; II)2010-2013; III)2014-2017.Survival analyses were run for 3-year survival in timeframes I-II.

Results: Out of 14,391 patients,8871(61.6%) received neoadjuvant treatment. Long-course chemo/radiotherapy was the most used approach(79.9%),followed by short-course radiotherapy±chemotherapy (7.6%). The use of neoadjuvant treatment for cancer of the upper third(15-11 cm) increased over time (31.5%vs 34.5%vs 38.6%,p=0.0018). The complete regression rate slightly increased over time (15.6% vs 16% vs 18.5%;p=0.0093);the proportion of patients with involved circumferential resection margins(CRM) went down from 8.2%to7.3%and 5.5%(p=0.0004). Neoadjuvant treatment significantly decreased positive CRM in lower third tumors(OR 0.71, 0.59-0.87, Cochrane-Mantel-Haenszel P=0.0008). Most ypN0 patients also received adjuvant therapy. In MR-defined stage III patients, preoperative treatment was associated with significantly longer local-recurrence-free survival(p<0.0001), and cancer-specific survival(p<0.0001). The survival benefit was smaller in upper third cancers.

Conclusion: There was an increasing trend and a potential overuse of neoadjuvant treatment in cancer of the upper rectum. Most ypN0 patients received postoperative treatment. Involvement of CRM in lower third tumors was reduced after neoadjuvant treatment. Stage III and MRcN+ benefited the most.

Key-words: rectal cancer; T stage; TNM; prognosis; neoadjuvant treatment; survival; radiotherapy; chemotherapy.

INTRODUCTION

Neoadjuvant treatment for rectal cancer combined with proper total mesorectal excision (TME) has been shown to increase local control after curative resection. Over the last years, indications as well as treatment modalities have greatly evolved. A significant variation on them can also be observed when comparing different guidelines for the management of rectal cancer[1-3].

The benefits of neoadjuvant treatment come at the cost of several side effects[4-6], which are often underplayed, due to the short-term outcomes reported in most trials[7]. In addition, an excess of noncancer deaths after neoadjuvant treatment has been reported[7,8]. This could be important, at a time when there is a trend for an increased use of neoadjuvant treatment for rectal cancer.

The need of assessing and improving the outcomes of rectal cancer treatment, led to the set-up of several multicentric registries and initiatives, aimed at capturing data on patients treated over the last decades. Examples include the Norwegian Registry[9] and the Optimizing Surgical Treatment of Rectal Cancer (OSTRiCh) Consortium in the US[10]. Similarly, the Spanish Association of Surgeons(AEC)[11] started in 2006 a national educational project to implement TME across the country, by means of an online database of patients treated for primary rectal cancer. The registry captured data on neoadjuvant and adjuvant treatment, as well as pathological and survival outcome. This article aims at reporting on the trends of use and oncological results of neoadjuvant treatment for rectal cancer over ten years in the context of a quality-improvement initiative.

MATERIAL AND METHODS

This is a retrospective analysis of a prospective national database. The report complies with the Strengthening the Reporting of Observational Studies in Epidemiology(STROBE) statement[12]. The AEC Registry followed the same principles of the Norwegian Registry[9]. The eventual aims were to improve the quality of treatment incorporating TME and multimodal treatment for patients with rectal cancer nationally.

Between 2006 and 2017, 105 hospitals joined the registry with nearly 19,000 patients. All patients, who underwent surgery with curative intent between 2006 and 2017 were evaluated for inclusion. The analyses were conducted after obtaining Ethical Committee approval.

Inclusion criteria

Patients were excluded if they did not receive surgery, if surgery was with palliative intent or if it did not involve resection of the tumor, and if they had metastatic disease at presentation.

Definitions

Neoadjuvant treatment was captured in the database. Data on adjuvant treatment were also collected. Patients were stratified in three timeframes: I) 2006-2009; II) 2010-2013; III) 2014-2017. Local recurrence (LR) was defined as peritoneal, pelvic, or perineal tumor re-growth after curative resection. Distant recurrences were defined as evidence of disease in any other location. Cancer-specific survival (CSS) was defined as death as a consequence of cancer. For overall survival (OS), death for any cause was assessed.

Preoperative assessment was performed by means of CT, MRI, endoscopy, and endorectal ultrasonography, as available. A rigid proctoscopy was used to define tumour height. Definitions and scope of the registry have been previously reported in details[13-15].

Endpoints

The primary endpoint was the rate of patients that received neoadjuvant treatment.

Secondary endpoints included the type of treatment used, the trends of treatment over time, and likeliness of receiving postoperative treatment.

Sub-analyses correlated neoadjuvant treatment with pathologic regression and rates of circumferential margin (CRM) involvement.

Additional analyses included 3-year CSS, OS, LR-free survival, and disease-free survival (DFS) after neoadjuvant treatment in the timeframes I (2006-2009) and II (2010-2013).

Statistical analysis

Continuous variables are reported as median (range), categorical variables are reported as number with percentage (%).

Categorical variables were compared with Fisher's exact test and Chi Square Test for trends as appropriate, whereas continuous variables were compared with Mann-Whitney U and Kruskal-Wallis test.

The Cochrane-Mantel-Haenszel test was used to assess the global risk of CRM involvement and positive resection margins in the different timeframes, stratifying patients according to whether a neoadjuvant therapy was used or not[16]. Results are reported as Odds Ratio (OR) with 95% confidence intervals (95%CI). OR>1 is associated with increased risk.

Binomial logistic regression analyses were run to identify factors associated with neoadjuvant and adjuvant treatment. Only patients that underwent preoperative MRI were included in the regression models, on condition that adequate quantity and quality of information was available. The variables included in the regression for neoadjuvant treatment included sphincter complex status, T stage at MRI (MRcT) and N stage at MRI (MRcN), gender, status of the mesorectal fascia (MRF), tumor height, age, and treatment timeframe. In the regression for adjuvant treatment, pathologic outcomes were also included along with intraoperative perforation, complications, and preoperative treatment.

Kaplan-Meier survival curves were generated to assess survival, and LogRank test was used for comparisons. Cox test was used to estimate the Hazard Ratio (HR). Sensitivity analyses included survival in MRcT3-4 patients and radiological Stage III patients. Sub-analyses according to MRcN and cancer height were performed. Only patients with available data on preoperative MRI scan were included.

The statistical Package for Social Sciences (SPSS version 24.0.0; IBM SPSS statistics, IBM Corporation, Armonk, NY) was used for the analyses. P values <0.05 were considered statistically significant.

RESULTS

Overall, data on 18,782 patients were uploaded on the Registry. After removing 954 patients that did not receive surgery or for whom data were not available, those who underwent emergency surgery, surgery with palliative intent, surgery without resection, pelvic exenteration, local excision, proctocolectomy, transanal TME, and patients with Stage IV disease, a total of 14,391 patients fit in inclusion criteria. Characteristics of patients are summarized in **Table 1**.

Type of neoadjuvant treatment

A total of 8,871 (61.6%) patients received neoadjuvant treatment. This consisted of long course radiation therapy (RT) or chemoradiation therapy (CRT) in 7,377 (79.9%), short course RT with or without chemotherapy in 674 (7.6%), chemotherapy followed by RT in 600 (6.8%), chemotherapy alone in 93(1%), and other modalities in 126(1.4%). Preoperative assessment included MRI in 94.2% of patients that received neoadjuvant treatment.

Trends of neoadjuvant treatment over time

Patients receiving neoadjuvant treatment went slightly up from 58.2% during the first timeframe to 62.5% and 62.6% in the more recent timeframes (**Supplementary Figure 1A**). Long course RT alone was less frequently advocated over time (4.5% vs 3.1% vs 2.8%, p=0.0051). CRT decreased during the second timeframe and increased during the third one (88.9% vs 76.2% vs 80.6%), and always represented the most used modality. (**Supplementary Figure 2**).

In terms of tumor height, the rate of patients receiving preoperative therapy for cancer of the upper third (15-11 cm) increased over time, being 31.5%, 34.5%, and 38.6% in period I, II and III (p=0.0018) (**Figure 1**). Radiological stage I tumors treated with neoadjuvant treatment decreased over time (26% vs 10.1% vs 3.3%, p<0.0001), whereas the rates of stage II remained stable (48.2% vs 52.2% vs 48.7%, p=0.89). Stage III patients receiving neoadjuvant treatment significantly

increased over time (73.1% vs 80.6% vs 82.5%, p<0.0001). There was an increasing use of pre-treatment MRI (88.1% vs 95.2% vs 96.3%, p<0.0001). More advanced MRcT and MRcN were observed in more recent timeframes.

Pathological outcome of neoadjuvant treatment

Complete pathological regression was achieved in 15.7% of patients, whereas 6.6% had no response. We observed an increasing trend over the three timeframes (15.6% vs 16% vs 18.5%; p=0.0093). pNx and pN0 were increasingly observed during time compared with pN1-2 (70.6% vs 71.9% vs 72.9%, p=0.009).

The involved CRM after neoadjuvant treatment decreased over time (8.2% vs 7.3% vs 5.5%, p=0.0004). The same occurred in patients who did not receive preoperative treatment (10.7% vs 8.5% vs 4.6%, p<0.0001). In patients with cancer of the distal rectum, the risk of +ve CRM was significantly reduced by neoadjuvant treatment over the three timeframes (OR 0.71, 0.59-0.87, Cochran-Mantel-Haenszel P=0.0008). However, no significant differences were observed comparing all patients who received vs those who did not receive neoadjuvant treatment in the three different timeframes (OR 0.88, 0.64-1.20, Cochrane-Mantel-Haenszel P=0.42).

The median number of nodes retrieved on the specimen was lower after neoadjuvant treatment compared with no neoadjuvant treatment (12[0-100] vs 15[0-150], p<0.0001), with no significant differences in positive node ratio. Trends were stable over time (**Table 1**).

Postoperative treatment

Up to 76.4% of patients that received neoadjuvant treatment, also received postoperative treatment (**Supplementary Figure 1B**). Most ypN0 patients also received adjuvant therapy in all the timeframes (72.1% vs 73% vs 69.7%, p=0.262).

Factors associated with indication to neoadjuvant and adjuvant treatment

Factors associated with the use of neoadjuvant treatment included threatened MRF (OR 1.285, 95%CI 1.038-1.592, p=0.022); tumor location, being 5 times higher for tumors of the lower third (OR 5.222, 95%CI 4.234-6.440, p<0.0001, advanced MRcT and MRcN stage. Female gender and advanced age (> 65 year-of-age) were associated with lower use of neoadjuvant treatment (**Table 2**).

Factors associated with the use of adjuvant treatment included preoperative treatment (OR 6.316, 95%CI 5.705-6.992, p<0.0001), perioperative complications (OR 1.694, 95%CI 1.544-1.858, p<0.0001), as well as pT and pN stage. Again, female gender and age > 65 years were associated with lower use of adjuvant treatment, along with cancers of the middle and lower rectum (**Table 3**).

Disease-free Survival, Cancer-specific and Overall Survival after Neoadjuvant Treatment over time

Overall, OS was significantly improved in timeframes 2006-2009 and 2010-2013 either with or without preoperative treatment (p<0.0001), whereas CSS survival significantly improved in patients who did not receive neoadjuvant treatment (**Table 4**). LR and DFS did not differ.

When considering tumor height, the benefits of neoadjuvant treatment in terms of LR tended to be more evident in patients with cancer of the lower third (p=0.144). CSS and OS were improved after neoadjuvant treatment, but patients with high rectal cancer had little benefit (p<0.0001) **(Suppl. Figure 3 and Suppl. Figure 4)**.

In patients with radiological stage III rectal cancer, preoperative treatment was associated with significantly longer LR free survival (p<0.0001), CSS (p<0.0001) and OS (p<0.0001) in both timeframes. These differences are particularly relevant in MRcN2 patients. A trend towards an improved DFS was observed with neoadjuvant treatment in Stage III and MRcN +ve patients (**Suppl. Figure 3**).

DISCUSSION

In this national registry, despite a wider use of MRI as staging tool, which currently defines the risk factors for a more selective approach, preoperative therapy has been consistently used and slightly increased over time. Patients with advanced locoregional stages such as a deep penetration into the mesorectal space, threatened or involved MRF, extramural vascular invasion or extensive nodal involvement are in general considered at risk and neoadjuvant treatment is recommended. After 2010, approximately 62.5% of all patients underwent preoperative treatment. This potential overuse was particularly detected in patients with upper rectal cancer, where the use of preoperative treatment can be more contentious[17]. The CSS benefit was more apparent in cancers of the lower third, whereas omitting preoperative treatment would have not affected much the survival of those with upper third cancers (**Figure 2**). Neoadjuvant treatment has significantly improved the outcome in terms of local disease control. These benefits must be weighed against undesired side effects[6]. The EURECCA consortium compared the rates of preoperative treatment for rectal cancer among five different European countries between 2008 and 2009, and found significant variation, ranging between 28% and 86%[18]. The highest rates were found in the Nederland. Following on this report, the Dutch Surgical Colorectal Cancer Audit Group performed a critical appraisal on the use of RT in Nederland[19]. After publication of the revised national guidelines in 2014, the use of RT decreased by 32.8%, 43.5% and 31.6% for cT1N0, cT2N0 and cT3N0 stage, respectively[19]. In the present series, we observed an increasing trend, reaching 62,5% in the last period, which warrants further investigation.

Discrepancies can be observed among the available guidelines concerning the indications to preoperative treatment[1]. In US, the trend is to offer widely neoadjuvant treatment based on MRcT and MRcN. Guidelines from US recommends neoadjuvant treatment in all patients with any cT3 rectal cancer (including N0), independently of the mesorectal spread of the tumor front[2]. However,

this is not the case in current European guidelines, in which selected cT3a/b cancers with minimal penetration into the mesorectal fat are considered amenable for surgical resection without preoperative treatment[1-3], even with suspicious nodes in the mesorectum[3,20,21]. Very recently, the so-called totally-neoadjuvant treatment (TNT) has been described, consisting of CRT followed by consolidation chemotherapy[22]. Although TNT has been associated with reasonable mid-term rates of rectal sparing in T3/T4 N0/N1 resectable cancers of the distal rectum, the role of such treatment should be further elucidated[22,23].

The presence of an involved or threatened MRF is the strongest predictor of LR after curative surgery for rectal cancer, and it should therefore be used to select patients for neoadjuvant treatment[20,21]. The most relevant finding of this study is the significant decrease in +ve CRM over time, ranging from 8.2% in the first timeframe to 7.3% in the second period and 5.5% in the last one. This positive outcome could be a key achievement of this national program. On the other hand, the assessment of surgical quality was based upon the surgical plane defined by the pathologist in the resected specimen, as mesorectal around 80% across the three timeframes. Patients who benefited more from preoperative treatment in terms of R0 resections, were those with cancers located at the lower rectum. Patients with clinical stage III, particularly those with N2 lymph nodal involvement, were those to benefit the most from neoadjuvant treatment in terms of LR, DFS, CSS and OS. In patients with upper third rectal cancer, the impact of neoadjuvant treatment on CSS and OS survival was smaller.

The present study found that neoadjuvant treatment was particularly beneficial for MR-defined stage-III patients, whereas this effect was questionable or less obvious when assessing MRcT and in MRcN0 stage alone. Recently, the QuickSilver trial proposed a combination of MRI-based features to identify patients suitable for surgery without CRT[24]. The MERCURY II study also recommended MRI assessment of low rectal cancers to reduce overtreatment and postoperative morbidity[25].

Limitations

This national study has several limitations, mostly derived from its retrospective analysis. Firstly, data were uploaded on a voluntary basis. The agents and dose used for treatment were not recorded. No data were available concerning the time between the completion of preoperative treatment and surgery. By spreading over 10 years, the herein reported analyses might have been influenced by the evolving treatment modalities over time. Lastly, long term toxicity and specific adverse events of preoperative treatment were not systematically recorded.

One of the main strengths of the study is the involvement of many multidisciplinary teams in different centers across the country in a step-wise educational program on proper TME surgery, sharing common criteria for radiological and pathology staging as well as neoadjuvant treatment. The increased performances in terms of both pathologic and survival outcomes confirmed the benefits of establishing the registry[11,13-15]. Some policies need further investigation, especially the management of patients with cancers of the upper rectum and those with early stages. Additional MRI-based factors and biomolecular markers[24, 26] are likely to provide more information on the open issues on multimodal treatment for rectal cancer, and allow the development of a complete prognostic index for treatment individualization[7].

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Figure Legends

Figure 1. Trends of neoadjuvant treatment over time, according to the height of the tumor. The rate of patients with cancer of the upper third of the rectum increased over time.

Figure 2. Survival according to MRI N status after surgery alone or with preoperative treatment. Patients with N +ve disease at MRI had longer local recurrence-free survival after neoadjuvant treatment ($p=0.001$), and longer cancer-specific survival ($p<0.0001$), especially those with MRcN2 disease. Even if not significant, disease-free survival seemed to be longer after preoperative treatment, but this was only observed in MRcN2 patients, suggesting a potential detrimental effect in N -ve individuals.

Supplementary Material Legends

Supplementary Figure 1. Trends of multimodal treatment over time. A: Neoadjuvant treatment. Overall, there was an increase in the proportion of patients receiving preoperative treatment over time. **B:** Adjuvant treatment over time. Most patients received postoperative treatment, the rates being stable over time. The majority of patients with node negative disease at pathology also received adjuvant treatment, although this strategy does not seem to be supported by strong evidence.

Supplementary Figure 2. Types of neoadjuvant treatments over time. Long course chemoradiation therapy was the most used regimen overall. There was an increased use of alternative treatment modalities during the last years. *RT: radiation therapy; CRT chemoradiation therapy; ChT: chemotherapy*

Supplementary Figure 3. Survival according to rectal cancer height after surgery alone or with preoperative treatment. Local recurrence-free survival seemed be ameliorated only in patients with low rectal cancer ($p=0.144$). Cancer-specific survival was improved after neoadjuvant treatment, but the effects were more apparent for cancer below the 10 cm ($p<0.0001$).

Supplementary Figure 4. Overall survival according to MRI N status and rectal cancer height after surgery alone or with preoperative treatment. Overall survival was improved after neoadjuvant treatment, but the effects were more apparent for cancer with N2 stage and below 10 cm ($p<0.0001$).

Table 1. Demographic and multimodal therapy details for patients treated in three timeframes.

Variable	2006-2009 (n=2923)	2010-2013 (n=7370)	2014-2017 (n=4098)	P value
Age, years	69 (23-95)	69 (22-100)	68 (21-94)	0.646
Female gender	985 (33.7)	2505 (34)	1465 (35.7)	0.06
ASA score:				**0.0001**
- I	171 (5.9)	442 (6.0)	277 (6.8)	
- II	1601 (54.8)	3904 (53)	2079 (50.7)	
- III	1057 (36.2)	2756 (37.4)	1641 (40)	
- IV	94 (3.2)	268 (3.6)	101 (2.5)	
Tumor height				**0.018**
- 11-15 cm	718 (24.6)	1749 (23.7)	1035 (25.3)	
- 7-10 cm	1051 (36)	2838 (38.5)	1583 (38.6)	
- 0-6 cm	1154 (39.5)	2783 (37.8)	1480 (36.1)	
MRcT:				**<0.0001***
- T0	22 (0.8)	43 (0.6)	36 (0.9)	
- T1	288 (9.9)	125 (1.7)	59 (1.4)	
- T2	1107 (37.9)	1354 (18.4)	803 (19.6)	
- T3	827 (28.3)	4136 (56.1)	2333 (56.9)	
- T4	120 (4.1)	912 (12.4)	497 (12.1)	
- Missing	559 (19.1)	800 (10.9)	370 (9.0)	
MRcN:				**0.003***
- N0	803 (27.5)	2161 (29.3)	1158 (28.3)	
- N1	940 (32.2)	2491 (33.8)	1420 (34.7)	
- N2	621 (21.2)	1918 (26)	1150 (28.1)	
- Missing	559 (19.1)	800 (10.9)	370 (9.0)	
Radiological Stage:				**<0.0001***
- I	617 (21.1)	1070 (14.5)	514 (12.5)	
- II	398 (13.6)	1288 (17.5)	620 (15.1)	
- III	1786 (61.1)	4658 (63.2)	2663 (65.0)	
- not formally stated	132 (4.2)	354 (4.9)	301 (7.3)	
Neoadjuvant treatment	1701 (58.2)	4603 (62.5)	2567 (62.6)	**<0.0001**
- Long course RT	76 (4.5)	141 (3.1)	72 (2.8)	
- Long course CRT	1512 (88.9)	3509 (76.2)	2067 (80.6)	
- ChT	14 (0.8)	60 (1.3)	19 (0.7)	
- Short Course RT +/- ChT	80 (4.7)	434 (9.4)	160 (6.2)	
- ChT followed by RT	19 (1.1)	443 (9.6)	138 (5.4)	
- other	- (-)	16 (0.3)	111 (4.3)	
Perforation	131 (4.5)	298 (4.0)	185 (4.5)	0.053
Adjuvant treatment	1788 (61.2)	4545 (61.7)	2087 (50.9)	**<0.0001**
ypT:	*in 1701 patients*	*in 4603 patients*	*in 2567 patients*	**<0.0001***
- Tx	52 (3.1)	95 (2.1)	23 (0.9)	
- T0	216 (12.7)	619 (13.4)	426 (16.6)	
- Tis	17 (1.0)	57 (1.2)	30 (1.2)	
- T1	108 (6.3)	237 (5.1)	157 (6.1)	
- T2	444 (26.1)	1255 (27.3)	697 (27.2)	
- T3 a,b	510 (30)	1554 (33.8)	873 (34)	
- T3 c,d	293 (17.2)	528 (11.5)	201 (7.8)	
- T4 a	39 (2.3)	136 (3.0)	68 (2.6)	
- T4 b	22 (1.3)	106 (2.3)	39 (1.5)	
- Missing	0 (0)	16 (0.3)	53 (2.1)	
ypN:	*in 1701 patients*	*in 4603 patients*	*in 2567 patients*	**0.008***
- Nx	588 (34.6)	1594 (34.6)	840 (32.7)	
- N0	612 (36.0)	1705 (37)	995 (38.8)	
- N1	342 (20.1)	867 (18.8)	505 (19.7)	
- N2	158 (9.3)	421 (9.1)	174 (6.8)	
- Missing	0 (0)	16 (0.3)	53 (2.1)	

Table 1. ***continued***

Variable	2006-2009 (n=2923)	2010-2013 (n=7370)	2014-2017 (n=4098)	P value
Number of isolated lymph nodes after neoadjuvant treatment	12 (0-58)	12 (0-91)	12 (0-107)	0.791
Distal margin affected after neoadjuvant treatment†	11 (0.6)	33 (0.7)	17 (0.7)	0.953
CRM affected after neoadjuvant treatment‡	140 (8.2)	336 (7.3)	139 (5.5)	**0.0004**
Quality of the mesorectum after neoadjuvant treatment§				0.308
- Complete	1348 (80)	3576 (79.8)	2026 (80.6)	
- Nearly complete	237 (14.1)	583 (13)	317 (12.6)	
- Incomplete	99 (5.9)	321 (7.2)	171 (6.8)	

Data are expressed as number of patients (%) or median (range)
* only including available information
† 5/1701 missing in 2006-2009; 44/4603 missing in 2010-2013; 53/2567 missing in 2014-2017
‡ 1/1701 missing in 2006-2009; 19/4603 missing in 2010-2013; 53/2567 missing in 2014-2017.
§ 17/1701 missing in 2006-2009; 123/4603 missing in 2010-2013; 53/2567 missing in 2014-2017
ASA: American Society of Anesthesiologists
ChT Chemotherapy
CRT chemoradiation therapy
MR Magnetic Resonance
RT radiation therapy

Table 2. Multivariate regression for factors associated with preoperative treatment (neoadjuvant treatment)

	OR	95%CI		p-value
Gender:				**<0.0001**
- Male	1	-	-	
- Female	0.758	0.648	0.885	
Age:				**<0.0001**
- < 65 year-of-age	1	-	-	
- ≥ 65 year-of-age	0.582	0.498	0.679	
Mesorectal fascia threatened	1.285	1.038	1.592	**0.022**
Sphincter complex involved	1.138	0.766	1.691	0.522
Tumor height:				**<0.0001**
- 15-11 cm	1	-	-	
- 7-10 cm	3.304	2.750	3.970	
- 0-6 cm	5.222	4.234	6.440	
MRcT stage:				**<0.0001**
- cT1	1	-	-	
- cT2	2.287	1.503	3.482	
- cT3	4.826	3.141	7.415	
- cT4	7.951	3.844	16.443	
MRcN stage:				**<0.0001**
- cN0	1	-	-	
- cN1	5.250	4.430	6.222	
- cN2	8.920	7.249	10.977	
Timeframe of treatment				0.247
- 2006-2009	1	-	-	
- 2010-2013	0.882	0.714	1.090	
- 2014-2017	1.010	0.774	1.319	

MR: magnetic resonance OR: Odds Ratio; 95%CI 95% confidence intervals
OR>1 associated with increased used of neoadjuvant treatment; statistically significant values **bold**

Table 3. Multivariate regression for factors associated with postoperative treatment (adjuvant treatment)

	OR	95%CI		p-value
Gender:				**0.025**
- Male	1	-	-	
- Female	0.897	0.816	0.986	
Age:				**<0.0001**
- < 65 year-of-age	1	-	-	
- ≥ 65 year-of-age	0.393	0.357	0.432	
Intraoperative perforation	1.011	0.790	1.293	0.932
Tumor height:				0.070
- 15-11 cm	1	-	-	
- 7-10 cm	0.874	0.773	0.989	
- 0-6 cm	0.874	0.770	0.992	
Lymph nodes on specimen:				0.832
- ≥ 12	1	-	-	
- < 12	1.022	0.836	1.249	
Involved circumferential margin	1.125	0.919	1.377	0.255
Involved distal margin	0.943	0.564	1.578	0.823
pT stage:				**<0.0001**
- pTx	1	-	-	
- pT0	1.147	0.761	1.728	
- pTis	0.467	0.278	0.785	
- pT1	0.579	0.382	0.879	
- pT2	0.803	0.542	1.189	
- pT3 a.b	1.359	0.916	2.017	
- pT3 c.d	1.424	0.942	2.152	
- pT4 a	2.013	1.247	3.251	
- pT4 b	2.298	1.345	3.928	
pN stage:				**<0.0001**
- pNx	1	-	-	
- pN0	0.741	0.592	0.928	
- pN1	2.748	2.262	3.339	
- pN2	2.543	2.006	3.225	
Timeframe of treatment				0.744
- 2006-2009	1	-	-	
- 2010-2013	0.971	0.862	1.094	
- 2014-2017	0.949	0.830	1.085	

OR: Odds Ratio; 95%CI 95% confidence intervals
OR>1 associated with increased used of adjuvant treatment; statistically significant values **bold**

Table 4. Oncologic outcome according to multimodal treatment for patients operated on in two timeframes with long term follow-up available. Only patients that underwent preoperative MRI assessment were included.

Variable	2006-2009	2010-2013	OR (95%CI)	P value
Local Recurrence				
- No neoadjuvant treatment	33/793 (4.16)	79/2034 (3.88)	1.08 (0.71-1.63)	0.73
- Neoadjuvant treatment	64/1407 (4.54)	145/4099 (3.54)	1.29 (0.96-1.75)	0.09
Distant recurrence				
- No neoadjuvant treatment	106/793 (13.37)	227/2034 (11.16)	1.23 (0.96-1.57)	0.10
- Neoadjuvant treatment	197/1407 (14)	588/4099 (14.34)	0.97 (0.82-1.16)	0.75
Death for cancer				
- No neoadjuvant treatment	67/793 (8.45)	126/2034 (6.2)	1.39 (1.03-1.90)	**0.03**
- Neoadjuvant treatment	75/1407 (5.33)	169/4099 (4.12)	1.31 (0.99-1.73)	0.06
Death for any cause				
- No neoadjuvant treatment	179/793 (22.57)	288/2034 (14.16)	1.77 (1.44-2.18)	**<0.0001**
- Neoadjuvant treatment	223/1407 (15.85)	475/4099 (11.59)	1.44 (1.21-1.71)	**<0.0001**

Data are expressed as number of patients (%). OR>1 favors the time frame 2010-2013 (increased risk for the time frame 2006-2009)
MRI Magnetic Resonance Imaging
OR Odds Ratio
95%CI 95% confidence intervals

Figure 1

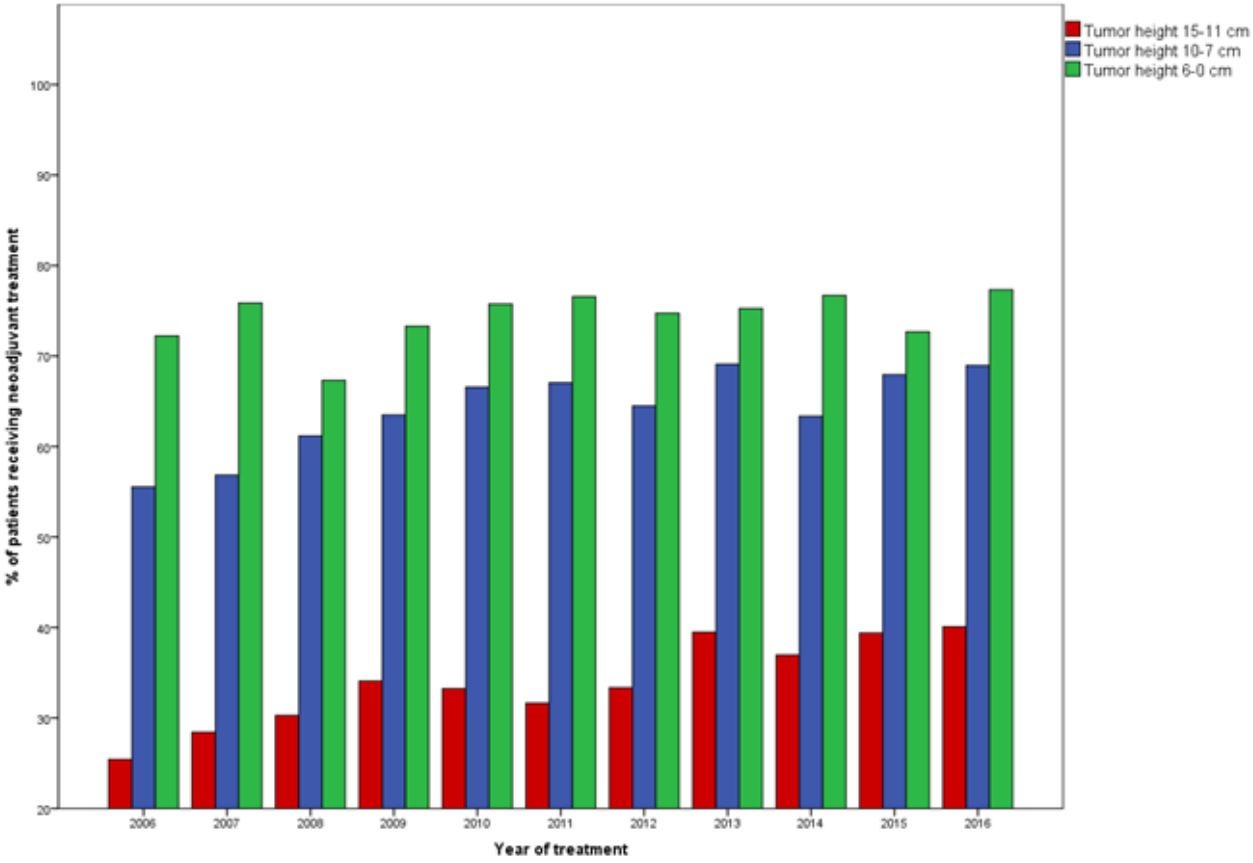

Tumor height 15-11 cm
Tumor height 10-7 cm
Tumor height 6-0 cm
% of patients receiving neoadjuvant treatment
100
90
80
70
60
50
40
30
20
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
Year of treatment

Figure 2

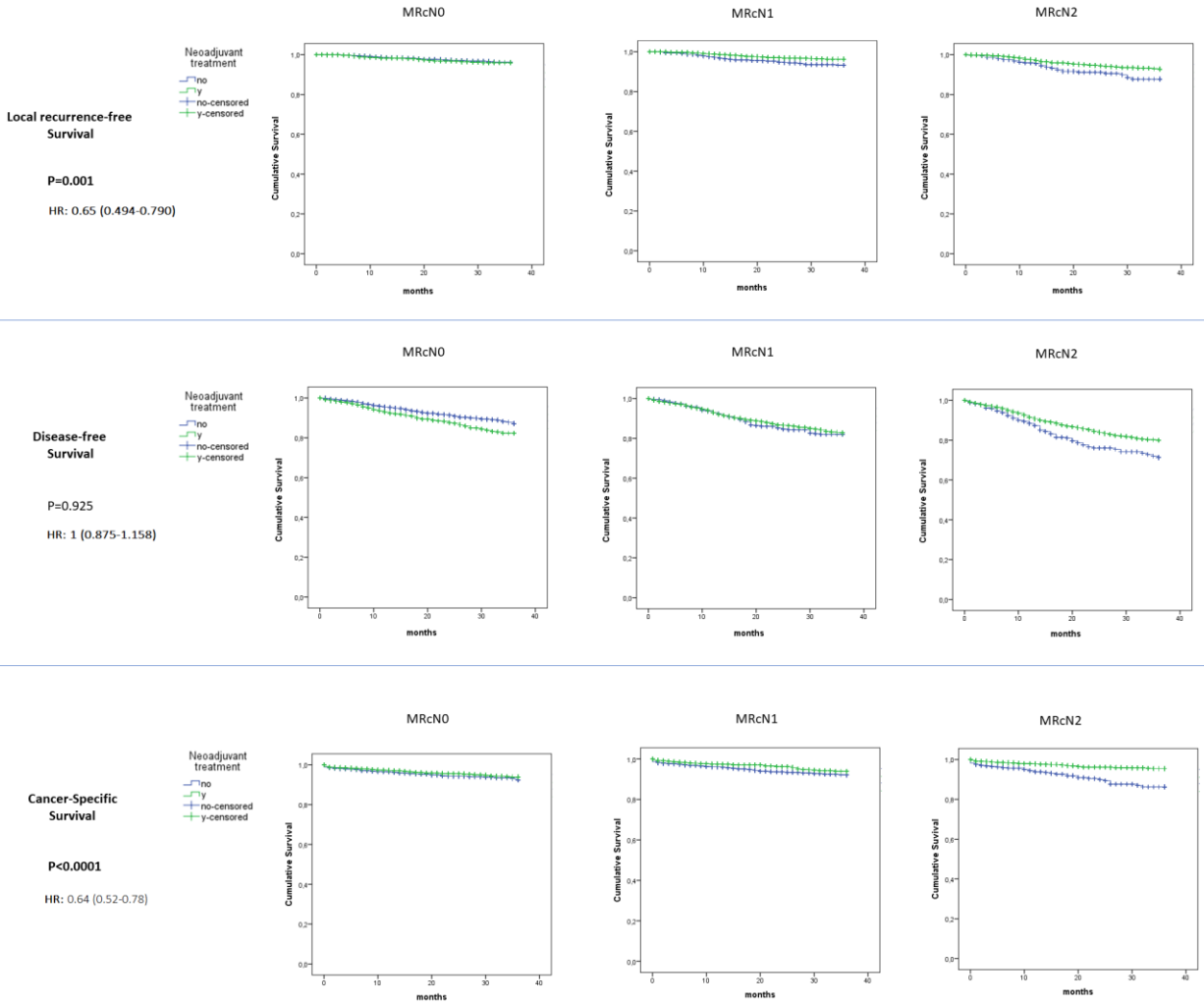

MRcN0
MRcN1
MRcN2
Neoadjuvant treatment
no
y
no-censored
y-censored
Local recurrence-free Survival
P=0.001
HR: 0.65 (0.494-0.790)
Disease-free Survival
P=0.925
HR: 1 (0.875-1.158)
Cancer-Specific Survival
P<0.0001
HR: 0.64 (0.52-0.78)
Cumulative Survival
months

Figure 3

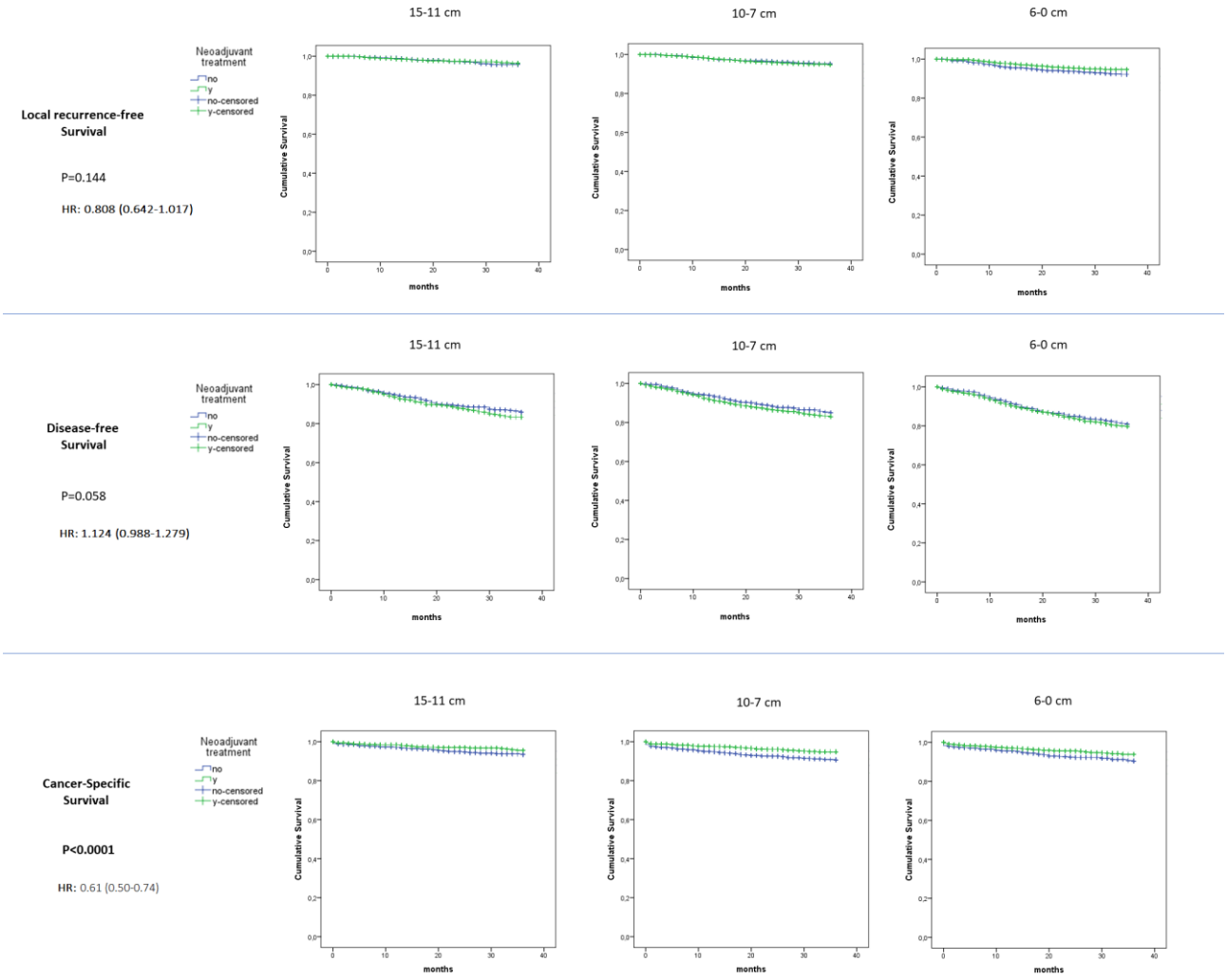
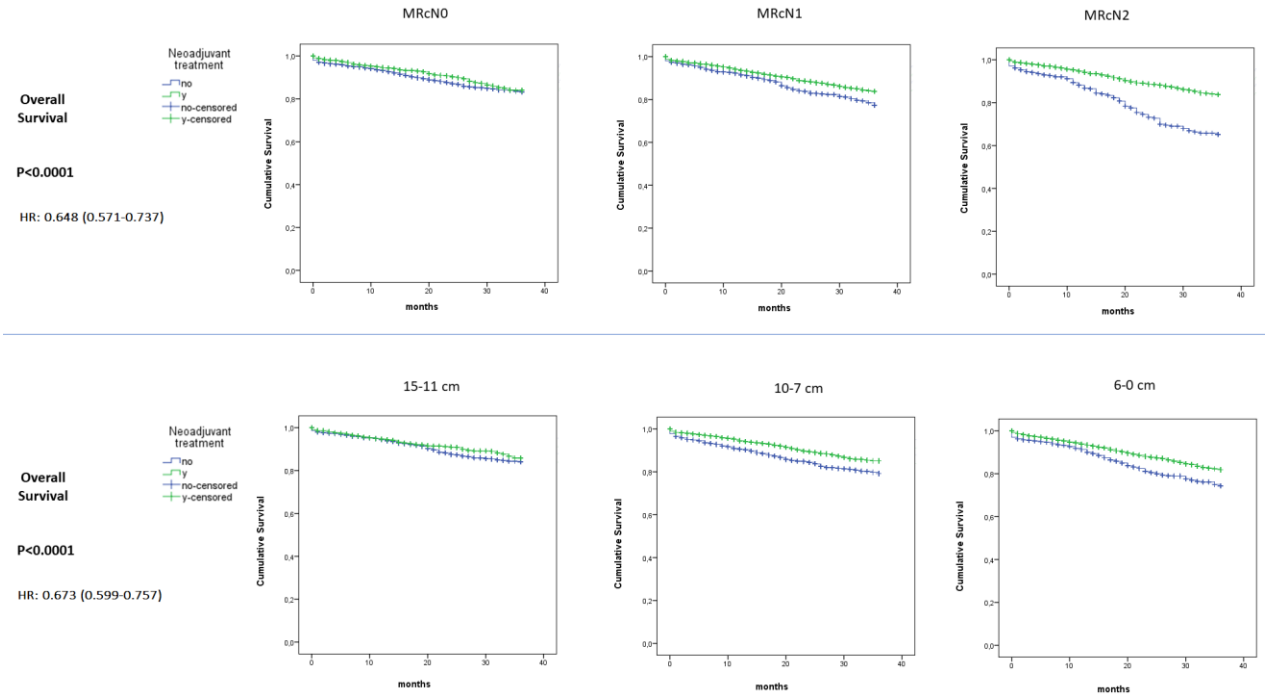
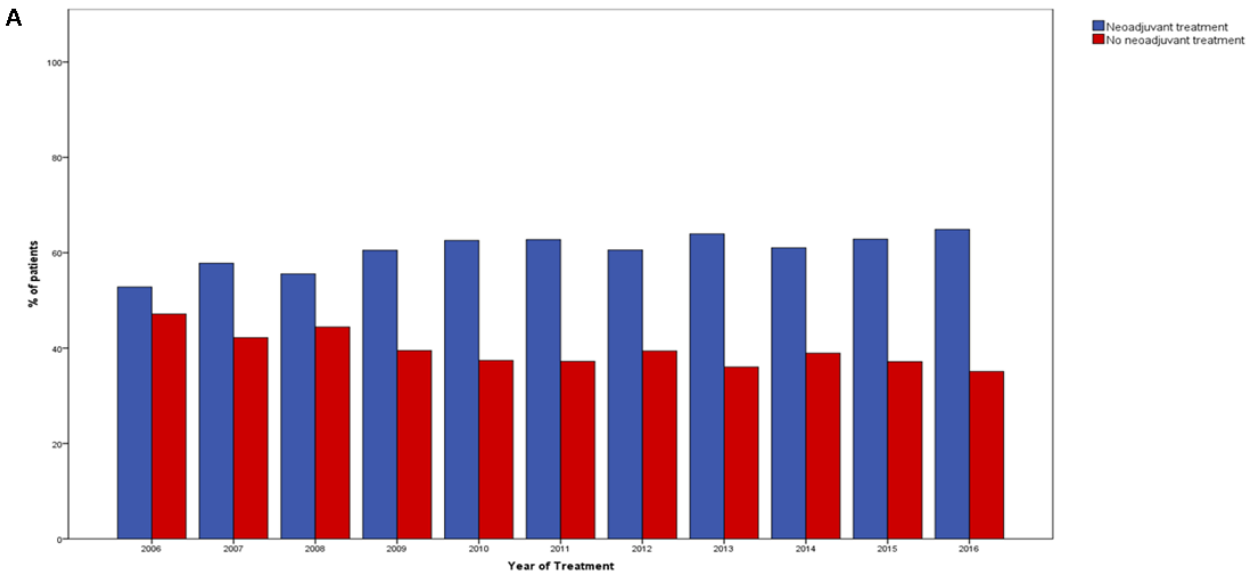

15-11 cm
10-7 cm
6-0 cm
Neoadjuvant treatment
no
y
no-censored
y-censored
Local recurrence-free Survival
P=0.144
HR: 0.808 (0.642-1.017)
Disease-free Survival
P=0.058
HR: 1.124 (0.988-1.279)
Cancer-Specific Survival
P<0.0001
HR: 0.61 (0.50-0.74)
Cumulative Survival
months

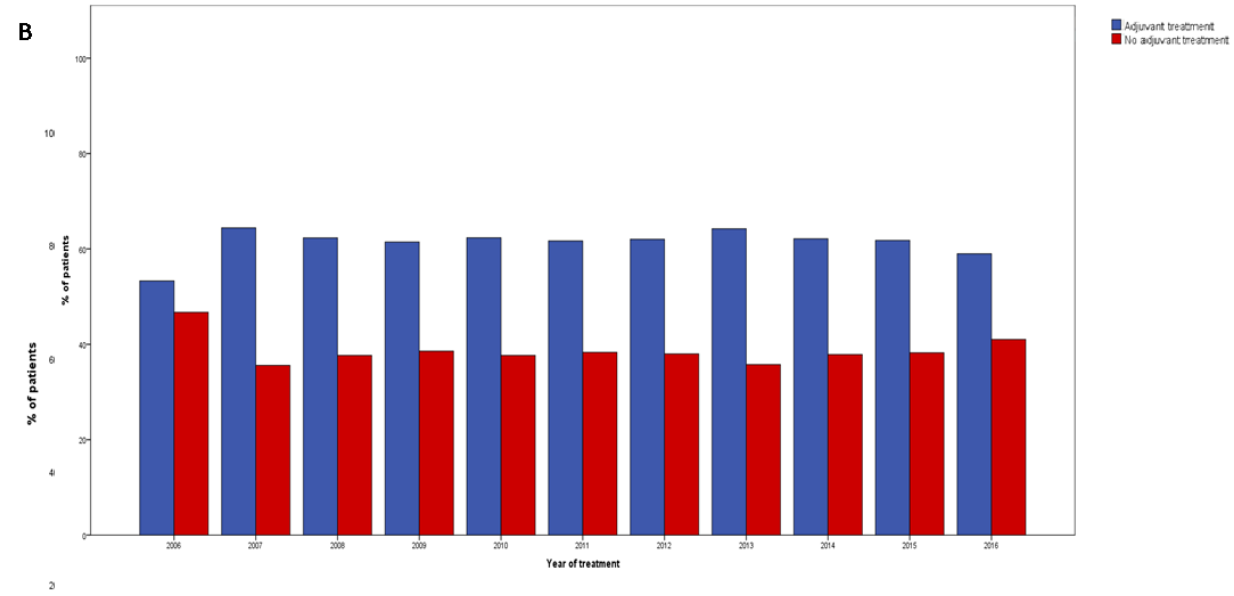
Figure 4


MRcN0
MRcN1
MRcN2
Neoadjuvant treatment
no
y
no-censored
y-censored
Overall Survival
P<0.0001
HR: 0.648 (0.571-0.737)
Cumulative Survival
months

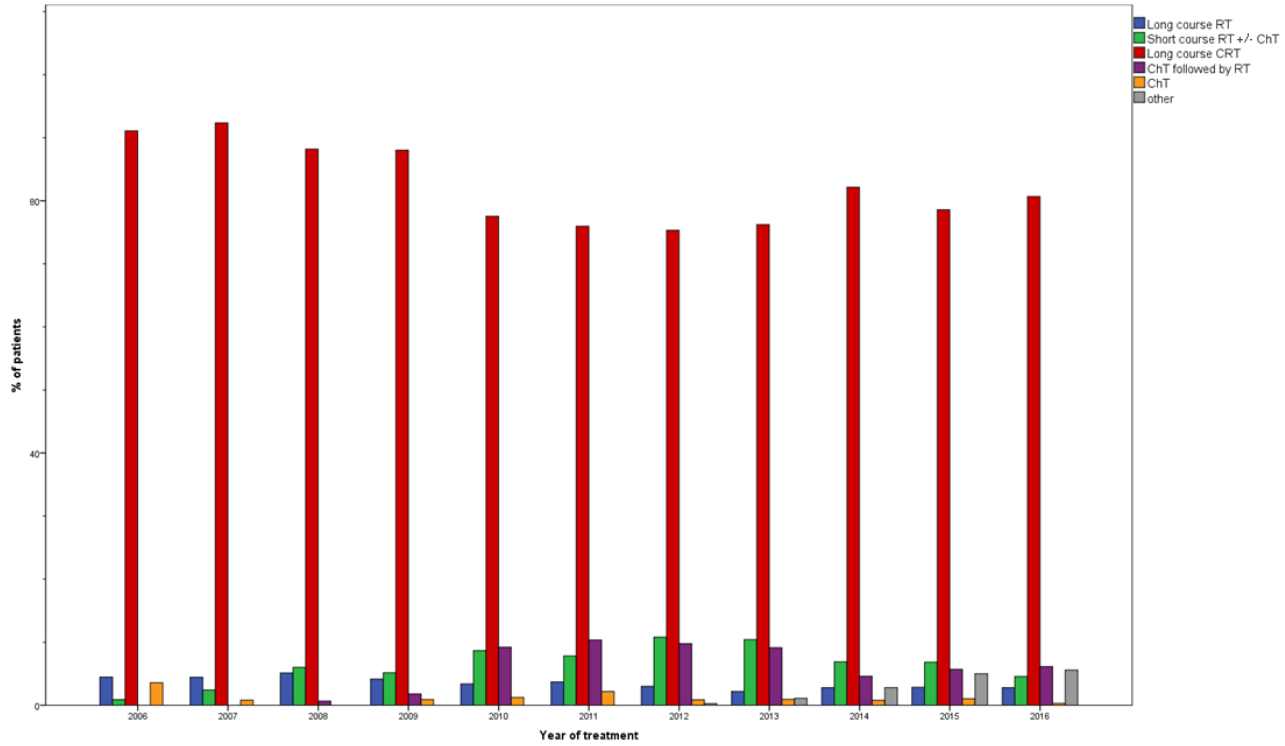
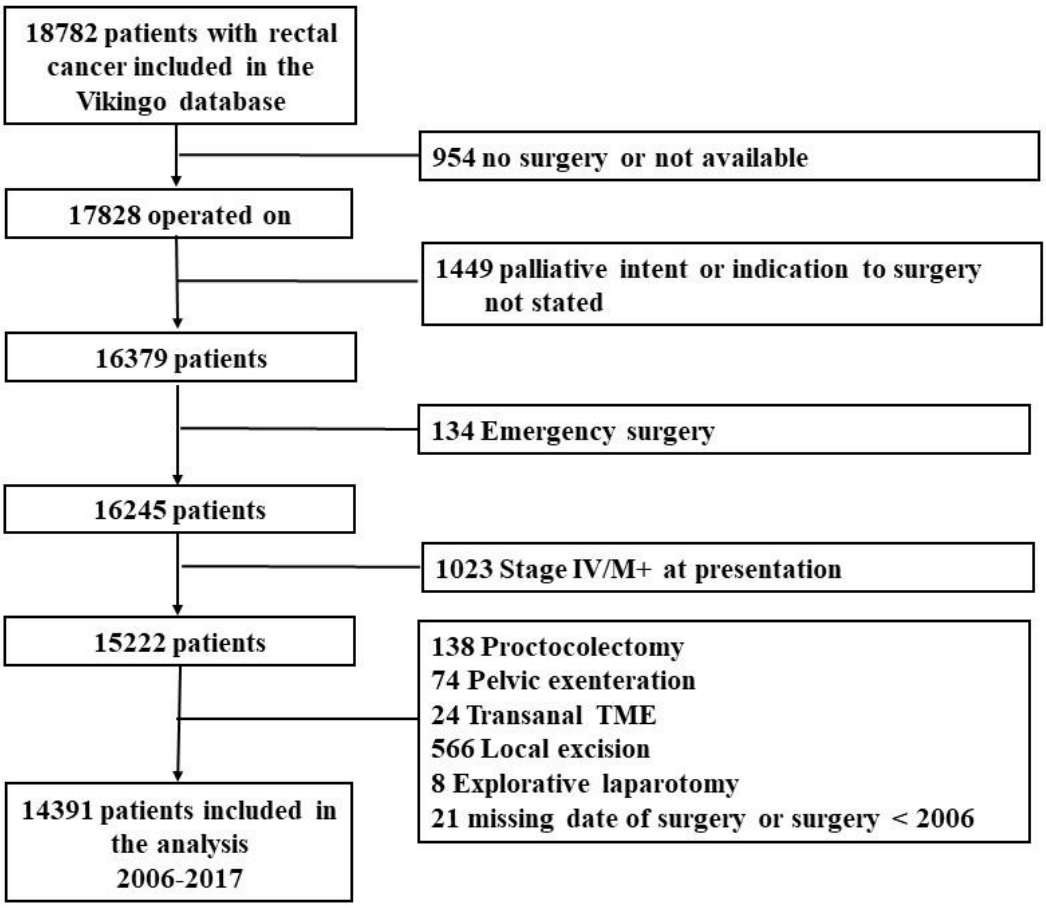
15-11 cm
10-7 cm
6-0 cm
Neoadjuvant treatment
no
y
no-censored
y-censored
Overall Survival
P<0.0001
HR: 0.673 (0.599-0.757)
Cumulative Survival
months

Suppl Fig 1


A
Neoadjuvant treatment
No neoadjuvant treatment
% of patients
Year of Treatment
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016


B
Adjuvant treatment
No adjuvant treatment
% of patients
Year of treatment
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016

Suppl Fig 2


Long course RT
Short course RT +/- ChT
Long course CRT
ChT followed by RT
ChT
other
% of patients
80
40
0
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
Year of treatment

STROBE Diagram