Comparison of Changes in Disease-Free and Overall Survival of Resectable Rectal Adenocarcinoma between 2010 and 2015

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Keywords

Rectal cancer surgery · Neoadjuvant therapy · Multidisciplinary approach · Magnetic resonance imaging · Survival

Abstract

Background: Management of rectal cancer (RC) has undergone many changes in recent decades. A multidisciplinary approach to this complex disease is essential, ensuring high-quality diagnostic, treatment, and outcomes. We aimed to compare treatment results of RC in a single-centre setting between 2010 and 2015. **Methods:** A retrospective comparative study included patients with newly diagnosed and operated resectable RC. Patients' diagnostic and treatment data were analysed. Postoperative morbidity was measured according to the Clavien-Dindo classification. Survival data were received from the Lithuanian Cancer Registry. Continuous variables were expressed as mean and SD. Student *t* test and one-way ANOVA were used for parametric data and the Mann-Whitney test for non-parametric. A multivariate logistic regression analysis was used to identify independent factors for increased survival. Association between categorical variables was verified using Pearson χ^2 . **Results:** The study included 179 patients: 80 from 2010 and 99 from 2015. Mean sample age was 67.1 ± 10.7 years. There was no significant

difference regarding age, gender, median ASA (3 in both groups), but mean hospital stay was 2 days shorter (8 vs. 10 days) in 2015 ($p = 0.002$). There were only 8 patients (4%) admitted to the hospital on an emergency basis. Pelvis MRI and abdominal CT were performed more often in 2015: from 37.5 to 77.8% ($p < 0.001$) and from 52.5 to 97% in 2015, respectively. Circumferential margin evaluation increased from 13.8 to 36.4% ($p = 0.001$). Neoadjuvant therapy increased from 20% in 2010 to 44.9% in 2015 ($p = 0.01$). The overall postoperative Clavien-Dindo complication rate was higher in 2015 (13.8 vs. 20.2%, $p = 0.596$), but in-hospital mortality was lower (1 vs. 0 patients). Comparison of radiological TNM and pathological TNM with one-way ANOVA showed a significant difference staging between 2010 ($p = 0.002$) and 2015 ($p = 0.001$). The 2-year overall survival (OS) increased from 76.3 to 86.9% ($p = 0.046$) and the median disease-free survival from 27 (range 0–35) months to 28 (range 0–35) months (72.5–83.5%, $p = 0.077$). Multivariate logistic regression analysis determined that availability and performance of MRI were associated with an increased OS (OR = 1.529, 95% CI 0.916–2.554, $p = 0.020$). **Conclusions:** The expanded quantity of preoperative imaging, an improved radiological staging, and compulsory multidisciplinary team board discussions have led to selective neoadjuvant treatment decision followed by surgery which can positively affect the 2-year OS rate.

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Introduction

Colorectal cancer is the most common malignant disease of the gastrointestinal tract and is the third most common malignancy in men (1,026,215 cases, 10.9% of total cancers) and the second in women (823,303, 9.5% of total cancers) worldwide [1]. Unfortunately, it is still a significant cause of morbidity and mortality worldwide, and the incidence is predicted to increase in both genders [1, 2]. To make matters worse, this number is growing in economically transitioning Eastern European countries, including Lithuania, where the risk has been historically low [2].

In 2018, an estimated 487,714 men and women will be diagnosed with colorectal cancer; 175,219 of them with rectal cancer (RC) [3]. In countries of the EU, the estimated incidence of RC is 15.8 cases per 100,000 population, and in Lithuania it is 16.2 cases per 100,000 population.

According to the most recent data, the 5-year survival rate for RC was analogous among the Nordic countries (64–69%) and among most southern European countries (61%), while in the Baltic countries survival was lower, ranging between 50 and 59% [4]. Survival trends between 2000 and 2014 were generally increasing. In Lithuania, the 5-year survival rate of RC patients has changed from 40.6 to 52.7% in patients diagnosed with RC [5].

The 5-year overall survival (OS) rate has increased from 55.4 up to 63.4% in the comparative observational cohort study conducted in the three Lithuanian cancer hospitals in 2005 and 2010 [5]. Preoperative diagnosis and surgical treatment as well as a pathological examination of the specimen, and postoperative course were associated with improved OS in RC patients. Though, accessibility of magnetic resonance imaging (MRI) and radiochemotherapy differs among centres.

Fortunately, the management of RC has undergone many changes in recent decades. Including the colorectal cancer management guidelines which were approved by the Ministry of Health of the Republic of Lithuania in 2012 and revised in 2014 [6]. As a result, a multidisciplinary approach to this complex disease is essential, ensuring high-quality treatment and outcomes [7].

Currently, there are various options for a neoadjuvant treatment (NT) regimen for locally advanced RC [8]. Though surgical resection is the main goal for potentially resectable RC. However, the first therapeutic act decided at the multidisciplinary team (MDT) meetings is crucial [9, 10].

The purpose of this study was to compare treatment results of RC in a single-centre setting from 2010 with those from 2015 and identify responsible factors in terms of national future perspectives.

Table 1. General characteristics

Variable	2010	2015	<i>p</i> value
Patients, <i>n</i>	80	99	NA
Median ASA (range)	3 (1–4)	3 (2–4)	0.692
Mean age, years	64.4±9.9	66.8±11.4	0.674
Emergency setting	2 (2.5%)	6 (6.1%)	0.154
Gender, <i>n</i>			
Male	47 (58.8%)	49 (49.5%)	0.218
Female	31 (31.2%)	50 (50.5%)	
Cancer stage			
I	12 (15%)	8 (8.1%)	0.249
II	16 (20%)	21 (21.2%)	
III	45 (56.3%)	58 (58.6%)	
IV	7 (8.8%)	12 (12.1%)	
Diagnostic workup			
Colonoscopy + biopsy	80 (100%)	99 (100%)	NA
Liver ultrasound	62 (77.5%)	67 (67.7%)	0.999
ERUS	18 (22.5%)	3 (3.0%)	0.929
Chest X-ray	60 (75.0%)	99 (100%)	0.816
Abdominal – pelvis CT	42 (52.5%)	96 (97.0%)	0.759
Chest CT	15 (18.6%)	67 (67.7%)	<0.001
Pelvis MRI	30 (37.5%)	77 (77.8%)	<0.001
Tumor site from linea dentata			
<5 cm	8 (10%)	15 (15.2%)	0.152
5–10 cm	51 (63.7%)	42 (42.4%)	
>10 cm	21 (26.3%)	42 (42.4%)	

ASA (American Society of Anesthesiologists) – Physical Status Classification System. ERUS, endorectal ultrasound; CT, computed tomography; MRI, magnetic resonance imaging; X-ray, Röntgen rays.

Materials and Methods

A retrospective comparative study included patients with newly diagnosed RC who received surgery during 2010 and 2015. Palliative operations without resection or transanal endoscopic microsurgery without removing lymph nodes were excluded from the study.

Preoperative investigations were performed by the senior radiologists at the Department of Radiology. Clinical tumour, node, metastasis (TNM) staging system was evaluated according to the guidelines of the 2012 European Society of Gastrointestinal and Abdominal Radiology (ESGAR) consensus meeting [11]. RC surgery was performed by 7 senior abdominal surgeons who specializes in coloproctology. Patients' diagnostic and treatment data were analysed. Postoperative morbidity was registered according to the Clavien-Dindo classification and follow-up data was received from the Lithuanian Cancer Registry [12, 13].

Preoperative first-line treatment regimens: 5 weeks of conventional chemoradiotherapy (CRT) (25 × 2 Gy per fraction + two cycles of 5-fluorouracil/leucovorin) with delayed surgery for 6–8 weeks or 5 days of short-term radiotherapy (RT) (5 × 5 Gy) with immediate surgery afterwards [8].

The study protocol was approved by the Bioethics Centre of the Lithuanian University of Health Sciences (LUHS) (approval number BEC-MF-790).

Statistical Analysis

Continuous variables were expressed as mean and standard deviation (SD). Student *t* test and one-way ANOVA were used for

Fig. 1. RC treatment. Surgery + CHT + RT – Neoadjuvant Chemoradiotherapy followed by surgery. Surgery + RT – Neoadjuvant radiotherapy followed by surgery. Surgery + CHT – Neoadjuvant chemotherapy followed by surgery. Surgery – Surgery alone without Neoadjuvant treatment.

parametric data and Mann-Whitney test for non-parametric. The time interval between the date of cancer diagnosis and the date of death or the end of the observation period was defined as the OS of RC patients. A multivariate logistic regression analysis was used to identify independent factors for increased survival. Association between categorical variables was verified using Pearson χ^2 . The level of significance was set at 0.05.

Results

General Information

A total of 80 patients with a mean age of 67.4 years (SD, 9.9) were compared with 99 patients with a mean age of 66.8 years (SD, 11.4), who were treated for CRC in 2010 and 2015, respectively. There were 33 (41.2%) females and 47 (58.8%) males in 2010. There was a similar gender ratio in 2015, 50 (50.5%) females and 49 (49.5%) males. Only 8 patients in total (2.5 and 6.1%) were on an emergency basis. The median ASA was 3 in both groups. The details of the general characteristics are specified in Table 1. According to our data, the cancer stage did not differ between 2010 and 2015. Unfortunately, there were 5.6% more patients diagnosed with cancer stages III and IV (65.1 vs. 70.1%) and 6.9% fewer patients with cancer stage I in 2015. The distribution of cancer stages is presented in Table 1.

Diagnostic Methods

Colonoscopy with biopsy and histological examination was performed for all patients (100%) both in 2010 and 2015. Pelvis MRI and chest CT were performed more often in 2015: the tests increased up to 77.8% ($p < 0.001$) and 67.7% ($p < 0.001$), respectively. In addition to this, the circumferential resection margin (CRM) evaluation increased by more than 20% ($p = 0.001$). There was no significant difference regarding other di-

Table 2. Details on the operative treatment

Variable	2010	2015	p value
Operative approach, <i>n</i>			
Open surgery	78 (97.4%)	93 (94.0%)	0.929
Laparoscopic surgery	2 (2.5%)	6 (6.0%)	0.875
Conversion to open	1 (1.3%)	3 (3.0%)	0.914
Operation method, <i>n</i>			
TME/anterior rectum resection	57 (71.3%)	78 (78.8%)	0.858
APR	21 (26.3%)	18 (18.2%)	0.743
Proctectomy	2 (2.6%)	3 (3.0%)	0.958
Ostomy, <i>n</i>			
Ostomy not performed	14 (17.5%)	8 (8.1%)	0.157
Colostomy	34 (42.5%)	40 (40.4%)	0.9
Loop ileostomy	32 (40.0%)	51 (51.5%)	0.929

TME, total mesorectal excision; APR, abdominal perineal resection.

agnostic methods. MRI was performed only for 30 (37.5%) and endorectal ultrasound (ERUS) for 18 patients (22.5%) in 2010. In 2015, ERUS was used for T1 or Tis tumours as an intention for transanal endoscopy instead of a major operation. There were more MRI ($n = 77$, 77.8%) and less ERUS ($n = 3$, 3%) performed in 2015. There was no significant difference among low, middle, and high RCs according to tumour site from linea dentata. Middle RCs were the most frequent in 2010 (63.7%), while middle and high rectal tumours allocated equally (both 42.4%) in 2015. Despite the fact that there was a higher number of low RCs in 2015 (10% in 2010 vs. 15.1% in 2015), we performed more sphincter-preserving operations instead of abdominal perineal resection (26.3 vs. 18.2%). All diagnostic workup is summarized in Table 1.

Table 3. Comparison of radiological T stage before treatment and pathological T stage after treatment

	Before treatment	After treatment	
2010			
T0	0 (0%)	5 (6.8%)*	<i>p</i> = 0.002
T1	0 (0%)	3 (4.1%)	
T2	2 (8.7%)	20 (27.0)	
T3	14 (60.9%)	41 (55.4)	
T4	7 (30.4%)	5 (6.8)	
2015			
T0	1 (1.5)	5 (5.6)*	<i>p</i> = 0.001
T1	2 (3.0)	4 (4.4)	
T2	12 (17.9)	22 (24.4)	
T3	42 (62.6)	59 (65.6)	
T4	10 (14.9)	0 (0)	
	<i>p</i> = 0.043	<i>p</i> = 0.897	

Before treatment means a period before rectal cancer treatment (any of neoadjuvant treatment option followed by surgery or surgery treatment alone) based on clinical pelvic MRI T stage evaluation. After treatment means a period after rectal cancer surgery (including any of neoadjuvant treatment option followed by surgery) based on pathological T stage evaluation.

Table 5. 2-year OS and DFS

Groups	Surgery ^a	Neoadjuvant ^b	Total	<i>p</i> value
<i>2-year OS, n (%)</i>				
2010	45 (76.7%)	15 (75%)	61 (76.3%)	0.046
2015	47 (83.9%)	39 (90.7%)	86 (86.9%)	
<i>Median DFS, months (range)</i>				
2010	27 (0–35)	28 (3–35)	27 (0–35)	0.077
2015	28 (0–35)	28 (0–34)	28 (0–35)	

^a The surgery group received no neoadjuvant treatment. ^b The neoadjuvant group received neoadjuvant treatment followed by surgery. OS, overall survival; DFS, disease-free survival.

Preoperative Treatment

Neoadjuvant chemoradiotherapy has doubled from 20% in 2010 to 45% in 2015 ($p = 0.01$). Results are shown in Figure 1.

Operative Treatment

The majority of the operative approach remained open with a slightly increased number of laparoscopies in 2015. The operating approach or method distribution did not differ between groups, conversely, there is a growing tendency of sphincter-preserving operations as well as loop ileostomies. The colostomy rate remained similar to that of 2010. The operative treatment is presented in Table 2.

Table 4. Postoperative period

Variable	2010	2015	<i>p</i> value
<i>Clavien-Dindo classification of postoperative complications</i>			
Grade 0	69 (86.3)	79 (79.8)	0.596
Grade I	4 (5.0)	6 (6.1)	
Grade II	4 (5.0)	6 (6.1)	
Grade III a	0 (0)	3 (3.0)	
Grade III b	2 (2.5)	1 (1.0)	
Grade IV a	0 (0)	2 (2.0)	
Grade IV b	0 (0)	2 (2.0)	
Grade V	1 (1.3)	0 (0)	
<i>Length of hospital stay</i>			
Median hospital stay, range	10 (5–43)	8 (5–37)	0.002
Median postoperative hospital stay, range	8 (2–25)	7 (4–36)	0.005

Histological Examination

Comparison of radiological TNM and pathological TNM with one-way ANOVA showed significant difference staging between 2010 ($p = 0.002$) and 2015 ($p = 0.001$). The results are summarized in Table 3.

Postoperative Period

The length of median hospital (8 vs. 10 days, $p = 0.002$) and postoperative stay (7 vs. 8 days, $p = 0.005$) was significantly shorter by 2 and 1 day in 2015, respectively. The distribution of postoperative complications grades according to the Clavien-Dindo classification was not significantly different between 2010 and 2015. However, there were more documented complications in 2015 (13.8 vs. 20.2%, $p = 0.596$). Conversely, there was no in-hospital mortality in 2015 compared to one death in 2010. The postoperative period is presented in Table 4.

The 2-year OS has increased by 10.6% ($p = 0.046$) and the median disease-free survival (DFS) by 11%. Data are displayed in Table 5. Multivariate logistic regression analysis determined that the availability and performance of MRI were associated with increased OS (OR = 1.529, 95% CI 0.916–2.554, $p = 0.020$).

Discussion/Conclusion

We found that the 2-year OS rate of resectable RC has significantly increased from 76.3% in 2010 to 86.9% in 2015. In *Lancet Oncology*, an immense population-based national registry study of Denmark, England, Norway, and Sweden has recently been published. For comparison, the 2-year OS was 78.2, 76.2, 80.3, and 79.8%, respectively [14]. The OS of our study is better due to the exclusion criteria used. Therefore, we observed that pre-treatment staging evaluation and preoperative treatment improved from 2010 to 2015.

Since the European Union and government-funded Radiological Diagnostic Center (RDC) of LUHS was established in 2012, availability of imaging modality and performance instantly enhanced: pelvis MRI and abdominal CT by 40.3 and 44.5% in 2015, respectively. As a consequence, patients waiting times for CT and MRI diagnostic tools had shortened and become a common routine in the examination of RC. Furthermore, our research proposes that clinical staging TNM compared with pathological TNM has improved in terms of quality in 2015.

Conversely, the usage of ERUS has dramatically decreased from 22.5 to 3% in 2015. In addition, Yimei et al. [15] support this statement, as ERUS has become an alternative only for early-stage RC (Tis, T1–2) due to lack of depth to evaluate other organ invasion, and besides, it is limited by the bulkiness of the tumour.

Pertaining to tumour invasion to organs and structures, thin-cut, high-resolution MRI has become the imaging gold standard to determine treatment options, especially for low RC. Currently, radiologists examine not only T and N, but also other parameters (e.g., the distance of a tumour to the potential CRM, the presence of a tumour within the extramural rectal vessels [EMVI], discontinuous tumour deposits [N1c], and intersphincteric plane according to the ESGAR consensus meeting) [11, 16].

MDT discussions by the LUHS have officially started in 2012 and become a mandatory step for every RC case. In 2015, Prades et al. [17] published a systematic review stating that MDT discussions resulted in better clinical outcomes, with evidence of improved survival among colorectal cancer patients. Intuitively, there appear to be undisputable benefits from MDT in RC, as the first therapeutic act is crucial. However, at the same time, the MDT has to deal with clinical issues when there is no gold standard [18].

Though, the best regimen for preoperative NT has not been established. However, adjuvant chemoradiotherapy has been a standard option for resectable RC until the German Rectal Cancer Study in 2004. Preoperative treatment (CRT or short-course radiotherapy) provides better local control, lower toxicity, and better compliance compared to postoperative treatment [19].

Kairevičė et al. [20] published a randomized controlled trial (RCT) of patients with resectable stage II–III RC stating that the 5-year DFS and OS were significantly better in the preoperative CRT than with delayed surgery in 6–8 weeks or in the preoperative short-course radiotherapy group.

While our study showed more preoperative NT prescribed and better 2-year survival in 2015, a survival benefit was not found until recently. There is a need for more RCTs and meta-analyses to find out the most suitable NT regimen.

On the other hand, we are unable to propose any new study of RC if each institution will not standardize the staging first. The new ESMO guidelines published in 2017 suggest that selection of treatment depends on pelvic MRI locoregional clinical staging (EMVI, T substage, distance to the CRM). As a result, we can expect a better patient selection for the respective preoperative management and to define the extent of surgery [21].

Can we improve in the assessment of nodal status? So far, no uniform criteria exist for defining a node-positive status [22]. Zhang et al. [23] present the chemical shift effect as evaluation criteria for the prediction of lymph node status using MRI imaging with node-for-node matched histopathology. According to their research, the chemical shift effect is predicting the nodal status (border, signal intensity) with high confidence and could be used for nodal staging. There is plenty of space to develop this idea in future prospective multicentre cohort studies.

Nevertheless, the length of hospital stay with the majority of open rectal resections was shorter by 2 days in 2015, yet still rather long (8 days). In their systematic review and meta-analysis, Martínez-Pérez et al. [24] found that hospital stay was 1.71 days shorter in the laparoscopic group, while median hospital stay of open surgery ranges from 7 to 8 days. Besides from laparoscopy, the implementation of an effective ERAS (Enhanced Recovery After Surgery) program [25] is another option for reducing hospital stay.

The main weakness of this research is the retrospective nature of inclusion into the database as well as it being a single-centre cohort study. For completeness, 5-year OS data are required in the future. Besides, it is worth adding all population cancers without removing transanal endoscopic microsurgery and palliative operations.

The other limitation of the study pertains to the radiological staging perspective which is due to the retrospective data collection as well as the absence of a united pelvic MRI evaluation form. As a result of this study, our centre established a standard pelvic MRI evaluation form for RC.

It is suggested that all patients with RC should undergo a detailed examination process as a compulsory routine, which should afterwards be discussed at multidisciplinary tumour boards. A standard proforma for MRI and pathology ensures a comprehensive report which leads to a more precise preoperative and operative treatment strategy.

Conclusions

The expanded quantity of preoperative imaging, an improved radiological staging, and compulsory MDT board discussion have led to a selective NT decision followed by surgery which can positively affect the 2-year OS rate.

Statement of Ethics

The study protocol was approved by the Bioethics Centre of LUHS (approval number BEC-MF-790).

Disclosure Statement

The authors have no conflicts of interest to declare.

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