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ORIGINAL ARTICLE

The Time Between Chemoradiation and Surgery for Rectal Carcinoma Negatively Influences Mesorectal Excision Quality

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Abstract

Total mesorectal excision quality (TMEq) is a prognostic factor associated with local recurrence in rectal adenocarcinoma. Neoadjuvant chemoradiotherapy (NCRT) reduces the risk of tumor recurrence, but may compromise TMEq. The time between NCRT and surgery (TTS) and how it influences TMEq and tumor control were evaluated. In prospective registry, 236 patients after NCRT and TME were analyzed. NCRT involved radiotherapy with 45 Gy to the pelvis, plus tumor boost dose 5.4 Gy with concurrent 5-fluorouracil infusion. NCRT was followed by TME after 9 weeks on average (median 9.4 ± SD 2.5). TMEq was parametrically analyzed by standard three-grade system. With median follow-up of 47.5 months, 3-year overall survival (OS) was 83.8%, disease-free survival (DFS) was 77.7%, and 6.4% was the rate of local recurrence (LR). TTS was not associated with OS, DFS, or LR. TMEq was found to be associated with LR in univariate analysis, but not in multivariate, where pathological tumor stage and resection margins remained dominant predictors. TMEq was negatively influenced by inferior location of the tumor, longer TTS, higher tumor and nodal stage, presence of tumor perforation, perineural invasion, and close/positive resection margins. Nonetheless, TTS remained a strong predictor of TMEq in multivariate analyses. TTS was proven to be an independent predictor of TMEq. With longer TTS, fewer complete TME with intact mesorectal plane were observed. However, TTS was not associated with survival deterioration or tumor recurrence. These were negatively influenced by other factors interfering with TMEq, especially by pathological tumor stage and resection margins.

Keywords Rectal carcinoma · Neoadjuvant chemoradiation · Mesorectal excision

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Introduction

Total mesorectal excision (TME) refers to the surgical removal of the complete perirectal soft tissue envelope, using sharp instruments under direct vision, and has become the contemporary standard of surgical care for patients with rectal cancer [1]. After introducing TME as a treatment to patients with rectal adenocarcinoma, locoregional recurrence rates and survival rates have significantly improved [2, 3]. The addition of preoperative (chemo) radiotherapy to TME surgery results in a more than 50% decrease in locoregional recurrences; however, the combination of neoadjuvant therapy and TME surgery does not improve overall or disease-free survival significantly [4, 5]. Neoadjuvant chemoradiotherapy (NCRT) has been established as standard treatment for locally advanced rectal cancer after publication of the "German trial" in 2004 [6]. This trial has shown an improved local control rate in comparison to postoperative chemoradiotherapy, again without survival benefit reported with a median follow-up of 134 months [7].

A three-grade MERCURY system of macroscopic pathological evaluation is standardly used to describe the total mesorectal excision quality (TMEq) [1, 8]. TMEq score is linked to patient and tumor characteristics and is a well-known prognostic factor associated with local tumor recurrence and disease progression [9–13]. In contrast, NCRT reduces the risk of tumor recurrence in rectal adenocarcinoma, but may negatively influence TMEq [9, 11].

This prospective registry study describes the influence of NCRT and time to surgery (TTS) on TMEq with survival and tumor-control consequences.

Methods

We performed a prospective database-based registry trial consisting of 236 patients (159 men and 77 women), who had complete records after NCRT and TME. All patients with locally advanced histologically confirmed rectal adenocarcinoma were treated between years 2010 and 2017 with a homogeneous NCRT protocol and consequent TME. All patients were in a good performance status (PS 0 or 1) with absence of distant metastases. Clinical tumor staging (cT-stage and cN-stage) was based on physical examination, endoscopy and endosonography, with pelvic MRI (Magnetic Resonance Imaging), abdominal CT (computed tomography) and lung X-ray imaging. Patient and tumor characteristics were prospectively recorded into the unitary form and inserted into the interdisciplinary registry. Detailed patient and tumor characteristics are summarized in Table 1.

Treatment

NCRT protocol consisted of external beam radiotherapy (EBRT) to the pelvic area (rectum, pararectal, presacral, and internal iliac lymph nodes) with 45Gy in 25 fractions (each fraction of 1.8Gy) over 5 weeks (Monday to Friday), together with subsequent EBRT boost to the tumor itself of 5.4Gy in 3 fractions. All patients received pelvic EBRT using either a four-field box technique (anterior to posterior, posterior to anterior and two laterals), or a three field technique (posterior to anterior and two laterals), or IMRT (intensity modulated radiotherapy) with megavoltage photon beams (6 or 18 MV) from a linear accelerator (Varian Medical Systems, Palo Alto, CA, USA). During EBRT, concomitant continuous infusion of 5-fluorouracil was applied at a dose of 200 mg/m^2/day, and interrupted during the weekends. NCRT was followed by TME after 9 weeks on average (median 9.4 ± SD 2.5, range 3.6–19). There was no systematic reason for earlier or later surgery in the studied patients. The range of TTS was not due to patient or tumor related reasons. In 39 patients with upper rectal carcinoma, partial mesorectal excision was performed, with identical excision quality evaluation. TTS was measured as a continuous variable as the number of days between the last fraction of radiotherapy and the day of surgery. Detailed treatment characteristics are summarized in Table 1. Postoperative chemotherapy was applied in 191 patients (80.9%), while 45 patients (19.1%) had no adjuvant treatment. Patients who relapsed during the follow-up received standard palliative chemotherapy with or without targeted therapy at the discretion of the treating physician.

Pathological Evaluation

Resected tissue was evaluated by an experienced pathologist with resulting pathological staging (ypT-stage and ypN-stage). Both the specimen as a whole (fresh) and cross-sectional slices (fixed) were examined in order to make an adequate interpretation of TMEq and the circumferential radial margin (CRM). TMEq and CRM were parametrically analyzed by MERCURY classification as follows: I – complete TME with intact mesorectal plane or shallow defects <5 mm deep, smooth and regular CRM; II – nearly complete TME with intramesorectal plane defects ≥5 mm deep, irregular CRM with defects; III – incomplete TME and irregular CRM with defects to the muscularis plane (Fig. 1). CRM and aboral resection margins were always measured. Pathological complete remission (pCR) was defined as

Table 1 Patient, tumor and treatment characteristics ($n = 236$)

Patient characteristics		Tumor characteristics		Treatment characteristics	
Gender	Female 77 (32.6%) Male 159 (67.4%)	Pathological T-stage	T0 37 (15.7%) T1 23 (9.8%) T2 84 (35.6%) T3 72 (30.5%) T4 18 (7.6%) Tis 2 (0.8%)	Time to surgery [days]	Mean 63.5, Range 25–133 Median 66.0 ± SD 17.5
Age [years]	Mean 66.9; Range 35–87 Median 68.0 ± SD 9.28			Type of surgery	Laparoscopy 129 (54.7%) Classical 69 (29.2%) Conversion 36 (15.3%) Robotic 2 (0.8%)
ASA	I – 1 (0.4%) II – 175 (74.2%) III – 59 (25.0%) IV – 1 (0.4%)	Pathological N-stage	N0 163 (69.1%) N1 53 (22.5%) N2 20 (8.4%)	R0 resection	R0 202 (86.0%) R1 31 (13.2%) R2 2 (0.8%)
BMI	Mean 28.2; Range 14.6–41.9 Median 27.8 ± SD 4.22	Tumor grade	G1 16 (6.8%) G2 163% (69.1%) G3 38 (16.1%) NA 19 (8.0%)	No. of LN resected	Mean 15.5, Range 0–45 Median 14.0 ± SD 8.3
Genetic predisposition	No 197 (83.5%) Yes 30 (12.7%) NA 9 (3.8%)	Tumor location	Low 108 (45.8%) Middle 89 (37.7%) Upper 39 (16.5%)	≥ 12 LN resected	yes 166 (70.3%) No 70 (29.7%)
Diabetes mellitus	No 185 (78.4%) Yes 51 (21.6%)	Tumor fixation	No 214 (90.7%) Yes 22 (9.3%)	No. of LN positive	Mean 0.9, Range 0–15 Median 0.0 ± SD 2.2
CVS disease	No 133 (56.4%) Yes 103 (43.6%)	Circular vs. semicircular	Circular 60 (25.4%) Semicircular 166 (70.3%) NA 10 (4.2%)	pCR	Yes 34 (14.4%) No 202 (85.6%)
Pulmonary disease	No 221 (93.6%) Yes 15 (6.4%)	Stenosing tumor	No 159 (67.3%) Yes 62 (26.3%) NA 15 (6.4%)	Aboral margin [mm]	Mean 21.8, Range 0–90 Median 18.0 ± SD 17.2
Clinical T-stage	T2 5 (2.1%) T3 196 (83.1%) T4 35 (14.8%)	Perforation	No 217 (91.9%) Yes 19 (8.1%)	CRM [mm]	Mean 8.2, Range 0–45 Median 6.0 ± SD 9.2
Clinical N-stage	N0 15 (6.4%) N1 84 (35.6%) N2 137 (58.0%)	Lymphovascular space invasion	No 219 (91.9%) Yes 17 (7.2%)	TMEq	I 86 (36.4%) II 54 (22.9%) III 85 (36.0%) NA 11 (4.7%)
		Angioinvasion	No 210 (89.0%) Yes 26 (11.0%)		
		Perineural invasion	No 199 (84.3%) Yes 37 (15.7%)		

ASA American Society of Anesthesiologists Physical Status *classification*, *BMI* Body-Mass Index, *CVS* cardiovascular, *pCR* pathological complete remission, *LN* lymph nodes, *TMEq* total mesorectal excision quality, *SD* Standard Deviation

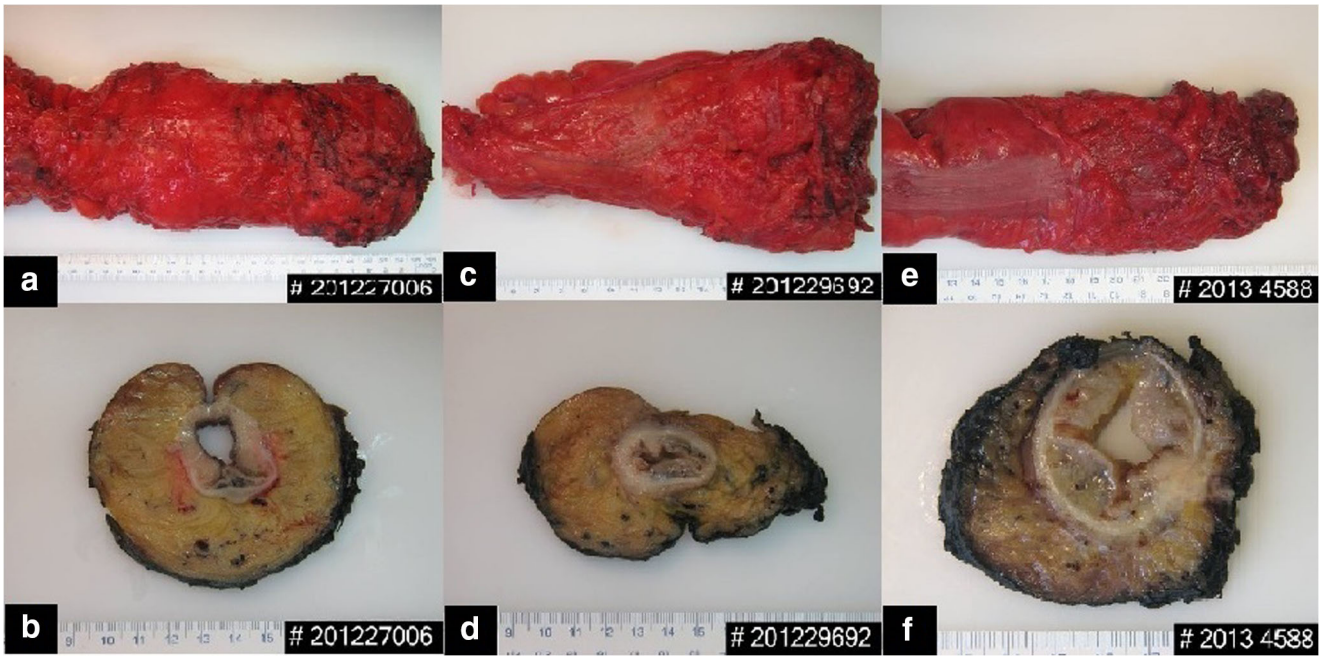

Fig. 1 **a**: TMEq I - Complete TME with intact mesorectal plane; **b**: TMEq I – Regular circumferential radial margin (CRM); **c**: TMEq II - Incomplete TME with intramesorectal plane defects; **d**: TMEq II - Irregular CRM with defects; **e**: TMEq III - Incomplete TME with defects to muscularis plane; **f**: TMEq III - Irregular CRM with defects to muscularis plane

ypT0ypN0 when no viable tumor cells were found in the resected specimen.

Statistical Analyses

Basic descriptive statistics were adopted for the analysis: median, mean, range, standard deviation, and 95% confidence interval for continuous data, and absolute and relative frequencies for categorical data. Kaplan-Meier and log-rank tests were used for survival analyses. Univariate and multivariate Cox regression analysis was used to determine the influence of patient, tumor, and treatment characteristics on survival. Logistic and linear univariate and multivariate regression analyses and chi-square tests were used to determine the influence of patient, tumor, and treatment characteristics on TMEq and TTP. We considered $p < 0.05$ to be statistically significant. All statistical analyses were performed using the NCSS 8 statistical software program (NCSS, Keysville, Utah).

Results

With a median follow-up of 47.5 months (6–97): 58 patients (24.6%) died, or were lost to follow-up; 64 patients (27.1%) had tumor recurrence, of whom 15 (6.4%) had isolated local recurrence (LR). Three-year overall survival (OS) was 83.8% (95%CI 78.9%–88.7%), with disease-free survival (DFS) of 77.7% (95%CI 72.1%–83.3%). TMEq was grade I in 86 patients (36.4%), grade II in 54 patients (22.9%), and grade III in 85 patients (36.0%). TMEq was not assessable in 11 patients (4.7%).

Several characteristics had a statistically significant impact on patients´ survival: clinical and pathological tumor (cT, pT) and nodal (cN, pN) stage; resection radicality (positive vs. negative CRM); perioperative tumor fixation or perforation; circular and stenosing type of tumor growth; presence of lymphangioinvasion, angioinvasion, or perineural tumor invasion in postoperative pathological evaluation. Furthermore, several factors were found to have a significant impact on local recurrence: resection radicality; pT stage; perineural invasion and angioinvasion; TMEq; tumor perforation or stenosing tumor growth; CRM distance; pN stage; type of surgery; and gender. Patient, tumor and treatment characteristics with statistically significant impact on survival and local recurrence are detailed in Table 2.

TTS was not associated with OS, DFS, or LR. TMEq was found to be associated with LR in univariate analysis, but not in multivariate, where pathological tumor stage and CRM status remained the dominant predictors. TMEq was negatively influenced mainly by inferior location of the

Table 2 Factors with statistically significant impact on survival and local recurrence

	Overall survival (OS)	Disease-free survival (DFS)	Local recurrence (LR)
Gender	$p = 0.23$	$p = 0.25$	$\mathbf{p = 0.04}$ (p = 0.58) F/M 2.57 (0.86–7.70)
Age	$p = 0.11$	$p = 0.13$	$p = 0.16$
ASA	$\mathbf{p = 0.016}$ (p = 0.28)	$\mathbf{p < 0.0001}$ ($\mathbf{p < 0.0001}$)	$p = 0.95$
BMI	$p = 0.49$	$p = 0.33$	$p = 0.15$
Genetic predisposition	$p = 0.62$	$p = 0.69$	$p = 0.29$
Diabetes mellitus	$p = 0.72$	$p = 0.78$	$p = 0.17$
CVS disease	$p = 0.58$	$p = 0.30$	$p = 0.48$
Pulmonary disease	$p = 0.06$	$p = 0.06$	$p = 0.95$
cT-stage	$\mathbf{p = 0.001}$ (p = 0.99)	$\mathbf{p < 0.0001}$ ($\mathbf{p < 0.0001}$)	$p = 0.96$
cN-stage	$p = 0.53$	$p = 0.44$	$p = 0.95$
Tumor grade	$p = 0.77$	$p = 0.57$	$p = 0.95$
pT-stage	$\mathbf{p = 0.0035}$ ($p = 0.99$)	$\mathbf{p < 0.0001}$ ($\mathbf{p < 0.0001}$)	$\mathbf{p = 0.0002}$ ($\mathbf{p = 0.0006}$)
pN-stage	$p = 0.06$	$\mathbf{p = 0.003}$ ($\mathbf{p < 0.0001}$)	$\mathbf{p = 0.02}$ ($p = 0.38$)
pCR	$p = 0.62$	$p = 0.28$	$p = 0.95$
Tumor location	$p = 0.12$	$p = 0.10$	$p = 0.19$
Tumor fixation	$\mathbf{p = 0.027}$ ($p = 0.82$) OR 2.12 (0.86–5.23)	$\mathbf{p = 0.004}$ ($\mathbf{p < 0.0001}$) OR 2.50 (1.00–6.28)	$p = 0.15$
Circular vs. semicircular	$\mathbf{p = 0.022}$ ($p = 0.20$) OR 1.80 (1.02–3.20)	$\mathbf{p = 0.030}$ ($\mathbf{p < 0.0001}$) OR 1.71 (1.00–2.98)	$p = 0.19$
Stenosing tumor	$\mathbf{p = 0.007}$ ($p = 0.58$) OR 2.03 (1.12–3.70)	$\mathbf{p = 0.006}$ ($\mathbf{p < 0.0001}$) OR 2.02 (1.14–3.58)	$\mathbf{p = 0.04}$ ($p = 0.66$) OR 3.46 (1.00–12.11)
Perforation	$p = 0.06$	$\mathbf{p = 0.008}$ ($p = 0.08$) OR 2.50 (0.90–6.95)	$\mathbf{p = 0.01}$ ($p = 0.89$) OR 5.69 (0.68–47.83)
Lymphovascular space invasion	$\mathbf{p = 0.016}$ ($p = 0.43$) OR 2.54 (0.79–8.18)	$\mathbf{p = 0.011}$ ($\mathbf{p < 0.0001}$) OR 2.51 (0.85–7.44)	p = 0.06
Angioinvasion	p = 0.33	$\mathbf{p = 0.034}$ ($\mathbf{p = 0.09}$) OR 1.89 (0.83–4.31)	$\mathbf{p = 0.0009}$ ($p = 0.78$) OR 6.43 (1.13–36.39)
Perineural invasion	$\mathbf{p = 0.007}$ ($p = 0.24$) OR 2.21 (1.02–4.80)	$\mathbf{p = 0.0004}$ ($\mathbf{p < 0.0001}$) OR 2.61 (1.23–5.52)	$\mathbf{p < 0.0001}$ ($p = 0.73$) OR 9.90 (2.22–44.23)
Time to surgery (TTS)	$p = 0.60$	$p = 0.81$	$p = 0.68$
Type of surgery	$p = 0.14$	$\mathbf{p = 0.04}$ ($p = 0.23$)	$\mathbf{p = 0.025}$ (p = 0.66)
Resection radicality	$\mathbf{p = 0.0001}$ ($p = 0.98$) OR 3.54 (1.44–8.71)	$\mathbf{p < 0.0001}$ ($\mathbf{p < 0.0001}$) OR 4.90 (1.98–12.10)	$\mathbf{p < 0.0001}$ ($\mathbf{p < 0.0001}$) OR 13.94 (2.18–89.19)
TMEq	$p = 0.66$	$p = 0.47$	$\mathbf{p = 0.002}$ ($p = 0.77$) OR 3.60 (1.14–11.33)
No. of LN resected	$p = 0.18$	$p = 0.29$	$p = 0.82$
No. of LN positive	$\mathbf{p = 0.012}$ ($p = 0.30$) OR 1.13 (1.03–1.25)	$\mathbf{p = 0.0003}$ ($\mathbf{p < 0.0001}$) OR 1.18 (1.08–1.30)	$p = 0.14$
Aboral margin distance	$p = 0.09$	$p = 0.054$	$p = 0.60$
CRM	$p = 0.23$	$p = 0.058$	$p = 0.07$

Significant results are highlighted in bold

Multivariate regression (results in brackets) was analysed in significant univariate analyses results

Odds ratios (OR) were analyzed in feasible significant univariate analyses results (95% CI of OR in brackets)

tumor, longer TTS, higher tumor and nodal stage, and presence of tumor perforation or perineural invasion. TMEq was also associated with close/positive resection margins. Nonetheless, TTS remained a strong predictor of TMEq after multivariate analyses. With prolonged TTS, fewer complete TME with intact mesorectal plane were observed (Fig. 2). Factors with significant association with TMEq and TTS are detailed in Table 3.

Discussion

Preoperative chemoradiotherapy is the standard care for patients with advanced rectal adenocarcinoma since the first results of the CAO/ARO/AIO-94 trial [6]. NCRT, compared with postoperative chemoradiotherapy, has been shown to significantly improve DFS and shows a trend toward improved OS [14]. Especially in the middle and low rectal tumors, NCRT significantly decreases the risk of pelvic recurrence, and increases the frequency of radical resections. Currently, the CRM status assessed in preoperative MRI is often used to decide for either TME alone or NCRT [15]. Long-course NCRT does not increase survival, local control or late toxicity compared with short-course (5 times 5 Gy) radiotherapy alone [16]; however, it is most often used as a standard treatment of advanced rectal carcinoma. Although there is some evidence that IMRT chemoradiation offers higher rates of pCR than other

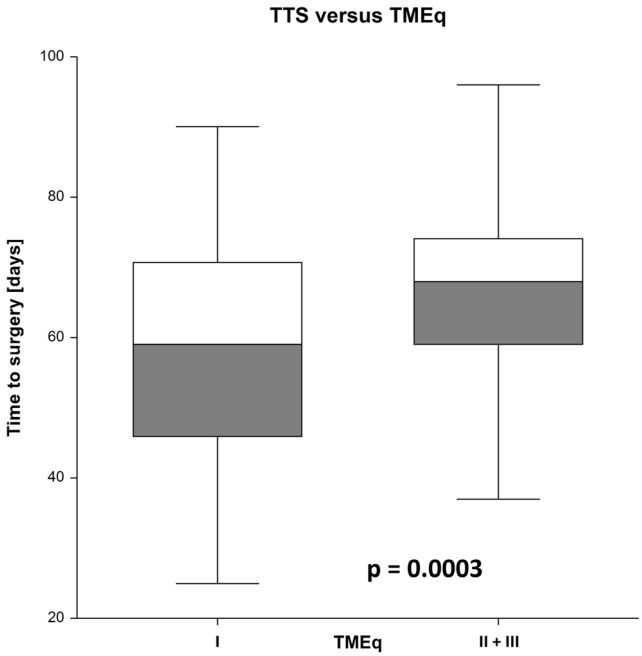

Fig. 2 Two-sample T-test showing the influence of TTS upon distribution of TMEq

techniques [17], the RT technique did not influence the treatment outcomes in our study.

On the contrary, NCRT may have some disadvantages as well, including more pelvic or perineal wound infection or late rectal and sexual dysfunction [18]. Moreover, it also seems to negatively compromise the TMEq [9, 11]. There may be several reasons for deterioration of the TME by NCRT. According to our experience, rectal tumor (without previous treatment) with its desmoplastic stroma causes some rigidity and lack of suppleness of the rectal wall. After NCRT, with tumor regression and downsizing, only scarry and fibrotic stroma persists in the place of previous tumor. In locally advanced cT3b,c-4 rectal carcinomas, fibrotic and regressive alterations invest the whole thickness of the rectal wall, sometimes with a slim or indistinct fibrotic rectal wall. In such cases, during mesorectal excision there is a mechanical traction affecting the extracted mesorectum envelope, that has no remaining rigid centreline at the level of the tumor or rectal wall. Soft fat tissue is predisposed to rupture more easily with resulting defects in the mesorectal plane and worse TMEq. Dissection of a proper plane is more difficult due to fibrosis. Therefore, we have presupposed that the better the tumor response, the worse would be the TMEq. Moreover, we have expected that such a TMEq deterioration should have no negative impact on tumor control or survival.

There is limited evidence to support decisions regarding when to resect rectal cancer following NCRT. There may be benefits in prolonging the interval between NCRT and surgery beyond the 6–8 weeks, with no significant differences in rates of surgical complications, sphincter preservation, or long-term recurrence and survival [19]. National Cancer Data Base constructed a study of 11,760 patients who were treated between 2006 and 2012. It objectively determined the optimal time for surgery after completion of NCRT based on completeness of resection and tumor downstaging, when 8 weeks was proven to be the critical threshold for optimal tumor response [20, 21]. However, resection even 10 to 11 weeks after NCRT may result in the highest pCR rate [22, 23]. On the contrary, in the GRECCAR-6 Trial, waiting 11 weeks after RCT did not increase the rate of pCR after surgical resection compared to 7 weeks, while a longer waiting period was associated with a higher morbidity rate and more difficult surgical resection in this trial [24]. In our study, we found no significant correlation between TTS and frequency of pCR, but there was significant deterioration of TMEq with prolonged TTS.

This study is one of the largest and most homogeneous investigations into the influence of long-course NCRT on the pathological TMEq evaluation and corresponding treatment outcomes. The objective of our paper was already partly a subject of the GRECCAR 6-Trial. In this prospectively randomized trial, comparing two different TTS after NCRT (7 versus 11 weeks), a similar number of patients were involved ($n = 265$). In the group subjected to the longer waiting period, the quality of specimens ("complete") was worse than that of the other group (78.8% vs. 90%), which supports our prospective investigation. This paper is part of our long-term investigation into the NCRT of rectal carcinoma [25–27].

Conclusions

The time between NCRT and surgery was proven to be a strong and independent predictor of TMEq in our prospective study, taking into account all eventual confounding factors. With a longer time between NCRT and surgery, fewer complete TME with intact mesorectal plane were observed. However, TTS was not associated with survival deterioration or increased tumor recurrence at three years. These were negatively influenced by other factors interfering with TMEq, especially pathological tumor stage and CRM positivity. Correct timing of TME after NCRT remains challenging with regard to adequate tumor downstaging on the one hand and risk of postoperative complications on the other. However, TTS seems to have no major influence on patients' survival or tumor control. We can recommend TTS

Table 3 Factors with significant association with TME quality and time to surgery

	TMEq I vs II + III	TMEq I + II vs. III	TMEq I vs. III	TMEq I vs. II vs. III	Time to surgery
Gender	$p = 0.15$	$p = 0.48$	$p = 0.23$	$p = 0.20$	$p = 0.09$
Age	**$p = 0.028$** ($p = 0.07$)	$p = 0.72$	$p = 0.15$	$p = 0.14$	$p = 0.95$
ASA	$p = 0.95$	$p = 0.94$	$p = 0.96$	$p = 0.96$	$p = 0.66$
BMI	$p = 0.45$	$p = 0.85$	$p = 0.75$	$p = 0.76$	$p = 0.31$
Genetic predisposition	$p = 0.88$	$p = 0.17$	$p = 0.42$	$p = 0.34$	$p = 0.39$
Diabetes mellitus	$p = 0.18$	$p = 0.80$	$p = 0.39$	$p = 0.13$	$p = 0.90$
CVS disease	$p = 0.75$	$p = 0.91$	$p = 0.81$	$p = 0.74$	**$p = 0.008$** ($p = 0.58$)
Pulmonary disease	$p = 0.49$	$p = 0.15$	$p = 0.21$	$p = 0.21$	$p = 0.79$
cT-stage	$p = 0.21$	$p = 0.13$	$p = 0.13$	$p = 0.12$	$p = 0.22$
cN-stage	$p = 0.45$	$p = 0.51$	$p = 0.44$	$p = 0.44$	$p = 0.12$
Tumor grade	$p = 0.21$	$p = 0.10$	$p = 0.15$	$p = 0.19$	$p = 0.40$
pT-stage	**$p = 0.06$ ($p = 0.01$)**	**$p = 0.002$** ($p = 0.10$)	**$p = 0.004$ ($p = 0.01$)**	**$p = 0.004$ ($p = 0.03$)**	$p = 0.36$
pN-stage	**$p = 0.02$ ($p = 0.01$)**	**$p = 0.049$** ($p = 0.06$)	**$p = 0.02$ ($p = 0.04$)**	**$p = 0.02$** ($p = 0.05$)	$p = 0.47$
pCR	**$p = 0.02$** ($p = 0.38$)	$p = 0.34$	$p = 0.08$	**$p = 0.03$** ($p = 0.41$)	$p = 0.98$
Tumor location	**$p < 0.0001$ ($p < 0.0001$)**	**$p = 0.0003$ ($p = 0.001$)**	**$p < 0.0001$ ($p < 0.0001$)**	**$p < 0.0001$ ($p < 0.0001$)**	$p = 0.13$
Tumor fixation	$p = 0.21$	$p = 0.10$	$p = 0.12$	$p = 0.11$	$p = 0.69$
Circular vs. semicircular	$p = 0.14$	$p = 0.33$	$p = 0.17$	$p = 0.17$	$p = 0.35$
Stenosing tumor	$p = 0.77$	$p = 0.84$	$p = 0.78$	$p = 0.78$	$p = 0.28$
Perforation	**$p = 0.026$** ($p = 0.40$)	**$p = 0.01$** ($p = 0.94$)	**$p = 0.01$** ($p = 0.70$)	**$p = 0.01$** ($p = 0.31$)	$p = 0.24$
Lymphovascular space invasion	$p = 0.08$	$p = 0.41$	p = 0.13	$p = 0.09$	$p = 0.12$
Angioinvasion	$p = 0.49$	$p = 0.84$	$p = 0.78$	$p = 0.32$	$p = 0.69$
Perineural invasion	**$p = 0.046$** (p = 0.38)	**$p = 0.03$** ($p = 0.92$)	**$p = 0.02$** ($p = 0.64$)	**$p = 0.02$** ($p = 0.33$)	$p = 0.17$
Time to surgery	**$p = 0.0005$ (p = 0.001)**	**$p = 0.05$ ($p = 0.05$)**	**$p = 0.0004$ ($p = 0.008$)**	**$p = 0.003$ (p = 0.01)**	–
Type of surgery	$p = 0.44$	$p = 0.07$	$p = 0.53$	$p = 0.41$	**$p = 0.02$** ($p = 0.99$)
Resection radicality	**$p = 0.0006$** ($p = 0.82$)	**$p = 0.0003$** ($p = 0.56$)	**$p = 0.001$** ($p = 0.63$)	**$p = 0.001$** ($p = 0.68$)	$p = 0.24$
No. of LN resected	$p = 0.36$	$p = 0.52$	$p = 0.30$	$p = 0.28$	$p = 0.15$
No. of LN positive	$p = 0.35$	$p = 0.83$	$p = 0.79$	$p = 0.77$	$p = 0.81$
Aboral margin distance	**$p = 0.02$ ($p = 0.003$) OR 1.02 (1.00–1.04)**	$p = 0.44$	$p = 0.09$	**$p = 0.02$** (p = 0.06)	$p = 0.96$
CRM distance	**$p = 0.01$** ($p = 0.81$)	**$p < 0.0001$ ($p = 0.03$)**	**$p = 0.0001$** (p = 0.06)	**$p < 0.0001$** ($p = 0.11$)	$p = 0.35$

Significant results are highlighted in bold

Multivariate regression (p value results in brackets) was analysed only in significant univariate analyses results

longer than 6 to 8 weeks without fearing worse treatment outcomes related to worse TMEq.

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Compliance with Ethical Standards

Conflict of Interest All authors declare no conflict of interest.

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