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Original Article

Short-course radiotherapy versus long-course chemoradiotherapy in total neoadjuvant therapy of rectal cancer – A multicenter analysis of early outcomes and toxicity

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ABSTRACT

Background and Purpose: Total neoadjuvant therapy (TNT) improves local control and complete response (CR) rates in locally advanced rectal cancer (LARC). CR is associated with favorable local tumor control, allowing non-operative management (NOM). However, it remains unclear whether short-course radiotherapy (SCRT) or long-course chemoradiotherapy (LCRT) is preferable within TNT.

Methods: LARC patients undergoing TNT between 2015 and 2024 were included in this retrospective multicenter analysis (DRKS00033000). The primary endpoint was CR. Secondary endpoints comprised NOM rates, toxicity, and tumor control. Multivariable logistic regression modelling was used to assess the influence of LCRT.

Results: Of 295 included patients with a median age at diagnosis of 62 (Q1-Q3: 54–68) years and 210 (71.2 %) men, 172 (58.3 %) underwent LCRT. CR was achieved in 46 (37.4 %) SCRT and 96 (55.8 %) LCRT patients. Acute toxicity grade $\geq$ 3 occurred in 24 (20.5 %) of 117 SCRT and in 62 (36.3 %) of 171 LCRT patients. Within a median follow-up of 19.4 months (SCRT) and 19.6 months (LCRT), 23 (19.8 %) of 116 and 30 (19.4 %) of 155 patients experienced recurrence, respectively. Regression modelling revealed an increased likelihood for CR (adjusted odds ratio: 3.11; 95 % confidence interval: 1.37–7.07) and NOM (4.40; 1.46–13.21) with LCRT, whereas no significant associations of LCRT with acute toxicity (0.90; 0.40–2.02), chronic toxicity (1.16; 0.48–2.78), postoperative complications (0.89; 0.62–1.28) or recurrence (0.81; 0.31–2.16) were observed.

Conclusion: LCRT was associated with higher CR and NOM rates. Whether it might be preferred over SCRT for intended NOM remains a relevant question to be answered by ongoing randomized trials.

Introduction

Total neoadjuvant therapy (TNT) has emerged as a promising approach for the treatment of locally advanced rectal cancer in the presence of certain risk factors, improving both local control and reducing metastatic spread [1–4]. This treatment intensification further increases complete response (CR) rates from 10-15 % after standard neoadjuvant chemoradiotherapy (CRT) to 25–65 % after TNT [5–7], allowing non-operative management (NOM) in an increasing number of patients [8,9]. Regarding the sequence of (chemo-)radiotherapy and the intensity or duration of chemotherapy, no standard has been established [10]. Local treatment practices often deviate from initial trial protocols, leading to various adaptations in the application of TNT beyond prospective clinical trials [11]. Within TNT approaches, consolidative chemotherapy is preferable to induction chemotherapy [3]. However, the optimal sequencing of treatment remains uncertain. Although short-course radiotherapy (SCRT) and long-course chemoradiotherapy (LCRT) have been equally studied within the TNT approach, their direct comparison is addressed for the first time within ongoing randomized clinical trials (e.g., NCT04246684 or NCT05673772 [12,13]). To address this current gap, we aimed to analyze the effects of different treatment protocols and sequences on outcome and toxicity. Herein, we evaluated SCRT and LCRT with respect to CR rates, tumor control, and toxicity.

Material and methods

Study design and setting

We conducted a retrospective multicenter study within the 'Young DEGRO' working group of the German Society for Radiation Oncology (DEGRO), involving 23 hospitals in Germany and Austria, which are listed in detail in Supplement S1. The study was approved by the local ethics committee of the Faculty of Medicine at Jena University Hospital (reference number: 2023–3042-Bef, amended to allow inclusion until 2024) and by each participating center's ethics committee. The study adhered to the Declaration of Helsinki. The study protocol was prospectively registered with the German Clinical Trials Registry (DRKS, No. 00033000) and accredited by the radiation oncology working group of the German Cancer Society (Arbeitsgemeinschaft Radiologische Onkologie, ARO). Analyses were conducted in accordance with the STROBE criteria [14].

Eligible patients were diagnosed with localized rectal cancer (TNM classification: T2-4 N0-2 M0 / UICC stage II or III) between 2015 and 2024 and underwent neoadjuvant SCRT or LCRT followed by consolidation chemotherapy with curative intent. SCRT was defined as hypofractionated radiotherapy, i.e., 25 Gy / 5 fractions, without concomitant chemotherapy. LCRT comprised different schedules of normofractionated radiotherapy over 5–6 weeks, such as 50.4 Gy / 28 fractions or 45 Gy / 25 fractions with simultaneous or sequential boost to gross tumor volume (GTV) and concomitant pyrimidine-based chemotherapy (such as 5-fluorouracil or capecitabine). Follow-up data were gathered through routine oncological follow-up visits according to institutional standards.

Endpoints

The primary endpoint was CR at first evaluation after completion of TNT. The secondary endpoints comprised NOM, toxicity, and postoperative complications. Exact definitions are provided below.

Definitions. The primary endpoint CR was defined as either pathological CR (in case of resection) or clinical CR. The latter required the absence of vital residual disease as determined by rectoscopy, rectal ultrasound, and pelvic magnetic resonance imaging (MRI). Minimal residual disease (i.e., a small ulcer or hyperplastic scars), which was considered as "near CR" per physician's discretion, was rated as CR if no histological evidence of invasive disease (TNM: ycT0cN0cM0) was found at the latest three months after the end of TNT.

The secondary endpoints were defined as follows: (1) A patient underwent NOM, if the patient followed a "watch and wait" approach after CR or received a local excision in case of "near CR". (2) Toxicity was rated according to CTCAE v5.0, whereas the highest toxicity within treatment or follow-up was determined. Grade $\geq$ 3 events during TNT were considered as severe acute toxicity, and grade $\geq$ 2 events during follow-up as chronic toxicity. Toxicities were assessed overall as well as by category. (3) Postoperative complications were rated according to the Clavien-Dindo classification [15].

Furthermore, tumor stage was classified according to the UICC TNM v8.0 [16]; grading was reported according to the 2019 classification of the World Health Organization (WHO) [17]. Response to TNT was further assessed per Neoadjuvant Rectal Score (NAR) [18], and the pretreatment tumor risk classification was categorized according to the 2017 ESMO guidelines [19]. The general health condition was classified per Karnofsky Performance Status (KPS) [20]. For survival, we assessed overall survival (OS) from the start of treatment, i.e., first radiotherapy fraction, to death from any cause or last consultation, and failure-free

survival (FFS) from the start of therapy to first progression, inoperability, R2-resection, disease-related death, or last consultation.

FOLFOX protocols are given every two weeks (q2w), whereas CAPOX is given every three weeks (q3w). We thus standardized these cycle numbers to "FOLFOX-equivalent cycles", i.e., q2w, to allow for comparisons between different protocols (see Supplement S2 for details).

Statistical analysis

Before conducting the study, the required sample size for the analysis of the primary endpoint yielding a statistical power of 80 % was estimated (see Supplement S3 for details). Patient characteristics were described using the median, together with the first and third quartiles (Q1, Q3), as well as absolute and relative frequencies. For descriptive purposes, survival analyses were conducted using the Kaplan-Meier method and log-rank tests. As follow-up times differed between the treatment groups, observations were censored for log-rank tests at the first time point at which no patients remained at risk in one of the two groups [21].

The endpoints were analyzed in terms of uni- and multivariable logistic regression modelling applying generalized estimating equations (GEE) with firth-type penalty [22] and, based on Ishii et al. [23], the covariance estimator proposed by Morel et al. [24]. The treatment group and predefined potential risk factors were considered as independent variables (see Supplement S4 for detailed specification of the models). The treatment center was included as a cluster. For each endpoint, patients with missing information on at least one of the variables included in the related multivariable GEE model were excluded from both the uni- and multivariable modelling; the number of patients included in the respective models was provided.

As all analyses were explorative, we applied a two-sided significance level of 0.05 and did not correct for multiple testing. To maximize the use of available information, missing values were handled by pairwise deletion, which may lead to varying numbers of patients included per characteristic and regression model, respectively. Survival analyses and visualization were conducted with JASP v0.19.3 (JASP Team, 2025, [25]) and Numbers v14.4 (Apple, Cupertino, CA / USA). Patient descriptions were performed with R (version 4.2.2), applying the R package 'haven' (version 2.5.4) [26], and with SPSS (v29.0, IBM SPSS Statistics, Armonk, NY). Regression modelling was performed with R (version 4.2.2) and the R package geessbin (version 1.0.0) [23]. Data collection and management were performed using REDCap electronic data capture tools [27,28] hosted at Jena University Hospital (Jena, Germany).

Results

We included 295 patients with a median age at diagnosis of 62 (Q1-Q3: 54–68) years. Among them, 210 (71.2 %) were male. SCRT was performed in 123 (41.7 %) patients and LCRT in 172 (58.3 %) patients. Most patients were in good general condition (median KPS of 90 % in both groups). The majority of the included patients had "bad" or "advanced" tumors according to the 2017 ESMO risk classification (SCRT: 100/117 (85.5 %), LCRT: 113/164 (65.7 %); see also Fig. 1(A)). The tumors were most commonly located in the lower rectum in both groups. Microsatellite instability (MSI) was rare. The patient characteristics are summarized in Table 1.

Regarding the treatment characteristics (Table 2), a median of 9.0 (8.0–9.0) cycles of consolidation chemotherapy were administered in the SCRT group and 6.0 (5.5–8.0) in the LCRT group. The related median TNT duration was 4.4 (4.0–4.7) months in the SCRT group and 5.0 (3.9–5.5) months in the LCRT group. Additional information on the fractionation schedule, as well as protocols of both concomitant chemotherapy and sequential chemotherapy, is provided in Supplement S5. In short, SCRT consisted of 25 Gy / 5 fractions of pelvic radiotherapy, whereas different schedules were applied within the LCRT group. The

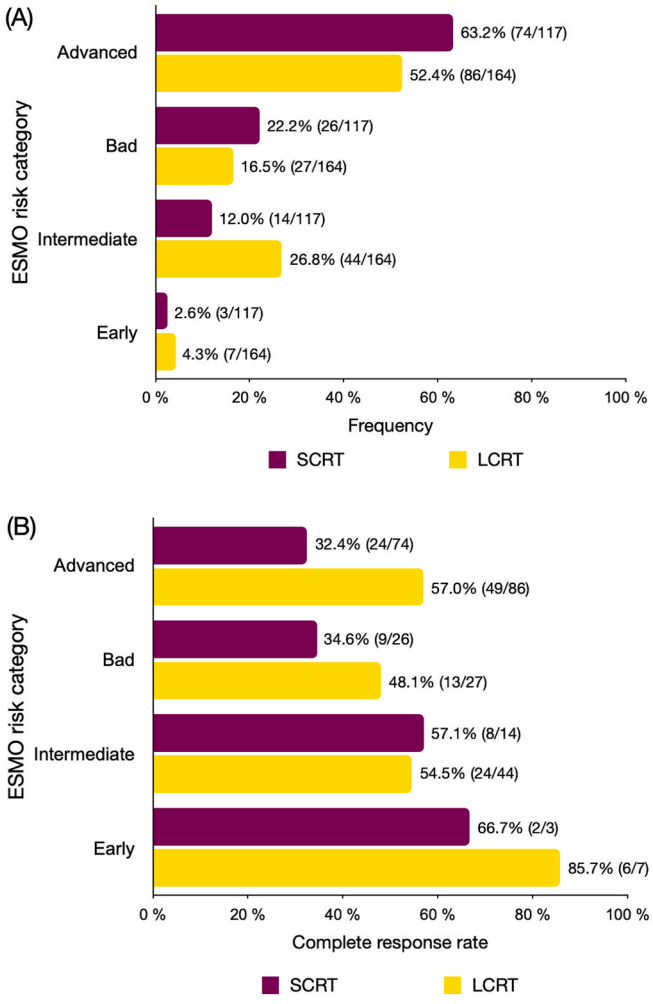

Fig. 1. (A) ESMO risk category distribution and (B) complete response (CR) rates after total neoadjuvant therapy (TNT) (stratified by ESMO risk category) among short-course radiotherapy (SCRT) and long-course chemoradiotherapy (LCRT) patients, respectively. Besides the bars, the relative frequencies are provided together with underlying raw counts. Due to missing ESMO risk category, 6 SCRT patients and 8 LCRT patients were excluded from these presentations.

most common schedules among LCRT comprised normofractionated CRT in 133 (77.3 %) patients and 45 Gy in 25 fractions, followed by a sequential boost in 30 patients (17.4 %). Regarding concomitant chemotherapy during LCRT, this was 5-fluoropyrimidine-based for 124 (72.1 %) patients (of which 92 (53.5 %) additionally received concomitant oxaliplatin) and capecitabine monotherapy for the remaining 40 (23.3 %) patients. Sequential chemotherapy was typically administered according to FOLFOX or CAPOX protocols in both groups.

An overview of outcome and toxicity is provided in Table 2. CR was achieved in 46 (37.4 %) of 123 patients after SCRT and in 96 (55.8 %) of 172 patients after LCRT; of these, 32 (26.0 %) and 44 (25.5 %), respectively, had a pathological CR. In these patients, tumors were dominantly located in the lower third in LCRT patients and, similarly, in the lower and middle third in SCRT patients (Supplement S6). Regarding the CR rate stratified by ESMO risk category (Fig. 1 (B), Supplement S7), the highest CR rate was observed in patients with early tumors. Severe acute toxicity occurred in 24 (20.5 %) of 117 SCRT patients and 62 (36.3 %) of 171 LCRT patients. No treatment-related deaths were reported. The most frequent toxicities were hematological, gastrointestinal, and neurological (see Table 2, detailed results in Supplement S8). Severe postoperative complications were reported for 23 (22.6 %) of

Table 1
Patient characteristics for short course radiotherapy (SCRT) and long course chemoradiotherapy (LCRT). Absolute (n) with relative frequencies (%) and median together with first and third quartile (Q1, Q3), respectively, are provided. For each characteristic, the number of patients with available data (N) is indicated separately per group. Please note that N may vary between variables due to missing data (pairwise deletion). Due to rounding, percentages may not add up to exactly 100%. Further abbreviations: 5-FU, 5-fluorouracil; BMI, body mass index; dMMR, deficient mismatch repair genes; EMVI, extramural vascular invasion; KPS, Karnofsky Performance Status; MRF, mesorectal fascia; MSI, microsatellite instability.

Characteristic	SCRT (123 patients)		LCRT (172 patients)	
	N	Distribution	N	Distribution
Male patient; n (%)	123	85 (69.1 %)	172	125 (72.7 %)
Age, in years; median (Q1, Q3)	123	61.0 (55.0, 66.0)	172	63.0 (54.0, 69.0)
KPS prior to TNT; median (Q1, Q3)	121	90.0 (80.0, 100.0)	171	90.0 (90.0, 100.0)
BMI, in kg/m^2; median (Q1, Q3)	119	25.5 (23.2, 29.2)	169	26.2 (23.9, 29.0)
TNM classification (at diagnosis)				
Tumor size; n (%)	123		172	
T1		1 (0.8 %)		2 (1.2 %)
T2		5 (4.1 %)		10 (5.8 %)
T3a/b		56 (45.5 %)		75 (43.6 %)
T3c/d		30 (24.4 %)		47 (27.3 %)
T4		31 (25.2 %)		38 (22.1 %)
Involvement of (regional) lymph nodes; n (%)	123		172	
N0		12 (9.8 %)		20 (11.6 %)
N1		24 (19.5 %)		66 (38.4 %)
N2		60 (48.8 %)		62 (36.0 %)
N+		26 (21.1 %)		23 (13.4 %)
Nx		1 (0.8 %)		1 (0.6 %)
Distant metastasis at diagnosis; n (%)	123		172	
M0		123 (100.0 %)		172 (100.0 %)
Localization (from anal verge); n (%)	123		171	
0 to 6 cm		61 (49.6 %)		99 (57.9 %)
>6 to 12 cm		59 (48.0 %)		69 (40.4 %)
>12 cm		3 (2.4 %)		3 (1.8 %)
Grading; n (%)	110		165	
G1		5 (4.5 %)		7 (4.2 %)
G2		100 (90.9 %)		148 (89.7 %)
G3		5 (4.5 %)		10 (6.1 %)
ESMO risk category; n (%)	117		164	
Very early		0 (0.0 %)		0 (0.0 %)
Early		3 (2.6 %)		7 (4.3 %)
Intermediate		14 (12.0 %)		44 (26.8 %)
Bad		26 (22.2 %)		27 (16.5 %)
Advanced		74 (63.2 %)		86 (52.4 %)
Infiltration of mesorectal fascia (MRF +); n (%)	115		159	
MRF involved (<1 mm)		59 (51.3 %)		76 (47.8 %)
MRF threatened (1 to 2 mm)		11 (9.6 %)		19 (11.9 %)
MRF clear (>2 mm)		45 (39.1 %)		64 (40.3 %)
EMVI; n (%)	108	37 (34.3 %)	133	35 (26.3 %)
Involved lateral pelvic nodes; n (%)	120	27 (22.5 %)	160	42 (26.2 %)
Microsatellite instability (MSI / dMMR); n (%)	91	2 (2.2 %)	106	2 (1.9 %)

102 SCRT patients and 25 (21.0 %) of 119 LCRT patients.

The median follow-up interval was 19.4 (Q1-Q3: 14.2–27.5) months for SCRT and 19.6 (Q1-Q3: 14.5–31.1) months for LCRT (see Table 2). Regarding chronic toxicity, any CTCAE grade ≥ 2 was reported for 47 (47.5 %) of 99 SCRT patients and 60 (45.8 %) of 131 LCRT patients (see also Supplement S9). Among them, polyneuropathy (PNP), fatigue, pain, diarrhea, and fecal incontinence were the most frequent. During follow-up, 23 (19.8 %) of 116 SCRT patients and 30 (19.4 %) of 155 LCRT patients were diagnosed with recurrent disease, which most frequently manifested as distant metastases (SCRT: 11/116 (9.5 %), LCRT: 22/155

Table 2
Treatment characteristics, outcome, resection management, and overview of acute toxicity during total neoadjuvant therapy (TNT) for short-course radiotherapy (SCRT) and long-course chemoradiotherapy (LCRT). Absolute (n) with relative frequencies (%) and median together with first and third quartile (Q1, Q3), respectively, are provided. For each characteristic, the number of patients with available data (N) is indicated separately per group. Please note that N may vary between variables due to missing data (pairwise deletion). A more detailed description of fractionation and chemotherapy schedules can be found within Supplement S4. Further abbreviations: APR, abdomino-perineal resection; CR, complete response; CRM, circumferential resection margin; KPS, Karnofsky Performance Score; NOM, Non-operative management; TEM, transanal endoscopic microsurgery; TME, total mesorectal excision; TNT, total neoadjuvant therapy.

Characteristic	SCRT (123 patients)		LCRT (172 patients)	
	N	Distribution	N	Distribution
Number of consolidation chemotherapy cycles*; median (Q1, Q3)	117	9.0 (8.0, 9.0)	159	6.0 (5.5, 8.0)
Duration of TNT, in months; median (Q1, Q3)	119	4.4 (4.0, 4.7)	168	5.0 (3.9, 5.5)
Interval between end of TNT and restaging / resection, in months; median (Q1, Q3)	95	1.5 (1.1, 2.3)	138	1.6 (1.2, 2.4)
Complete response (CR), n (%)	123		172	
Overall		46 (37.4 %)		96 (55.8 %)
Pathological CR		32 (26.0 %)		44 (25.5 %)
Clinical CR		14 (11.4 %)		52 (30.2 %)
NOM, n (%)	123		172	
Overall		16 (13.0 %)		56 (32.6 %) ***
Clinical response assessment / if performed: biopsy only		14 (11.4 %)		52 (30.2 %)
After local excision (e.g. TEM)		2 (1.6 %)		4 (2.3 %)
Type of resection; n (%)	122		167	
Radical (e.g., TME, APR)		106 (86.9 %)		110 (65.9 %)
Local / endoscopic excision (i.e. TEM)		2 (1.6 %)		5 (3.0 %)
None / biopsy only (i.e., watch and wait)		14 (11.5 %)		52 (31.1 %) ***
yTNM classification**				
Primary tumor size; n (%)	120		164	
yT0		42 (35.0 %)		86 (52.4 %)
yT1		10 (8.3 %)		9 (5.5 %)
yT2		22 (18.3 %)		29 (17.7 %)
yT3		40 (33.3 %)		36 (22.0 %)
yT4		6 (5.0 %)		4 (2.4 %)
Involvement of (regional) lymph nodes; n (%)	121		163	
yN0		92 (76.0 %)		134 (82.2 %)
yN1		23 (19.0 %)		20 (12.3 %)
yN2		6 (5.0 %)		9 (5.5 %)
Distant metastasis; n (%)	120		163	
yM0		118 (98.3 %)		159 (97.5 %)
yM1		2 (1.7 %)		4 (2.5 %)
KPS after TNT; median (Q1, Q3)	110	80.0 (80.0, 90.0)	168	80.0 (80.0, 90.0)
Neoadjuvant Rectal Score; median (Q1, Q3)	120	3.7 (0.9, 12.6)	163	0.9 (0.9, 8.4)
Quality of resection specimen: MERCURY Grading; n (%)	87		101	
Grade 1		66 (75.9 %)		86 (85.1 %)
Grade 2		14 (16.1 %)		12 (11.9 %)
Grade 3		7 (8.0 %)		3 (3.0 %)
Involvement of circumferential resection margin (CRM) post resection; n (%)	101		106	
CRM involved (<1 mm)		2 (2.0 %)		1 (0.9 %)
CRM threatened (1 to 2 mm)		10 (9.9 %)		8 (7.5 %)
CRM clear (>2 mm)		89 (88.1 %)		97 (91.5 %)
Postoperative complications per Clavien-Dindo classification; n (%)	102		119	
None / grade 0		51 (50.0 %)		52 (43.7 %)
Grade 1		12 (11.8 %)		28 (23.5 %)

(continued on next page)

Table 2 (*continued*)

Characteristic	SCRT (123 patients)		LCRT (172 patients)	
	N	Distribution	N	Distribution
Grade 2		16 (15.7 %)		14 (11.8 %)
Grade 3		19 (18.6 %)		22 (18.5 %)
Grade 4		4 (3.9 %)		3 (2.5 %)
Acute toxicity****; n (%)				
Any CTCAE grade ≥ 3	117	24 (20.5 %)	171	62 (36.3 %)
Neutropenia with CTCAE grade ≥ 3	81	5 (6.2 %)	144	14 (9.7 %)
Leukopenia with CTCAE grade ≥ 3	90	5 (5.6 %)	165	22 (13.3 %)
Diarrhea with CTCAE grade ≥ 3	109	4 (3.7 %)	167	14 (8.4 %)
Proctitis with CTCAE grade ≥ 3	109	2 (1.8 %)	165	13 (7.9 %)
Polyneuropathy with CTCAE grade ≥ 3	115	5 (4.3 %)	165	12 (7.3 %)
Chronic toxicity****; n (%)				
Any CTCAE grade ≥ 2	99	47 (47.5 %)	131	60 (45.8 %)
Any CTCAE grade ≥ 3	99	11 (11.1 %)	131	25 (19.1 %)
Polyneuropathy with CTCAE grade ≥ 2	96	29 (30.2 %)	131	32 (24.4 %)
Diarrhea with CTCAE grade ≥ 2	93	14 (15.1 %)	130	9 (6.9 %)
Fecal incontinence with CTCAE grade ≥ 2	92	8 (8.7 %)	127	12 (9.4 %)
Pain with CTCAE grade ≥ 2	88	5 (5.7 %)	131	16 (12.2 %)
Fatigue with CTCAE grade ≥ 2	88	7 (8.0 %)	130	18 (13.8 %)
Follow-up interval since start of TNT, in months; median (Q1, Q3)	115	19.4 (14.2, 27.5)	158	19.6 (14.5, 31.1)
Recurrence; n (%)	116	23 (19.8 %)	155	30 (19.4 %)
Patients under watch and wait at the last follow-up; n (%)	117	14 (12.0 %)	153	50 (32.7 %)

*Standardized to FOLFOX-equivalent cycles (q2w).
**including ycTNM and ypTNM.
***One patient refused resection despite residual disease and was managed with palliative systemic treatment. He was, thus, excluded from NOM.
****The 5 most frequent toxicity categories are displayed. The complete results are provided in Supplement S7 (acute toxicity) and S8 (chronic toxicity).

(14.2 %); Supplement S10). The local recurrence rates between both groups were comparable (SCRT: 9/116 (7.8 %), LCRT: 12/155 (7.7 %)). In the subgroup of patients receiving NOM, recurrence was observed in 3 (20.0 %) of 15 SCRT and 10 (19.2 %) of 52 LCRT patients (Supplement S10).

Based on the Kaplan-Meier estimates (see Fig. 2), the 18-month FFS rate was 81.2 % (95 % CI 73.7 %-89.5 %) for SCRT and 85.3 % (95 % CI 79.3 %-91.7 %) for LCRT patients. The corresponding 18-month OS rate was 94.7 % (95 % CI 90.2 %-99.4 %) for SCRT and 97.5 % (95 % CI 94.7 %-100.0 %) for LCRT patients. There was no evidence of differences in FFS ($p = 0.261$, censored at 36.2 months) and OS ($p = 0.256$, censored at 43.6 months) between the two groups. The FFS and OS stratified by the resection types are provided in Supplement S11.

The results from regression modelling for primary and secondary outcomes are presented in Table 3 and in Supplement S12. For the primary endpoint, patients receiving LCRT (adjusted OR 3.11; 95 % CI 1.37–7.07) and patients with early tumors (adjusted OR 5.20; 95 % CI 1.07–25.31) were more likely to experience a CR. The latter is also illustrated in Fig. 1 (B). Similarly, NOM was more often observed in LCRT patients (adjusted OR, 4.40; 95 % CI 1.46–13.21). For acute toxicity, the likelihood decreased with an increasing number of consolidation chemotherapy cycles (adjusted OR 0.85; 95 % CI: 0.73–0.99), and male patients were less likely to experience toxicity than female patients (adjusted OR 0.46; 95 % CI: 0.25–0.86). This association was also observed for the most frequent acute toxicity categories: diarrhea, leukopenia, and neutropenia. Contrasting acute toxicity, the likelihood for chronic toxicity increased with increasing number of consolidation chemotherapy cycles (adjusted OR 1.20, 95 % CI 1.02–1.41). Patients with a larger body mass index (BMI) were more likely to experience severe postoperative complications (adjusted OR 1.09; 95 % CI 1.02–1.18). For LCRT, we did not observe evidence for any associations with acute toxicity, chronic toxicity, or postoperative complications. For recurrence, we observed no evidence for associations with the predefined variables.

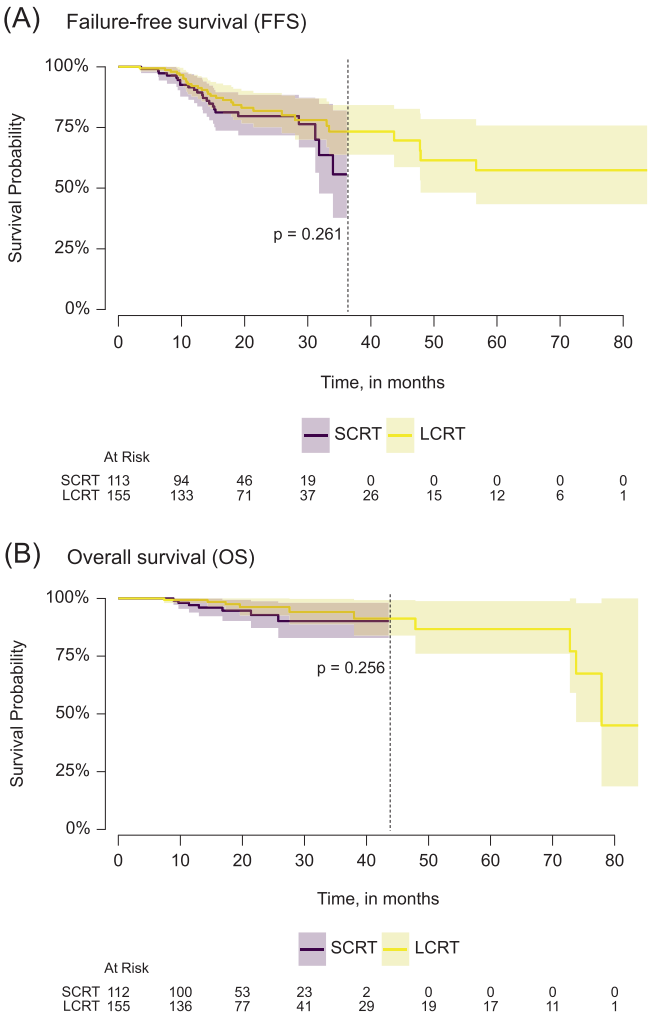

Fig. 2. (A) Failure-free survival (FFS) and (B) overall survival (OS) curves for short-course radiotherapy (SCRT) and long-course chemoradiotherapy (LCRT) patients. The survival probabilities are accompanied by the respective 95 % confidence intervals (CI). The number of patients at risk is provided for both treatment groups below the plot. The p-value (p) from the log-rank test is provided. For this test, data was censored at the time point, where no patients at risk were remaining in one of the groups (vertical dashed line at 36.2 months for FFS, corresponding to 0 SCRT and 29 LCRT patients at risk, as well as at 43.6 months for OS, corresponding to 0 SCRT and 23 LCRT patients at risk, respectively). Due to missing survival information, 10 SCRT and 17 LCRT patients were excluded in the FFS analysis and 11 SCRT and 17 LCRT patients in the OS analysis.

Discussion

To the best of our knowledge, we conducted the first multicenter study comparing SCRT and LCRT within TNT. While recent analyses confirmed the oncological safety of NOM after CR [8,9], and benefits regarding functional outcomes and quality of life have been reported [29], we identified LCRT (compared to SCRT) as a significant factor associated with a higher likelihood for both CR and NOM.

A relevant proportion of intermediate as well as some early risk tumors were treated with TNT in this cohort, especially in the LCRT group. In these patients, the CR rate was remarkably high. However, TNT might be related to an overtreatment in these patients [30] and exceeds toxicity compared to standard CRT [1,31]. An additional factor that

Table 3
Results from regression modelling for the primary and secondary outcomes. (Adjusted) odds ratio (OR) with 95 % confidence interval (CI) and p-value from uni- and multivariable generalized estimation equations (GEE) modelling provided for (A) complete response, (B) non-operative management, (C) occurrence of severe toxicity, i.e., any CTCAE grade $\geq$ 3, (D) severe postoperative complications, i.e., any Clavien-Dindo grade $\geq$ 3, (E) recurrence, and (F) chronic toxicity, i.e., any CTCAE grade $\geq$ 2. The number of patients (N) included in the respective model is given; patients with missing data in any of the included variables were excluded from this respective model. A detailed description of all included variables is provided in Supplement S3. Further abbreviations: BMI, Body mass index; KPS, Karnofsky Performance Status; LCRT, long-course chemoradiotherapy; TNT, total neoadjuvant therapy.

Variable	Univariable logistic GEE models			Multivariable logistic GEE model		
	N	OR (95 % CI)	p-value	N	adjusted OR (95 % CI)	p-value
(A) Complete response						
LCRT	261	2.31 (1.39, 3.85)	0.001	261	3.11 (1.37, 7.07)	0.007
ESMO risk group (ref.: advanced)	261					
Bad		0.86 (0.48, 1.52)	0.596		0.92 (0.45, 1.88)	0.822
Intermediate		1.96 (0.87, 4.42)	0.105		1.71 (0.71, 4.12)	0.233
Early		4.41 (1.52, 12.80)	0.006		5.20 (1.07, 25.31)	0.041
Age, per 10 years	261	1.11 (0.89, 1.38)	0.359		1.06 (0.79, 1.42)	0.715
Male sex	261	0.91 (0.53, 1.58)	0.748		0.91 (0.45, 1.85)	0.801
Number of consolidation chemotherapy cycles*	261	1.05 (0.93, 1.19)	0.426		1.20 (0.97, 1.48)	0.093
Duration of TNT, in months	261	1.16 (0.94, 1.42)	0.163		0.92 (0.65, 1.28)	0.610
(B) Non-operative management						
LCRT	259	4.03 (1.84, 8.82)	<0.001	259	4.40 (1.46, 13.21)	0.008
ESMO risk group (ref.: advanced)	259					
Bad		0.71 (0.37, 1.36)	0.304		0.82 (0.37, 1.79)	0.612
Intermediate		1.90 (0.95, 3.81)	0.071		1.58 (0.66, 3.82)	0.308
Early		3.48 (1.00, 12.07)	0.050		3.31 (0.67, 16.37)	0.143
Age, per 10 years	259	1.20 (0.89, 1.63)	0.233		1.20 (0.81, 1.79)	0.367
Male sex	259	0.77 (0.41, 1.45)	0.414		0.82 (0.38, 1.79)	0.618
Number of consolidation chemotherapy cycles*	259	0.95 (0.86, 1.06)	0.379		1.11 (0.87, 1.42)	0.381
Duration of TNT, in months	259	1.05 (0.85, 1.29)	0.661		0.86 (0.59, 1.25)	0.431
KPS prior to TNT, per 10 %	259	1.16 (0.87, 1.56)	0.307		1.26 (0.88, 1.80)	0.208
(C) Severe acute toxicity (CTCAE grade $\geq$ 3)						
LCRT	271	1.23 (0.60, 2.51)	0.570	271	0.90 (0.40, 2.02)	0.789
Age, per 10 years	271	0.97 (0.71, 1.32)	0.848		0.93 (0.68, 1.28)	0.668
Male sex	271	0.42 (0.25, 0.71)	0.001		0.46 (0.25, 0.86)	0.014
Number of consolidation chemotherapy cycles*	271	0.82 (0.72, 0.93)	0.003		0.85 (0.73, 0.99)	0.039
KPS prior to TNT, per 10 %	271	0.98 (0.77, 1.25)	0.861		0.98 (0.73, 1.30)	0.872
(D) Severe post-operative complications (Clavien-Dindo grade $\geq$ 3)						
LCRT	202	0.89 (0.66, 1.19)	0.419	202	0.89 (0.62, 1.28)	0.527
Age, per 10 years	202	0.91 (0.64, 1.29)	0.598		0.89 (0.59, 1.33)	0.566
Male sex	202	1.65 (0.65, 4.19)	0.288		1.87 (0.67, 5.21)	0.230
Number of consolidation chemotherapy cycles*	202	0.92 (−, −)**	−**		0.95 (0.86, 1.03)	0.217
KPS prior to TNT, per 10 %	202	0.69 (0.51, 0.93)	0.014		0.71 (0.49, 1.02)	0.067
BMI prior to TNT, in kg/m^2	202	1.09 (1.03, 1.15)	0.004		1.09 (1.02, 1.18)	0.018
(E) Recurrence						
LCRT	138	0.69 (0.30, 1.61)	0.393	138	0.81 (0.31, 2.16)	0.677
Age, per 10 years	138	0.75 (0.55, 1.04)	0.081		0.80 (0.50, 1.27)	0.340
Male sex	138	0.93 (0.51, 1.72)	0.829		0.93 (0.38, 2.31)	0.877
Number of consolidation chemotherapy cycles*	138	1.05 (0.89, 1.23)	0.568		0.98 (0.78, 1.25)	0.888
NAR score, in points	138	1.04 (1.01, 1.07)	0.007		1.03 (1.00, 1.06)	0.058
Presence of EMVI	138	1.59 (0.71, 3.56)	0.259		1.64 (0.57, 4.69)	0.360
Involvement of lateral pelvic nodes	138	1.89 (0.82, 4.35)	0.135		1.21 (0.32, 4.60)	0.776
Resection status / CRM positivity (ref.: CRM involved)	138					
CRM threatened		0.51 (0.05, 5.17)	0.567		1.48 (0.08, 28.38)	0.796
CRM clear		0.15 (0.02, 1.37)	0.093		0.64 (0.03, 15.60)	0.782
MERCURY Grading (ref.: grade 1)	138					

(*continued on next page*)

Table 3 (*continued*)

Variable	Univariable logistic GEE models			Multivariable logistic GEE model		
	N	OR (95 % CI)	p-value	N	adjusted OR (95 % CI)	p-value
Grade 2		2.12 (0.66, 6.80)	0.208		1.96 (0.48, 8.04)	0.352
Grade 3		3.31 (0.72, 15.09)	0.123		1.19 (0.18, 7.63)	0.857
Follow-up interval, in months	138	0.96 (0.92, 1.00)	0.065		0.99 (0.94, 1.03)	0.576
(F) Chronic toxicity (CTCAE grade ≥ 2)						
LCRT	217	0.69 (0.40, 1.19)	0.178	217	1.16 (0.48, 2.78)	0.747
Age, per 10 years	217	0.77 (0.61, 0.98)	0.035		0.74 (0.52, 1.03)	0.077
Male sex	217	0.94 (0.47, 1.87)	0.864		0.84 (0.37, 1.92)	0.676
Number of consolidation chemotherapy cycles*	217	1.17 (1.05, 1.31)	0.005		1.20 (1.02, 1.41)	0.030
KPS prior to TNT, per 10 %	217	0.86 (0.63, 1.17)	0.335		0.78 (0.51, 1.20)	0.259
NOM	217	0.42 (0.24, 0.74)	0.002		0.48 (0.22, 1.08)	0.076
Follow-up interval, in months	217	1.00 (0.97, 1.02)	0.740		1.00 (0.97, 1.03)	0.995

*Standardized to FOLFOX-equivalent cycles (q2w).
**No convergence reached.

might influence the CR rate is the number of consolidation chemotherapy cycles and, consequently, the duration of TNT, as demonstrated by the TIMING trial [32]. Gani et al. [33] recently demonstrated that a "near CR", i.e., small residual disease, frequently evolved into CR after extended follow-up, enabling NOM in 40 % of patients in their cohort. LCRT usually spans over 5 to 6 weeks, whereas SCRT is completed within one week. As SCRT patients generally receive more cycles of consolidation chemotherapy than LCRT patients within our study, there was only a slight difference (2 weeks) in the median overall treatment duration.

Randomized trials with similar protocols applying LCRT followed by consolidation chemotherapy [1,3,4,34] reported 3-year disease-free survival (DFS) rates of > 75 % and OS rates of > 85 %. As the median follow-up in our cohort was limited to 19 months, no direct comparison with studies reporting 3-year survival is feasible. However, the outcomes observed during the first 18 months do not suggest any unexpected deviation from the patterns reported in large randomized trials [1,35]. Long-term data of the RAPIDO trial suggest worse local control after TNT (i.e., combination of SCRT and consolidation chemotherapy) compared with standard CRT with or without adjuvant chemotherapy [36], which was postulated to be attributed to mesorectal breach, i.e., worse MERCURY grading [37]. Aligning with the findings of the RAPIDO cohort [1,36], MERCURY grading appeared to be higher after SCRT in our study. We observed no differences regarding the relative frequency of local recurrences between the treatment groups. In particular, these were also comparable in NOM patients and align with local recurrence rates between 16 % and 25 % reported in the literature [9,38].However, the short median follow-up period (compared to 5.6 years in the RAPIDO trial) and the relatively small number of patients with recurrence must be considered. As CR is associated with low risk for local recurrence [39,40], longer follow-up periods are required to examine if the CR benefit observed in the LCRT group of our study translates into improved FFS.

Regarding severe toxicity during TNT, the observed rate of CTCAE grade ≥ 3 events within the LCRT group of about 36 % aligns with the experimental arm of the ARO-12 trial (37 %) [3], ARO-16 trial (36 %) [33] and the consolidation-chemotherapy arm of the OPRA trial (36 %) [4]. The related rate in our SCRT group can be compared with the experimental arm of the RAPIDO trial [1], where 38 % of the patients showed such an event, exceeding the observed rate of about 21 % in our study. Although severe toxicity was more frequent in the LCRT group, we found no evidence of an association with treatment group after adjusting for covariates in the regression models. We are awaiting new insights in this regard from larger, prospective trials, such as the ongoing ACO/ARO/AIO-18.1 (NCT04246684) or SOLAR (NCT05673772) trials.

In our analyses, female sex was associated with an increased likelihood for severe acute toxicity (overall as well as for some subcategories). Other studies also reported a higher risk of treatment-related toxicity in female patients [41–44]. Suggestions of complex sex-depending interactions regarding tumor response can be found [42], but the existence of sex effects regarding outcome is not consistent across all TNT cohorts [45,46], including our results presented here. The observed association between higher BMI and an increased risk of postoperative complications is also in line with the literature [47–49].

Limitations and future implications

Although the inclusion criteria and statistical analyses were prespecified in the study protocol, the significance of this analysis is limited by its retrospective, non-randomized design and the small number of events, which precluded further stratification or subgroup analyses. To address the limitations associated with the absence of randomization, we adjusted our regression analyses for potential cofounders, namely age, sex, ESMO risk group, number of consolidation chemotherapy cycles, and TNT duration.

This study did not address the intention of NOM. While pathological CR rates were similar between groups, clinical CR was higher after LCRT, suggesting more patients in this group may have been considered for NOM. Furthermore, the tumor diameter, known to influence CR rates [50], was not assessed in this study. As this study primarily focused on CR rates, conclusions regarding long-term effects on tumor control and survival are limited. The study might be underpowered for analyses related to recurrence rates and survival (FFS and OS), as the frequencies of recurrences, failure and death, respectively, were relatively low during the follow-up. This may also explain why we were unable to detect effects of proven risk factors, such as circumferential resection margin (CRM) or extramural vascular invasion (EMVI) positivity, on the likelihood of recurrence.

An inverse relationship was observed between chemotherapy cycles and acute toxicity, suggesting that patients with better tolerance were more likely to complete treatment. The LCRT group was heterogeneous in concomitant and consolidative chemotherapy, leading to variable cumulative doses. Their impact on CR rates and toxicity remains unclear, warranting a dedicated dose–effect analysis to be reported separately.

Conclusion

We identified LCRT (compared to SCRT) as an influential factor for a higher likelihood of both CR and NOM after TNT, whereas no association with severe toxicity, postoperative complications, short-term tumor control, or survival rates was observed. LCRT might be preferred over SCRT in the case of intended NOM. However, the results of prospective randomized trials must be awaited to confirm our findings.

CRediT authorship contribution statement

Georg Wurschi: Writing – review & editing, Writing – original draft, Visualization, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Miriam Kesselmeier:** Writing – original draft, Methodology, Formal analysis. **Melanie Schneider:** Writing – review & editing, Investigation. **Jan-Niklas Becker:** Writing – review & editing, Investigation. **Bernd Frerker:** Writing – review & editing, Investigation. **Samuel M. Vorbach:** Writing – review & editing, Investigation. **Felix Ehret:** Writing – review & editing, Investigation. **Markus Diefenhardt:** Writing – review & editing, Investigation. **Fabian Schunn:** Writing – review & editing, Investigation. **Maria-Elena von Gruben:** Writing – review & editing, Investigation. **Marcel Büttner:** Writing – review & editing, Investigation. **Elgin Hoffmann:** Writing – review & editing, Investigation. **Alexander Rühle:** Writing – review & editing, Investigation, Conceptualization. **Josephine Beier:** Writing – review & editing, Investigation. **Simone Ferdinandus:** Writing – review & editing, Investigation. **Maike Trommer:** Writing – review & editing, Investigation. **Ezgi Ceren Sahin:** Writing – review & editing, Investigation. **Julian Hlouschek:** Writing – review & editing, Investigation. **Kynann Aninditha:** Writing – review & editing, Investigation. **Daphne Schepers von Ohlen:** Writing – review & editing, Investigation. **Justus Kaufmann:** Writing – review & editing, Investigation. **Alina Depardon:** Writing – review & editing, Investigation. **Hai Minh Ha:** Writing – review & editing, Investigation. **Simon Trommer:** Writing – review & editing, Investigation. **Christopher Kessler:** Writing – review & editing, Investigation. **Adrianna Cieslak:** Writing – review & editing, Investigation. **Alexander Fabian:** Writing – review & editing, Investigation. **Florian Rißner:** Writing – review & editing, Resources, Project administration. **Maximilian Römer:** Writing – review & editing, Investigation. **Matthias Mäurer:** Writing – review & editing, Investigation. **Klaus Pietschmann:** Writing – review & editing, Supervision, Resources, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2025.111194.

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