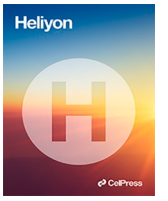
Heliyon 10 (2024) e27684

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



Research article

Differential clinical outcomes after 3 versus 5 years in a comparison of preoperative chemotherapy with and without radiotherapy in locally advanced rectal cancer: A national cohort propensity score-matched study

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ARTICLE INFO

Keywords:
Neoadjuvant therapy
Locally advanced rectal cancer
Survival
Prognostic factors
Propensity Score Matching
FOWARC trial
PROSPECT trial

ABSTRACT

Background: Preoperative chemotherapy alone might be a good alternative to preoperative chemoradiotherapy for patients with locally advanced rectal cancer, yet long-term real-world data from the same cohort are lacking.

Methods: Patients diagnosed with stage II-III rectal adenocarcinoma from 2011 to 2015 were randomly sampled from the SEER-Plus database to evaluate the superiority of preoperative chemoradiotherapy versus preoperative chemotherapy alone.

Findings: A total of 1314 eligible patients were enrolled, with a median follow-up of 74.0 months. At 3-year follow-up, neither overall survival (OS) nor cancer-specific survival (CSS) was significantly different between the two treatment groups. At 5-year follow-up, CSS was similar across groups (HR 0.768, 95% CI 0.532–1.108; P = 0.156), but the 5-year OS was significantly better in the preoperative chemoradiotherapy group than in the preoperative chemotherapy group (HR 0.682, 95% CI 0.538–0.866; P = 0.002). Besides, the landmark analysis indicated a direct contrast in the CSS within 3 years (HR 1.101, 95% CI 0.598–2.029; P = 0.756) versus that at 3–5 years (HR 0.597, 95% CI 0.377–0.948; P = 0.027). The landmark analysis also showed directly contrasting OS outcomes within 3 years (HR 0.761, 95% CI 0.533–1.086; P = 0.130) versus those at 3–5 years (HR 0.621, 95% CI 0.451–0.857; P = 0.003).

Interpretation: In patients with locally advanced rectal cancer under real-world treatment practices, the addition of preoperative radiotherapy to chemotherapy improves survival outcomes at 3–5 years' follow-up but not at 3-year follow-up.

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https://doi.org/10.1016/j.heliyon.2024.e27684
Received 28 March 2023; Received in revised form 1 March 2024; Accepted 5 March 2024
Available online 11 March 2024

1. Research in context

1.1. Evidence before this work

More than half of the 46,000 new rectal cancer cases in the United States each year are diagnosed at locally advanced stage (stage II and III). For this group, the standard treatment recommended by the guidelines is a combination of total mesorectal excision, concurrent preoperative chemotherapy with ionizing radiation to the pelvis, and postoperative chemotherapy. However, some recent studies considered that the addition of preoperative radiotherapy to chemotherapy would have no significant impact on survival outcome, and instead resulted in more toxicity or complications.

2. Added value of this work

This propensity score-matched cohort study is the first to report long-term, real-world results of chemoradiotherapy versus chemotherapy alone in the neoadjuvant setting for locally advanced rectal cancer. The result is representative at a national level due to the characteristics of the database used.

3. Implications of all the available evidence

Rectal cancer mortality has declined in the US, in part because of advances in treatment. Better evidence supporting decisions of high impact in public health may further reduce mortality. Our findings demonstrate the long-term superiority of preoperative chemoradiotherapy compared with preoperative chemotherapy alone for patients with locally advanced rectal cancer under real-world treatment practices. Besides, careful and appropriate drug selection should be used when attempting to provide neoadjuvant chemotherapy alone in lieu of a multimodal neoadjuvant approach.

4. Introduction

Multimodal treatment of locally advanced rectal cancer typically includes total mesorectal excision (TME), concurrent preoperative chemotherapy with ionizing radiation to the pelvis, and postoperative chemotherapy [1,2]. Preoperative chemoradiotherapy has been shown to increase the rates of pathologic complete response, downstaging and sphincter preservation relative to preoperative chemotherapy alone [3]. These effects are associated with a significant increase in local control. However, some recent studies have considered that the addition of preoperative radiotherapy to chemotherapy would have no significant impact on survival outcome.

The FOWARC trial initially demonstrated that the addition of preoperative radiotherapy to chemotherapy did not significantly improve 3-year overall survival (OS) or disease-free survival (DFS) in patients with locally advanced rectal cancer [4]. These findings were further supported by long-term follow-up results presented at the 2023 ASCO Annual Meeting. The study emphasized that there were no significant differences in survival outcomes between preoperative FOLFOX with or without radiation, and the standard regimen of fluorouracil plus radiation. Furthermore, the PROSPECT trial also indicated that preoperative FOLFOX was noninferior to preoperative chemoradiotherapy with fluorouracil in terms of 5-year DFS [5,6]. This approach could spare patients of the morbidities associated with radiotherapy, but the National Comprehensive Cancer Network (NCCN) panel considers investigational at this time [7].

Some systematic reviews have suggested that preoperative chemotherapy alone is a good alternative to chemoradiotherapy for patients with locally advanced rectal cancer, as it is associated with low toxicity, low anastomotic leakage, and high survival rates [8,9]. However, the two groups in the systematic review came from heterogeneous study cohorts. Their baseline variables are so inconsistent that they are not sufficiently comparable.

These controversial results warrant further validation with long-term real-world data from head-to-head comparisons of neoadjuvant therapy approaches. In this study, we present the 5-year clinical outcomes for 1314 patients with locally advanced rectal cancer receiving routine clinical care and allocated to treatment with either preoperative chemoradiotherapy or chemotherapy alone, using a data set in existence for the United States population: the National Cancer Institute's (NCI's) Surveillance, Epidemiology, and End Results (SEER)-Plus database.

5. Methods

5.1. Data source

We conducted a retrospective study using deidentified data from SEER-Plus. The NCI approved this analysis and waived the need for informed consent from the patients (No. SAR0019360). The SEER Program of the NCI is responsible for the collection and reporting of cancer incidence and survival data from several population-based central cancer registries. This study was limited to the SEER-17 registries, which cover approximately 26.5% of the U.S. population (consisting of Utah, Seattle-Puget Sound, New Jersey, New Mexico, Louisiana, Los Angeles, Kentucky, Iowa, Hawaii, Greater California, San Francisco-Oakland, San Jose-Monterey, Rural Georgia, Greater Georgia, Atlanta, Connecticut, and the Alaska Native Tumor Registry) with complete longitudinal data necessary for the analyses.

5.2. Patient selection and study parameters

Patients diagnosed with stage II or III rectal adenocarcinoma were eligible for inclusion. Patients were enrolled from 2011 to match the present patterns of rectal cancer care in the United States [10]. Key exclusion criteria were as follows: (a) treatment regimens other than those being studied; (b) the absence of important clinicopathological factors, such as histologic grade, N stage and treatment information. Finally, patients assigned to receive preoperative chemoradiotherapy or preoperative chemotherapy alone followed by resection with/without postoperative chemotherapy were divided into two groups for comparison. This study evaluated the superiority of preoperative chemoradiotherapy versus preoperative chemotherapy alone.

Propensity score-based weighting was used to adjust for covariate differences between the treatment groups [11]. We used nearest neighborhood matching to estimate the propensity scores and stabilized them to improve covariate balance [12]. Adjustments were made for sex, age, marital status, race, T category, N category, American Joint Committee on Cancer (AJCC) stage, histologic grade, tumor size, number of nodes examined, perineural invasion, tumor deposits, pretreatment carcinoembryonic antigen (CEA) and postoperative chemotherapy use via propensity score–based weighting. Race was included in the analysis to make the results more

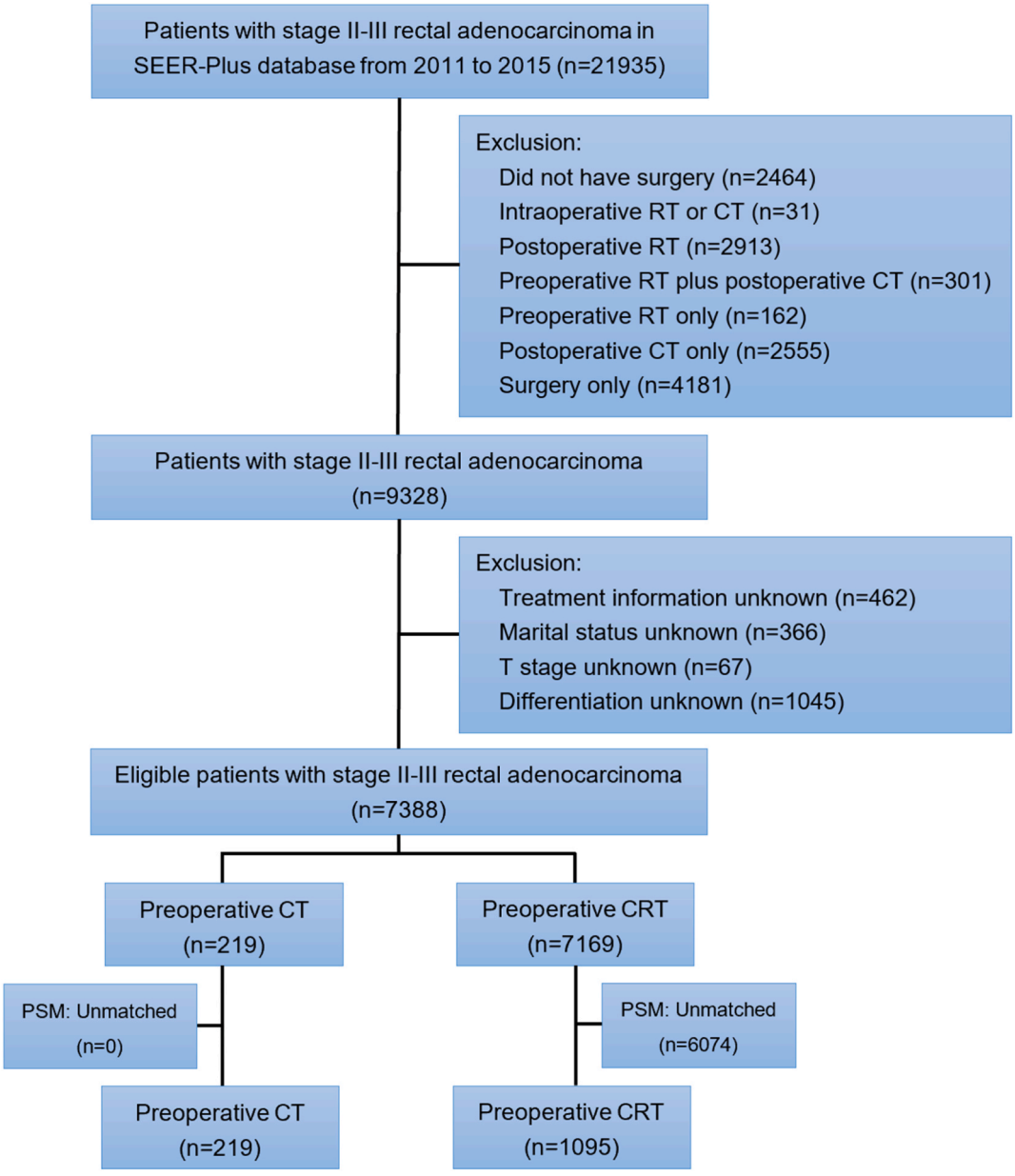

Fig. 1. Flow chart of SEER-Plus population recruitment. RT = radiotherapy; CT = chemotherapy; CRT = chemoradiotherapy; PSM = propensity score matching.

generalizable to the US population. Patients were uniformly reviewed and staged according to the seventh edition of the TNM classification. Stage II included T3 or T4 tumors with no positive regional lymph nodes, and stage III included any T1 to T4 tumors with regional lymph node involvement.

Table 1
Baseline characteristics of patients between both treatment groups in the unmatched and matched populations.

Characteristics	Unmatched population (n = 7388)			Matched population (n = 1314)		
	Pre CT(n = 219)	Pre CRT(n = 7169)	P value	Pre CT(n = 219)	Pre CRT(n = 1095)	P value
Sex			0.339			0.896
Female	76 (34.7)	2733 (38.1)		76 (34.7)	372 (34.0)	
Male	143 (65.3)	4436 (61.9)		143 (65.3)	723 (66.0)	
Age at diagnosis, yr			0.999			0.961
<60	111 (50.7)	3631 (50.6)		111 (50.7)	560 (51.1)	
≥60	108 (49.3)	3538 (49.4)		108 (49.3)	535 (48.9)	
Marital status[a]			0.642			0.860
Not married	89 (40.6)	2785 (38.8)		89 (40.6)	435 (39.7)	
Married	130 (59.4)	4384 (61.2)		130 (59.4)	660 (60.3)	
Race[b]			0.544			0.734
White	175 (79.9)	5838 (81.4)		175 (79.9)	886 (80.9)	
Black	15 (6.8)	545 (7.6)		15 (6.8)	83 (7.6)	
Other/unknown	29 (13.2)	786 (11.0)		29 (13.2)	126 (11.5)	
T category			0.008			0.999
T1-3	183 (83.6)	6413 (89.5)		183 (83.6)	912 (83.3)	
T4	36 (16.4)	756 (10.5)		36 (16.4)	183 (16.7)	
N category			0.702			0.725
N0	89 (40.6)	2769 (38.6)		89 (40.6)	444 (40.5)	
N1	96 (43.8)	3349 (46.7)		96 (43.8)	502 (45.8)	
N2	34 (15.5)	1051 (14.7)		34 (15.5)	149 (13.6)	
AJCC stage[c]			0.594			0.999
II	89 (40.6)	2769 (38.6)		89 (40.6)	444 (40.5)	
III	130 (59.4)	4400 (61.4)		130 (59.4)	651 (59.5)	
Histologic grade			0.648			0.559
Well/moderately	195 (89.0)	6293 (87.8)		195 (89.0)	992 (90.6)	
Poor/undifferentiated	24 (11.0)	876 (12.2)		24 (11.0)	103 (9.4)	
Tumor size, cm			0.326			0.762
<5	113 (51.6)	3332 (46.5)		113 (51.6)	554 (50.6)	
≥5	78 (35.6)	2823 (39.4)		78 (35.6)	415 (37.9)	
Unknown	28 (12.8)	1014 (14.1)		28 (12.8)	126 (11.5)	
Nodes examined[d], No.			0.336			0.330
<12	65 (29.7)	2367 (33.0)		65 (29.7)	287 (26.2)	
≥12	154 (70.3)	4802 (67.0)		154 (70.3)	808 (73.8)	
Characteristics	Unmatched population (n = 7388)			Matched population (n = 1314)		
	Pre CT(n = 219)	Pre CRT(n = 7169)	P value	Pre CT(n = 219)	Pre CRT(n = 1095)	P value
Perineural Invasion[e]			0.721			0.775
Negative	164 (74.9)	5496 (76.7)		164 (74.9)	842 (76.9)	
Positive	27 (12.3)	763 (10.6)		27 (12.3)	130 (11.9)	
Unknown	28 (12.8)	910 (12.7)		28 (12.8)	123 (11.2)	
Tumor Deposits[e]			0.609			0.729
Negative	170 (77.6)	5688 (79.3)		170 (77.6)	872 (79.6)	
Positive	23 (10.5)	776 (10.8)		23 (10.5)	112 (10.2)	
Unknown	26 (11.9)	705 (9.8)		26 (11.9)	111 (10.1)	
CEA Pretreatment			0.377			0.323
Normal	86 (39.3)	2847 (39.7)		86 (39.3)	425 (38.8)	
Elevated/borderline	62 (28.3)	2278 (31.8)		62 (28.3)	360 (32.9)	
Unknown	71 (32.4)	2044 (28.5)		71 (32.4)	310 (28.3)	
Postoperative CT			0.023			0.957
No	154 (70.3)	4484 (62.5)		154 (70.3)	765 (69.9)	
Yes	65 (29.7)	2685 (37.5)		65 (29.7)	330 (30.1)	

Abbreviations: Pre, preoperative; CT, chemotherapy; CRT, chemoradiotherapy; AJCC, American Joint Committee on Cancer; CEA, carcinoembryonic antigen.

[a] This variable identifies the patient's marital status at the time of diagnosis for rectal adenocarcinoma; the data item 'Not married' includes single, widowed, divorced and separated statuses.

[b] The race information was recoded into three major categories to make them compatible with available annual population estimates used as denominators for the rates: White, Black and Other (I.e. American Indian/Alaska Native and Asian/Pacific Islander).

[c] In determining AJCC stage, the seventh AJCC edition was used; substages (e.g., IIA, IIB) were collapsed; the existing AJCC 7th ed. T, N, M and stage data for 2011–2015 can be either a clinical or pathologic stage due to the limitations of the SEER-Plus database.

[d] NCCN guidelines recommend that the adequate staging of colorectal cancer demands sampling at least 12 lymph nodes.

[e] Perineural invasion and tumor deposit status were diagnosed by pathology.

5.3. Endpoint

The primary analytic endpoint was OS from initial diagnosis to the date of death or censoring at the last follow-up. The secondary endpoint was cancer-specific survival (CSS), calculated as the proportion of enrollees who were alive or died from the cancer-specific disease in a defined period of time; patients who died from causes other than the disease being studied were not counted.

5.4. Statistical analyses

We performed a post hoc analysis of sample sizes after propensity score matching. The sample parameters of the two treatment groups, such as the means, standard deviations, and sample sizes, were calculated to obtain an effect size of 0.30 (95% CI 0.15 to 0.44). Then, it was estimated that the study could provide a power of 98% with a type I error of 5% (two sided).

The median period of follow-up was calculated for the entire study cohort according to the reverse Kaplan–Meier method [13]. OS was determined using the Kaplan–Meier method. The differences between survival curves were assessed for statistical significance with the log-rank test. We estimated differences between groups by calculating hazard ratios (HRs) and 95% confidence intervals (CIs). Patients who received preoperative chemotherapy alone were used as the reference group in the analyses. Additionally, we performed landmark analyses to assess survival outcomes at 3 years and at 3–5 years. CSS was analyzed with the same methods as those used for the analysis of OS. Subgroup analyses of OS were performed by means of an interaction test to determine the consistency of the

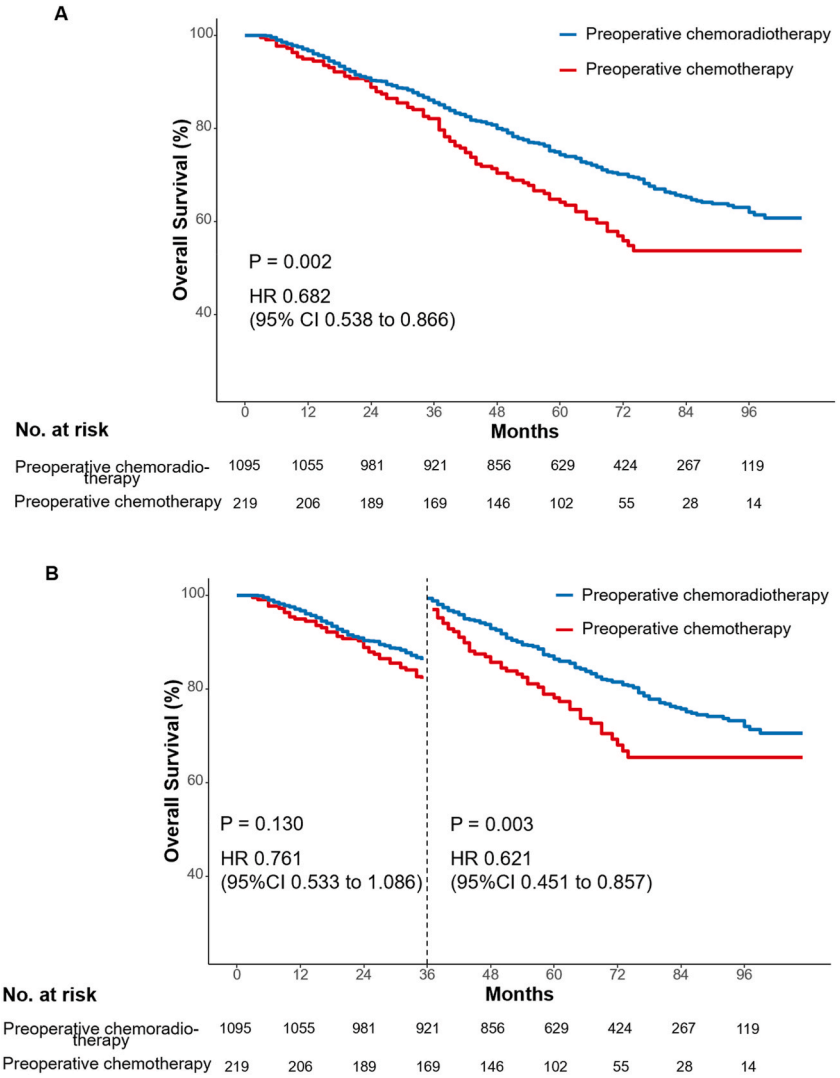

Fig. 2. Overall survival of preoperative chemoradiotherapy and preoperative chemotherapy groups in the matched population. (A) Kaplan–Meier estimates of overall survival. (B) Landmark analysis discriminating between overall survival before and after 3 years of follow-up. HR = hazard ratio.

treatment effect according to key baseline characteristics. A univariable Cox proportional hazards model was used to assess crude prognostic variables, and multivariable Cox proportional hazards models were used to evaluate independent prognostic factors related to 5-year OS.

The corresponding variable details were extracted with SEER*Stat software (version 8.4.0.1). All statistical analyses were performed by SPSS (version 25.0; IBM Corp., Armonk, New York, USA) and R software (version 4.1.2; http://www.r-project.org). All statistical tests were two-sided, with P values < 0.05 considered statistically significant.

6. Results

Fig. 1 shows the flow chart of SEER-Plus population recruitment. Between 2011 and 2015, a total of 7388 patients with stage II-III rectal adenocarcinoma were eligible. After propensity score matching, 1314 patients were finally available for our study, and among them, 219 patients in the preoperative chemotherapy group were matched with 1095 patients in the preoperative chemoradiotherapy group, leaving no statistically significant baseline differences between matched groups. Table 1 summarizes the patient baseline characteristics in both treatment groups.

In the matched population, the median follow-up was 74.0 months. The mean OS was 84.2 months in the preoperative chemoradiotherapy group and 76.4 months in the preoperative chemotherapy group. Fig. 2A illustrates that the 5-year OS was significantly different (HR 0.682, 95% CI 0.538–0.866; P = 0.002), while OS appeared similar within 3 years. The landmark analysis confirmed that

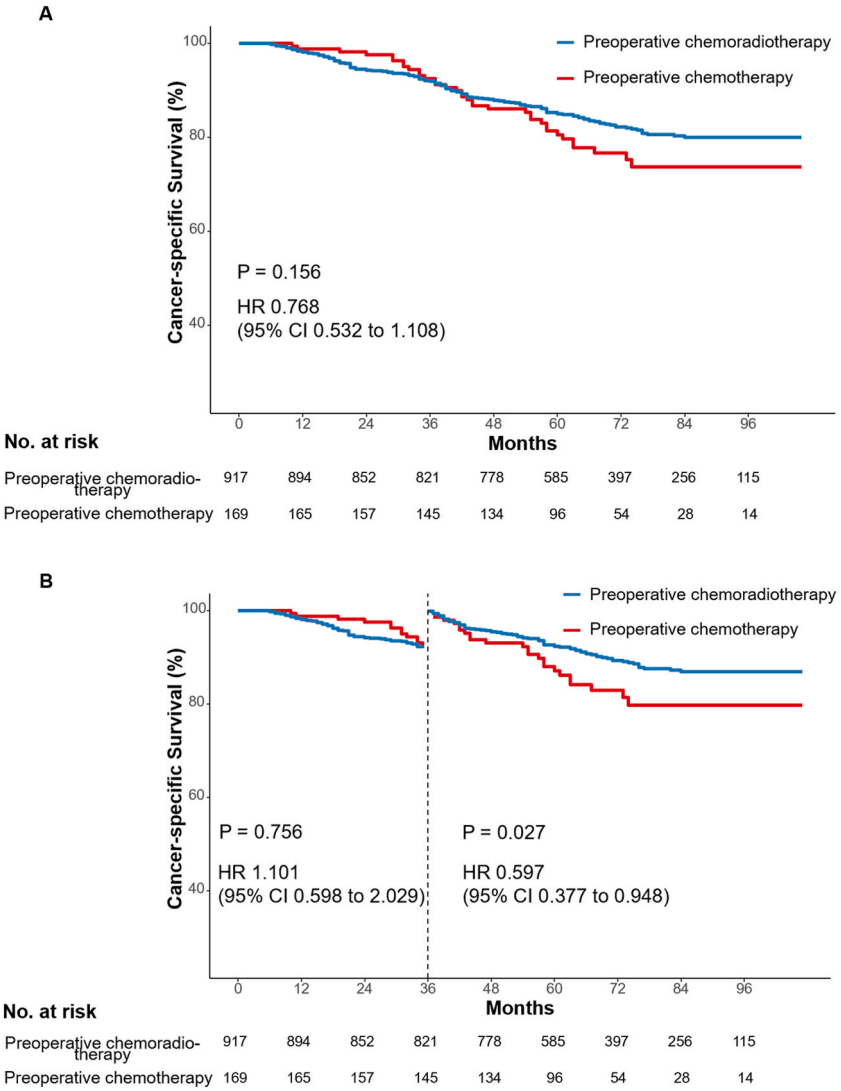

Fig. 3. Cancer-specific survival of preoperative chemoradiotherapy and preoperative chemotherapy groups in the matched population. (A) Kaplan–Meier estimates of cancer-specific survival. (B) Landmark analysis discriminating between cancer-specific survival before and after 3 years of follow-up. HR = hazard ratio.

survival outcomes did not differ significantly between the two groups at 3-year follow-up (HR 0.761, 95% CI 0.533–1.086; P = 0.130); however, at 3–5 years' follow-up, OS was significantly greater in the preoperative chemoradiotherapy group than in the preoperative chemotherapy group (HR 0.621, 95% CI 0.451–0.857; P = 0.003) (Fig. 2B).

At 5-year follow-up, CSS was similar between patients who received preoperative chemoradiotherapy and preoperative chemotherapy (HR 0.768, 95% CI 0.532–1.108; P = 0.156) (Fig. 3A). This finding at 5 years is indicative of directly contrasting results for survival outcomes within 3 years versus 3–5 years. Patients in the preoperative chemoradiotherapy group had worse CSS outcomes

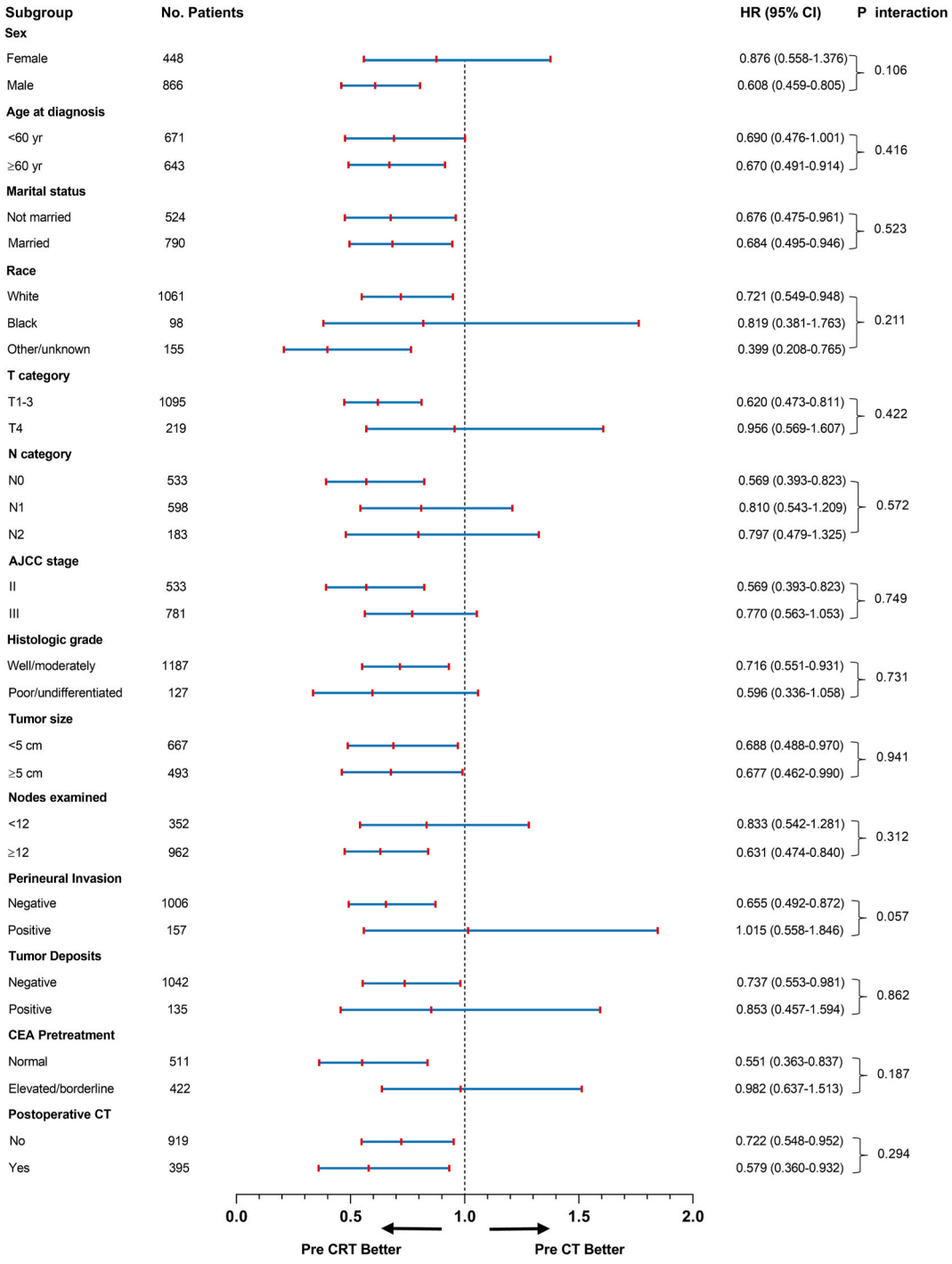

Fig. 4. Forest plot of the treatment effect on overall survival in subgroup analyses. HR = hazard ratio; AJCC=American Joint Committee on Cancer; CEA = carcinoembryonic antigen; Pre = preoperative; CRT = chemoradiotherapy; CT = chemotherapy.

within 3 years (HR 1.101, 95% CI 0.598–2.029; P = 0.756), but had better CSS outcomes beyond the third year (HR 0.597, 95% CI 0.377–0.948; P = 0.027) (Fig. 3B).

We also conducted a subgroup analysis to separate the risk factors when comparing survival outcomes. Prespecified subgroup analyses favored patients treated with preoperative chemoradiotherapy. The advantage of preoperative chemoradiotherapy in terms of 5-year OS was consistent across all subgroups (Fig. 4). Furthermore, subgroup analyses did not reveal any significant interaction between baseline characteristics and treatment effect.

Univariate Cox regression analysis identified 13 underlying prognostic factors and variables with a P < 0.05 in the univariate analysis were selected for multivariate analysis. In the multivariable analysis, factors significantly associated with a worse 5-year OS only were preoperative chemotherapy alone, older age, unmarried status, T4, N2, poor/undifferentiated grade, less than 12 nodes examined, presence of perineural invasion, presence of tumor deposits, elevated pretreatment CEA and no use of postoperative chemotherapy (Table 2).

7. Discussion

It is an interesting finding of this study that the addition of preoperative radiotherapy to chemotherapy improves long-term survival despite no difference in short-term survival. The study also showed independent predictors for poor OS in patients with locally advanced rectal cancer.

According to the study by Murphy CC et al. (2015) [10], the NCI 's SEER program documented a variety of therapy sequences and chemotherapy agents used in the treatment of locally advanced rectal cancer in the United States. Among chemotherapy treated patients, the use of fluorouracil alone decreased from 35.8% in 2000 to 10.3% in 2010, and there was an increase in the use of FOLFOX (32.3% in 2005 to 44.0% in 2010).

Contrary to the findings of our study, the FOWARC and PROSPECT trials indicated that preoperative FOLFOX was similar to preoperative chemoradiotherapy with fluorouracil in terms of 5-year survival. Furthermore, the FOWARC trial revealed that there were no significant differences in 5-year survival outcomes between preoperative FOLFOX with and without radiation. A plausible explanation might be that the efficacy of modified FOLFOX is sufficiently robust to reach a plateau in survival benefits, and additional radiotherapy cannot further improve survival. However, for other chemotherapy agents, preoperative fluorouracil would be inferior to preoperative chemoradiotherapy with fluorouracil with respect to 5-year survival. Our study utilized real-world data to represent current treatment practices for locally advanced rectal cancer in the United States, particularly including the diverse chemotherapy agents. This may be responsible for the different results between these studies.

The point of time for endpoint assessment in a clinical study comparing various treatment methods is meant to represent a true and long-lasting study result. The follow-up evaluation and event monitoring of the PROSPECT trial will continue up to 58.0 months post randomization. Our study had a median follow-up of 74.0 months. We found that a 3-year primary endpoint does not necessarily capture long-term outcomes after receiving neoadjuvant therapy. Notably, with 73% of the included patients still alive after 5 years, long-term outcomes, even beyond 5 years, seem to be of the utmost importance. This was justified in the era of TME when very low mortality and local recurrence rates were not an issue [14–16], and the high cumulative incidence of distant recurrence was the main

Table 2
Univariate and multivariate analyses of the effects of prognostic factors on overall survival in the **matched population**.

Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Pre treatment (Pre CRT vs. Pre CT)	0.682 (0.538–0.866)	0.002	0.707 (0.556–0.899)	0.005
Sex (Male vs. Female)	1.219 (0.990–1.501)	0.062		
Age (≥60 vs. <60 yr)	1.611 (1.326–1.958)	<0.001	1.550 (1.267–1.896)	<0.001
Marital status (Married vs. Not married)	0.720 (0.594–0.872)	0.001	0.777 (0.638–0.946)	0.012
Race (Black vs. White)	1.610 (1.179–2.199)	0.003	1.314 (0.958–1.802)	0.091
T category (T4 vs. T1-3)	2.020 (1.621–2.519)	<0.001	1.596 (1.273–2.000)	<0.001
N category		<0.001		<0.001
N0	Reference		Reference	
N1	0.942 (0.759–1.169)	0.586	1.090 (0.872–1.363)	0.448
N2	1.930 (1.488–2.503)	<0.001	1.922 (1.446–2.554)	<0.001
AJCC stage (III vs. II)	1.141 (0.936–1.390)	0.192		
Grade (Poor/undifferentiated vs. Well/moderately)	1.831 (1.395–2.403)	<0.001	1.698 (1.289–2.235)	<0.001
Tumor size (≥5 vs. <5 cm)	1.173 (0.957–1.439)	0.124		
Nodes examined (≥12 vs. <12)	0.754 (0.613–0.928)	0.008	0.774 (0.623–0.962)	0.021
Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Perineural Invasion (Positive vs. Negative)	2.018 (1.565–2.602)	<0.001	1.555 (1.182–2.044)	0.002
Tumor Deposits (Positive vs. Negative)	2.050 (1.576–2.667)	<0.001	1.422 (1.064–1.901)	0.017
CEA Pretreatment (Elevated/borderline vs. Normal)	1.880 (1.489–2.374)	<0.001	1.641 (1.293–2.083)	<0.001
Postoperative CT (Yes vs. No)	0.695 (0.556–0.869)	0.001	0.732 (0.583–0.919)	0.007

Abbreviations: HR, hazard ratio; CI, confidence interval; Pre, preoperative; CRT, chemoradiotherapy; CT, chemotherapy; AJCC, American Joint Committee on Cancer; CEA, carcinoembryonic antigen.

limitation of long-term survival [17,18]. Therefore, 3-year results in head-to-head comparisons of neoadjuvant therapy approaches in locally advanced disease might change over time and long-term follow-up of at least 5 years should be incorporated into the design of such studies. The role of different neoadjuvant approaches in reducing distant recurrence remains a priority area for future research.

Although radiotherapy results in more toxicity or complications [19,20], we found, via subgroup analysis of age, that the addition of preoperative radiotherapy to chemotherapy could still improve long-term survival in elderly patients. Just as caution must be used when interpreting these results, there should be reasonable awareness of the beneficial effects of radiation on multidisciplinary treatment. On the one hand, combining chemotherapy with a novel delivery of radiotherapy could achieve chemo-sensitization and site-directed chemotherapy. A multi-institutional phase I study combining low-dose ultrafractionated radiotherapy as a chemo-sensitizer for standard-dose gemcitabine and erlotinib was found to be well tolerated with encouraging efficacy [21]. Another study reported that the anticancer chemotherapy prodrug can be activated using clinically relevant doses of ionizing radiation, enabling site-directed chemotherapy, rather than systemic chemotherapy, with real-time drug decaging at the tumor site [22]. On the other hand, radiotherapy-induced effects on the tumor microenvironment can block the immune camouflage of tumor cells and enhance the recruitment of immunostimulatory T cells. Recently, it has been demonstrated that ionizing radiation may exert interesting effects on the tumor microenvironment, increasing the effectiveness of patients' antitumor immune responses in the primary tumor site, even at distant sites [23,24].

This study showed that perineural invasion was a significant independent predictor for poor OS in patients with locally advanced rectal cancer. In addition, other studies revealed that patients with perineural invasion could be categorized as high-risk for local or distant recurrence [25,26]. Interestingly, perineural invasion can be controlled by postoperative chemotherapy [27,28], but not by preoperative chemoradiotherapy [29,30]. All these studies highlight the importance of perineural invasion and suggest that greater surveillance and a more intensive treatment strategy may be required for patients with this risk factor.

This study has several limitations. First, the main limitation is the inherent selection bias present in SEER-Plus database studies. Second, some treatment details, including definitive drug, dose, duration and toxicity in rectal cancer, are lacking in SEER-Plus database, even if we could see chemotherapy agents documented by the NCI 's SEER program from Murphy CC et al.' s (2015) study. Therefore, we call upon the NCI to further open access to the SEER database in the future, thereby validating our speculation by analyzing treatment regimens with different chemotherapy/radiotherapy strategies. Finally, a potential limitation of landmark analyses is the fact that events, in particular mortality, that occur before the landmark are not included in the analysis beyond the landmark. Luckily, 3-year mortality was similar in the preoperative chemoradiotherapy and chemotherapy groups and therefore unlikely to have affected the 3–5 years' analyses.

8. Conclusion

In patients with locally advanced rectal cancer under real-world treatment practices, the addition of preoperative radiotherapy to chemotherapy improves survival outcomes at 3–5 years' follow-up but not at 3-year follow-up. Careful and appropriate drug selection should be used when attempting to provide neoadjuvant chemotherapy alone in lieu of a multimodal neoadjuvant approach.

Data sharing statement

The data used for this article is publicly available from the SEER-Plus database (https://seer.cancer.gov, 17 registries).

Funding

National Natural Science Foundation of China; Sun Yat-sen University Clinical Research 5010 Program; Xinjiang Autonomous Region Technology Plan.

CRediT authorship contribution statement

Yuanxin Zhang: Writing – original draft, Data curation. **Rui Luo:** Methodology, Data curation. **Jingqi Peng:** Writing – review & editing, Funding acquisition. **Zichuan He:** Formal analysis, Data curation. **Delin Tan:** Software, Data curation. **Xueping Liu:** Investigation, Data curation. **Hui Wang:** Conceptualization. **Huaiming Wang:** Funding acquisition, 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.

Acknowledgements

This study was supported by the National Natural Science Foundation of China (Grant No. 82103084), the Sun Yat-sen University Clinical Research 5010 Program (Grant No. 2019021) and the Xinjiang Autonomous Region Technology Plan (Grant No. 2022E02125). The authors thank AJE Academic Services for English language editing and review services.

References

[1] P.-L. Hsu, C.-W. Chien, Y.-A. Tang, et al., Targeting BRD3 eradicates nuclear TYRO3-induced colorectal cancer metastasis, Sci. Adv. 9 (2023) eade3422.
[2] H. Bando, Y. Tsukada, K. Inamori, et al., Preoperative chemoradiotherapy plus Nivolumab before surgery in patients with Microsatellite stable and Microsatellite Instability-high locally advanced rectal cancer, Clin. Cancer Res. 28 (2022) 1136–1146.
[3] A. Li, T. Huang, R. Zheng, et al., Preoperative chemoradiotherapy with capecitabine and triweekly oxaliplatin versus capecitabine monotherapy for locally advanced rectal cancer: a propensity-score matched study, BMC Cancer 22 (2022) 789.
[4] Y. Deng, P. Chi, P. Lan, et al., Neoadjuvant modified FOLFOX6 with or without radiation versus fluorouracil plus radiation for locally advanced rectal cancer: final results of the Chinese FOWARC trial, J. Clin. Oncol. 37 (2019) 3223–3233.
[5] D. Schrag, Q. Shi, M.R. Weiser, et al., Preoperative treatment of locally advanced rectal cancer, N. Engl. J. Med. 389 (2023) 322–334.
[6] E. Basch, A.C. Dueck, S.A. Mitchell, et al., Patient-reported outcomes during and after treatment for locally advanced rectal cancer in the PROSPECT trial (Alliance N1048), J. Clin. Oncol. 41 (2023) 3724–3734.
[7] A.B. Benson, A.P. Venook, M.M. Al-Hawary, et al., Rectal cancer, version 2.2018, NCCN clinical practice guidelines in Oncology, J Natl Compr Canc Netw 16 (2018) 874–901.
[8] D.K. Manatakis, N. Gouvas, J. Souglakos, E. Xynos, Neo-adjuvant chemotherapy alone for the locally advanced rectal cancer: a systematic review, Int. J. Clin. Oncol. 25 (2020) 1570–1580.
[9] O. Jalil, L. Claydon, T. Arulampalam, Review of neoadjuvant chemotherapy alone in locally advanced rectal cancer, J. Gastrointest. Cancer 46 (2015) 219–236.
[10] C.C. Murphy, L.C. Harlan, J.L. Lund, C.F. Lynch, A.M. Geiger, Patterns of Colorectal Cancer Care in the United States: 1990–2010. *JNCI*, Journal of the National Cancer Institute, 2015, p. 107, https://doi.org/10.1093/jnci/djv198.
[11] J.K. Lunceford, M. Davidian, Stratification and weighting via the propensity score in estimation of causal treatment effects: a comparative study, Statist Med 23 (2004) 2937–2960.
[12] O. Baser, Too Much Ado about propensity score models? Comparing methods of propensity score matching, Value Health 9 (2006) 377–385.
[13] F. Loupakis, C. Cremolini, G. Masi, et al., Initial therapy with FOLFOXIRI and Bevacizumab for metastatic colorectal cancer, N. Engl. J. Med. 371 (2014) 1609–1618.
[14] J.B. Lee, H.S. Kim, A. Ham, et al., Role of preoperative chemoradiotherapy in clinical stage II/III rectal cancer patients Undergoing total mesorectal excision: a retrospective propensity score analysis, Front. Oncol. 10 (2020) 609313.
[15] K.C.M.J. Peeters, C.A.M. Marijnen, I.D. Nagtegaal, et al., The TME trial after a median follow-up of 6 years: increased local control but no survival benefit in irradiated patients with resectable rectal carcinoma, Ann. Surg. 246 (2007) 693–701.
[16] J.K. MacFarlane, R.D. Ryall, R.J. Heald, Mesorectal excision for rectal cancer, Lancet 341 (1993) 457–460.
[17] J.-F. Bosset, L. Collette, G. Calais, et al., Chemotherapy with preoperative radiotherapy in rectal cancer, N. Engl. J. Med. 355 (2006) 1114–1123.
[18] A.C. Lord, A. Corr, A. Chandramohan, et al., Assessment of the 2020 NICE criteria for preoperative radiotherapy in patients with rectal cancer treated by surgery alone in comparison with proven MRI prognostic factors: a retrospective cohort study, Lancet Oncol. 23 (2022) 793–801.
[19] T.W.A. Koedam, B.T. Bootsma, C.L. Deijen, et al., Oncological outcomes after anastomotic leakage after surgery for Colon or rectal cancer: increased risk of local recurrence, Ann. Surg. 275 (2022) e420–e427.
[20] X. Guan, R. Wei, R. Yang, et al., Association of radiotherapy for rectal cancer and Second Gynecological Malignant Neoplasms, JAMA Netw. Open 4 (2021) e2031661.
[21] A. Konski, J.E. Meyer, M. Joiner, et al., Multi-institutional phase I study of low-dose ultra-fractionated radiotherapy as a chemosensitizer for gemcitabine and erlotinib in patients with locally advanced or limited metastatic pancreatic cancer, Radiother. Oncol. 113 (2014) 35–40.
[22] J. Geng, Y. Zhang, Q. Gao, et al., Switching on prodrugs using radiotherapy, Nat. Chem. 13 (2021) 805–810.
[23] S.C. Formenti, S. Demaria, Systemic effects of local radiotherapy, Lancet Oncol. 10 (2009) 718–726.
[24] L. de la Cruz-Merino, A. Illescas-Vacas, A. Grueso-López, A. Barco-Sánchez, C. Míguez-Sánchez, Cancer Immunotherapies Spanish group (GETICA). Radiation for Awakening the Dormant immune System, a Promising Challenge to be Explored, Front. Immunol. 5 (2014) 102.
[25] P. Chablani, P. Nguyen, X. Pan, et al., Perineural invasion Predicts for distant metastasis in locally advanced rectal cancer treated with neoadjuvant Chemoradiation and surgery, Am. J. Clin. Oncol. 40 (2017) 561–568.
[26] S. Kim, J.W. Huh, W.Y. Lee, et al., Prognostic impact of Lymphatic invasion, Venous invasion, perineural invasion and tumor Budding in rectal cancer treated with neoadjuvant chemoradiotherapy followed by total mesorectal excision, Dis. Colon Rectum (2022), https://doi.org/10.1097/DCR.0000000000002266 published online Feb 21.
[27] S.-Y. Sung, S.H. Kim, H.S. Jang, et al., Pathologic Implications of radial resection Margin and perineural invasion to adjuvant chemotherapy after preoperative chemoradiotherapy and surgery for rectal cancer: a multi-institutional and Case-matched control study, Cancers 14 (2022) 4112.
[28] J.H. Song, M. Yu, K.M. Kang, et al., Significance of perineural and lymphovascular invasion in locally advanced rectal cancer treated by preoperative chemoradiotherapy and radical surgery: can perineural invasion be an indication of adjuvant chemotherapy? Radiother. Oncol. 133 (2019) 125–131.
[29] S. Yokoyama, K. Matsuda, T. Watanabe, et al., Perineural invasion is associated with poor survival after preoperative Chemoradiation therapy for advanced lower rectal cancer, Dig. Surg. 34 (2017) 387–393.
[30] C.H. Kim, S.-S. Yeom, S.Y. Lee, et al., Prognostic impact of perineural invasion in rectal cancer after neoadjuvant chemoradiotherapy, World J. Surg. 43 (2019) 260–272.