Hong Kong J Radiol. 2023;26:174-84. Epub 7 Sep 2023 | https://doi.org/10.12809/hkjr2217659

ORIGINAL ARTICLE **CME**

Effect of Elective Inguinal Irradiation in Low Rectal Cancer with Anal Canal Invasion

HS Wong, WYL Choi, KT Yuen

Department of Oncology, Princess Margaret Hospital, Hong Kong SAR, China

ABSTRACT

Introduction: *We investigated whether omitting elective inguinal irradiation during neoadjuvant or adjuvant radiation/chemoradiation therapy is feasible for patients with low rectal cancer with anal canal invasion (ACI) and nonpalpable inguinal lymph nodes (ILNs) at presentation.*

Methods: *Ninety low rectal cancer patients with ACI who underwent neoadjuvant or adjuvant radiation/chemoradiation therapy with or without elective inguinal radiotherapy (RT) between 2011 and 2021 were recruited. None had palpable ILN. The failure pattern, ILN recurrence rate, survival data, and prognostic factors were analysed.*

Results: *Among 81 patients omitting elective inguinal RT, the 3-year ILN failure rate was 4.9%. Meanwhile, there was no inguinal failure with elective RT. One case of isolated ILN failure was successfully salvaged by surgery. In multivariate Cox regression analysis, positive pathological lymph node(s) after neoadjuvant treatment predicted a worse locoregional recurrence-free survival (odds ratio [OR] = 9.066; $p \leq 0.001$), distant metastasis recurrence-free survival (OR = 6.426; $p = 0.002$), and overall survival (OR = 11.750; $p \leq 0.001$). Chemotherapy concurrent with RT was associated with better locoregional recurrence-free survival (OR = 33.338; $p = 0.001$) and overall survival (OR = 13.917; $p = 0.006$). Grade ≥3 acute and chronic toxicities occurred in 33.3% and 19.8%, respectively, of patients with elective inguinal irradiation, compared with 11.1% and 7.4%, respectively, in patients who did not receive it.*

Conclusion: *Omission of elective inguinal irradiation resulted in a low inguinal failure rate and similar survival outcomes for low rectal cancer patients with ACI. Additionally, it might spare patients from unnecessary acute and chronic RT toxicities.*

Key Words: *Chemoradiotherapy; Chemoradiotherapy, adjuvant; Neoadjuvant therapy; Rectal neoplasms*

Correspondence: *Dr HS Wong, Department of Oncology, Princess Margaret Hospital, Hong Kong SAR, China*
Email: whs871@ha.org.hk

Submitted: 26 Oct 2022; Accepted: 12 Dec 2022.

Contributors: HSW designed the study, acquired and analysed the data, and drafted the manuscript. WYLC and KTY critically revised the manuscript for important intellectual content. All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of Interest: The authors have disclosed no conflicts of interest.

Funding/Support: This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Data Availability: All data generated or analysed during the present study are available from the corresponding author on reasonable request.

Ethics Approval: This research was approved by the Kowloon West Cluster Research Ethics Committee of Hospital Authority, Hong Kong [Ref No.: KW/EX-22-035 (171-04)]. A waiver of patient consent was obtained from the Committee due to the retrospective nature of the study.

Declaration: This manuscript was posted on Research Square as a registered online preprint (https://doi.org/10.21203/rs.3.rs-1914914/v1).

中文摘要

伴肛門侵犯的低位直腸癌患者進行預防性腹股溝照射的影響

王曉生、蔡源霖、袁錦堂

引言：我們探討為臨床上出現肛門侵犯及觸摸不到腹股溝淋巴結的低位直腸癌患者進行前輔助放療或輔助放療／放化療時不接受預防性腹股溝照射是否可行。

方法：本研究招募了90名出現肛門侵犯的低位直腸癌患者，他們在2011至2021年間曾進行前輔助放療或輔助放療／放化療，部分有接受預防性腹股溝放療，部分則沒有。全部患者均沒有觸摸到的腹股溝淋巴結。本研究分析了失敗模式、腹股溝淋巴結復發率、存活數據及預後因素。

結果：在81名沒有接受預防性腹股溝放療的患者中，三年腹股溝淋巴結失敗率為4.9%。同時，預防性放療並沒有腹股溝失敗的情況。一例個別的腹股溝淋巴結失敗成功通過手術挽救。多變量Cox迴歸分析顯示，前輔助放療後的陽性病理性淋巴結預測較差的局部無復發存活（勝算比 = 9.066；$p \leq 0.001$）、無遠端轉移復發存活（勝算比 = 6.426；$p = 0.002$）及整體存活（勝算比 = 11.750；$p \leq 0.001$）。放療期間同時進行化療與較佳的局部無復發存活（勝算比 = 33.338；$p = 0.001$）及整體存活（勝算比 = 13.917；$p = 0.006$）相關。在接受預防性腹股溝照射的患者中，分別有33.3%及19.8%出現≥3級急性及慢性毒性；沒有接受該照射的患者出現上述兩種毒性的比例則分別為11.1%及7.4%。

結論：沒有接受預防性腹股溝照射的伴肛門侵犯的低位直腸癌患者，其腹股溝失敗率低，與有接受該照射的患者相比，存活結果相近，而且可能避免出現不必要的急性及慢性放療毒性。

INTRODUCTION

Neoadjuvant chemoradiotherapy (CRT) reduces the risk of a positive circumferential margin and local recurrence in patients with low rectal cancer.[1] Prospective randomised trials have demonstrated significantly lower locoregional recurrence rates with adjuvant CRT when compared with observation or either modality alone in stage II/III rectal cancer.[2]

The clinical target volume (CTV) during radiation/chemoradiation therapy must cover areas with potential metastatic risk while avoiding organs at risk to avoid radiation-related complications. In low rectal cancer with anal canal invasion (ACI), tumour can spread to inguinal lymph nodes (ILNs) through the perirectal and pudendal lymphatics, as well as the lymphatics draining the infradentate and perianal skin. An advanced rectal primary tumour can cause proximal lymphatic obstruction and retrograde lymph node metastasis.[3] The European Society for Medical Oncology Clinical Practice Guidelines proposed in 2010 recommends prophylactic irradiation of medial ILNs if the rectal tumour extends below the dentate line.[4] Radiation of ILNs in cases where tumour extends into the anal sphincter has been advocated by the 2016 international consensus guidelines on CTV delineation.[5] According to the 2020 American Society for Radiation Oncology Clinical Practice Guidelines, ILNs and external iliac nodes should be conditionally included in the CTV for patients with rectal malignancies with ACI.[6] However, the contouring atlas of the Radiation Therapy Oncology Group has no consensus on the subject.[7]

In three retrospective trials,[8-10] the ILN failure rates in rectal cancer patients with ACI who received neoadjuvant or adjuvant radiation/chemoradiation therapy without elective inguinal irradiation were not high enough (3-year failure rate: 3.7%[8]; 5-year actuarial rate: 3.5%-4%[9,10]) to justify inguinal irradiation as a standard procedure.

The treatment policy at our institution for low rectal cancer with ACI and clinically negative ILN at presentation has been based on the practice of the attending oncologists. We looked at the feasibility of omitting elective inguinal irradiation for patients with low rectal cancer with ACI and clinically negative ILN.

METHODS

Data Collection

From 2011 to 2021, the clinical data of 110 patients with

low rectal cancer with ACI who received neoadjuvant or adjuvant radiation/chemoradiation therapy in our tertiary oncology centre were collected from the institutional database and retrospectively reviewed. The inclusion criteria were: (1) histologically confirmed locally advanced rectal adenocarcinoma without distant metastasis (based on the Eighth Edition of the American Joint Committee on Cancer Staging Manual); (2) tumours with ACI, defined as the tumour's lower edge being within 3 cm of the anal verge (or being located at or below the dentate line) on digital rectal examination, colonoscopy or magnetic resonance imaging; and (3) an Eastern Cooperative Oncology Group performance status score of 0 to 2.

The exclusion criteria were: (1) inguinal metastasis on presentation by clinical and imaging studies; (2) occurrence of distant failure before surgery; (3) ineligibility for radical surgery as determined by clinical and imaging studies; (4) local excision; (5) incomplete radiation/chemoradiation therapy; (6) in the setting of recurrence indicated for radiation/chemoradiation therapy; and (7) second malignancies within 5 years.

Missing data were dealt with by listwise deletion. Patients lost to follow-up were censored and their life expectancy was counted till the last follow-up date.

Pretreatment Workup

Pretreatment workup for clinical staging included digital rectal examination, complete blood count, liver and renal function tests, serum carcinoembryonic antigen, colonoscopy, chest radiography, computed tomography (CT) of the thorax, abdomen and pelvis with or without transrectal ultrasonography, and pelvic magnetic resonance imaging. Fluorine-18 fluorodeoxyglucose positron emission tomography/CT (PET/CT) was performed at the physician's discretion and patient accessibility.

Chemoradiotherapy Treatment

The patients received either long-course or short-course radiotherapy (RT). Long-course RT was administered to the entire pelvis at a dose of 45 Gy in 25 daily fractions, followed by a 5.4-Gy boost in three daily fractions over 5.5 weeks. Short-course RT was delivered to the whole pelvis at a dose of 25 Gy in 5 daily fractions over 1 week. All patients underwent CT simulation for three-dimensional conformal planning, with a comfortably full bladder and an empty rectum. In patients declining elective inguinal irradiation, a three-field treatment plan was adopted using a posterior-anterior field and lateral opposing beams. With patients electing inguinal irradiation, a pair of anterior-posterior opposing fields was used. The prescription dose was set at the 100% isodose line. The initial radiation field encompassed the gross tumour volume (GTV) (preoperative radiation/chemoradiation therapy) or tumour bed (postoperative CRT), and the regional lymphatics including the mesorectal, internal iliac, presacral, and distal common iliac lymphatics plus or minus ILN. The superior boundary was the L5-S1 junction; the inferior border was set 3 cm caudal to the GTV or tumour bed and the anterior border was placed 3 cm anterior to the sacral promontory, while the posterior border was placed 1 cm posterior to the sacrum. The GTV or tumour bed was included in the boost field, with 3-cm margins in all directions.

Chemotherapy was administered concurrently with long-course RT using bolus 5-fluorouracil (FU) [500 mg/m^2 intravenous bolus; Days 1-3 and Days 29-31].[11] As there has been evidence for better treatment outcomes with continuous oral capecitabine,[12,13] continuous oral capecitabine (825 mg/m^2 twice per day) was used as a concomitant chemotherapeutic agent since April 2021. If patients were deemed unsuitable for chemotherapy, long-course RT alone was an alternative. Either abdominal-perineal resection or low anterior resection with complete mesorectal excision was performed. Typically, the interval between preoperative CRT and surgery was 8 weeks, and that between surgery and postoperative CRT was 10 weeks. Four months of adjuvant chemotherapy was administered using six cycles of capecitabine and oxaliplatin, eight cycles of modified leucovorin/fluorouracil/oxaliplatin, or six cycles of capecitabine depending on patients' tolerance.

Study Endpoints

The 3-year inguinal failure rate, locoregional recurrence-free survival (LRFS), distant metastasis recurrence-free survival (DMRFS), overall survival (OS), and failure pattern were analysed. LRFS, DMRFS, and OS risk factors were also investigated. LRFS was measured from the start of treatment to locoregional relapse, death from any causes, or last follow-up. DMRFS was measured from the start of treatment to distant relapse, death from any causes, or last follow-up. OS was calculated from the date of the first treatment to the date of death or the last follow-up.

Follow-up
The patients were evaluated for symptoms, physical examination findings, and blood tests including carcinoembryonic antigen in outpatient clinics on a regular basis. A thorax, abdomen, and pelvic CT or PET/CT would be arranged if there was clinical suspicion of disease recurrence. Colonoscopies were performed 1 year after surgery and every 3 years thereafter.

Statistical Analysis
The 3-year LRFS, DMRFS, and OS rates were presented using the Kaplan-Meier method. Fisher's exact tests were used to explore the difference between categorical variables, while Mann–Whitney *U* tests were used to explore the difference between continuous variables. Clinicopathologic variables were entered into a Cox proportional hazard regression multivariable regression model and analysed for effects on LRFS, DMRFS and OS. All analyses were performed using SPSS (Windows version 21.0; IBM Corp, Armonk [NY], United States). A p value of <0.05 was considered statistically significant.

Research Reporting Guidelines
The STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) checklist for observational cohort studies was implemented in the preparation of the manuscript.

RESULTS
Patient Characteristics
This study enrolled 90 eligible individuals from a larger primary cohort of 110 patients. The full course of radiation/chemoradiation therapy was completed by all patients. The study excluded five patients who refused or were ineligible for surgery, six patients who had local excision only, one patient with upfront distant metastasis, four patients who developed distant metastasis after neoadjuvant radiation/chemoradiation, two patients with upfront inguinal metastasis, and two patients with recurrent rectal cancer.

The median duration of follow-up was 45 months (range, 2-118). Tables 1 and 2 list the clinical data, pathological data, and treatment characteristics of the patients.

Failure Rates and Patterns
Patients who did not receive elective inguinal radiation (n = 81) had a 3-year ILN failure rate of 4.9% (n = 4). Patients who received elective inguinal radiation (n = 9) did not experience any inguinal failure. Of the four patients with ILN failure, only one of them had isolated ILN failure, while the other three had synchronous locoregional recurrence and/or distant failure. In other words, omitting inguinal irradiation resulted in only one case (1.2%) of isolated inguinal nodal failure. Salvage surgery was successfully performed for this patient, who achieved disease remission and survived. Palliative chemotherapy was administered to patients with synchronous locoregional recurrence and/or distant failure, two of whom died due to disease progression. Failure patterns and characteristics of patients with ILN recurrence are listed in Table 3.

Survival Outcomes and Prognostic Factors
The Figure illustrates the Kaplan-Meier curves, depicting 3-year LRFS, DMRFS, and OS of 81.1%, 77.0%, and 86.8%, respectively.

In multivariable Cox regression analysis, positive pathological lymph node after neoadjuvant treatment predicted worse LRFS (odds ratio [OR] = 9.066, 95% confidence interval [CI] = 3.291-24.972; $p < 0.001$), DMRFS (OR = 6.426, 95% CI = 1.944-21.244; $p = 0.002$) and OS (OR = 11.750, 95% CI = 3.583-38.526; $p < 0.001$). Positive tumour resection margin correlated with worse LRFS (OR = 27.296, 95% CI = 5.592-133.241; $p < 0.001$) and OS (OR = 49.982, 95% CI = 4.561-547.759; $p = 0.001$). Chemotherapy concurrent with RT was associated with better LRFS (OR = 33.338, 95% CI = 4.525-245.633; $p = 0.001$) and OS (OR = 13.917, 95% CI = 2.095-92.437; $p = 0.006$). Meanwhile, elective inguinal RT was not associated with statistical differences in LRFS, DMRFS or OS. Details of simple and multivariable analyses are shown in Table 4.

Treatment Toxicities
Grade ≥3 acute toxicity occurred in 16 out of 81 of patients (19.8%) who did not receive inguinal radiation and 3 out of 9 patients (33.3%) who underwent inguinal RT. Inguinal irradiation caused 3 out of 9 patients (33.3%) to develop grade ≥3 perineal dermatitis, compared to 12 out of 81 patients (14.8%) who did not have inguinal irradiation. The above difference, however, did not reach statistical significance. Table 5 shows the acute toxicities profile (Common Terminology Criteria for Adverse Events Grade ≥3).

In terms of chronic toxicity, 1 out of 9 patients (11.1%) who had elective inguinal irradiation developed a protracted gap wound after excision of a perineal recurrence, while there were no recorded chronic perineal skin toxicities in patients who did not receive inguinal

Table 1. Baseline clinical and pathological characteristics of patients with and without elective inguinal irradiation.*

	Without elective inguinal irradiation (n = 81)	With elective inguinal irradiation (n = 9)	p Value
Sex			1.000
Male	56 (69.1%)	6 (66.7%)	
Female	25 (30.9%)	3 (33.3%)	
Age, y	67 (34-84)	69 (60-83)	0.282
ECOG performance status score	0.862		
0	35 (43.2%)	5 (55.6%)	
1	39 (48.1%)	4 (44.4%)	
2	6 (7.4%)	0	
Missing	1 (1.2%)	0	
Distance of lower edge of tumour from anal verge, cm			0.337
0	6 (7.4%)	2 (22.2%)	
1	10 (12.3%)	1 (11.1%)	
2	21 (25.9%)	1 (11.1%)	
3	42 (51.9%)	4 (44.4%)	
NA (located at or below dentate line)	2 (2.5%)	1 (11.1%)	
Baseline serum CEA level, ng/mL	4.80 (1-162)	2.5 (2-162)	0.066
≤4.7	35 (43.2%)	8 (88.9%)	0.013
>4.7	45 (55.6%)	1 (11.1%)	
Missing	1 (1.2%)	0	
cT stage			0.045
1	0	1 (11.1%)	
2	11 (13.6%)	2 (22.2%)	
3	57 (70.4%)	4 (44.4%)	
4	9 (11.1%)	2 (22.2%)	
Unknown	4 (4.9%)	0	
cN stage			0.624
0	18 (22.2%)	4 (44.4%)	
1	35 (43.2%)	4 (44.4%)	
2	12 (14.8%)	1 (11.1%)	
Equivocal/unknown	16 (19.8%)	0	
Tumour histological grade			0.105
Well differentiated adenocarcinoma	4 (4.9%)	0	
Moderate differentiated adenocarcinoma	59 (72.8%)	8 (88.9%)	
Poorly differentiated adenocarcinoma	11 (13.6%)	0	
Mucinous adenocarcinoma	1 (1.2%)	1 (11.1%)	
Unknown differentiated adenocarcinoma	6 (7.4%)	0	
Lymphovascular invasion			1.000
Positive	23 (28.4%)	2 (22.2%)	
Negative	53 (65.4%)	7 (77.8%)	
Missing	5 (6.2%)	0	
Perineural invasion			0.578
Positive	9 (11.1%)	6 (66.7%)	
Negative	45 (55.6%)	0	
Missing	27 (33.3%)	3 (33.3%)	
Circumferential resection margins			0.119
Positive (<1 mm)	3 (3.7%)	1 (11.1%)	
Close	6 (7.4%)	2 (22.2%)	
Negative	72 (88.9%)	6 (66.7%)	
Proximal and distal resection margin			1.000
Positive	2 (2.5%)	0	
Close	2 (2.5%)	0	
Negative	77 (95.1%)	9 (100%)	
ypT stage	n = 68	n = 6	0.206
0	7 (10.3%)	1 (16.7%)	
1	7 (10.3%)	1 (16.7%)	
2	17 (25%)	0	
3	34 (50%)	3 (50.0%)	
4	3 (4.4%)	1 (16.7%)	
ypN stage	n = 68	n = 6	0.733
0	48 (70.6%)	4 (66.7%)	
1	17 (25.0%)	2 (33.3%)	
2	3 (4.4%)	0	

Abbreviations: CEA = carcinoembryonic antigen; cN = clinical nodal; cT = clinical tumour; ECOG = Eastern Cooperative Oncology Group; NA= not available; ypN = posttreatment pathological nodal; ypT = posttreatment pathological tumour.

* Data are shown as No. (%) or median (range), unless otherwise specified.

Table 2. Treatment details.*

	Without elective inguinal irradiation (n = 81)	With elective inguinal irradiation (n = 9)	p Value
Type of (chemo)RT			0.049
Neoadjuvant	68 (84.0%)	6 (66.7%)	
Adjuvant	13 (16.0%)	3 (33.3%)	
RT schedule			0.100
Long-course	81 (100%)	8 (88.9%)	
Short-course	0	1 (11.1%)	
Concurrent chemotherapy			1.000
Bolus 5-FU/capecitabine	76 (93.8%)	9 (100%)	
No	5 (6.2%)	0	
Time interval between neoadjuvant (chemo)RT and surgery, wk	8 (3-35)	11 (6-17)	0.251
Time interval between surgery and adjuvant CRT, wk	9 (7-13)	7 (7-14)	0.412
Adjuvant chemotherapy			0.554
No	24 (29.6%)	1 (11.1%)	
Capecitabine	32 (39.5%)	5 (55.6%)	
CAPOX or mFOLFOX6	25 (30.9%)	3 (33.3%)	

Abbreviations: CAPOX = capecitabine and oxaliplatin; CRT = chemoradiotherapy; mFOLFOX6 = modified leucovorin/fluorouracil/oxaliplatin; FU = fluorouracil; RT = radiotherapy.
* Data are shown as No. (%) or median (range), unless otherwise specified.

Table 3. Failure patterns and characteristics of patients with inguinal lymph node recurrence.

Patient No.	Age, y	Sex	Clinical stage	Distance of lower edge of tumour from anal verge, cm	Tumour differentiation	yp stage or p stage	Lympho-vascular invasion	Failure pattern	Time to inguinal recurrence, mo*	Subsequent treatment	Survival after inguinal recurrence, mo†	Status
1	70	Male	cT3N0	0	Poorly differentiated	ypT3N2	No	Isolated	26.3	Salvage groin dissection	82.9	In remission
2	54	Male	cT3N1	2-3	Moderately differentiated	ypT3N2	Yes	Synchronous locoregional	43.0	Palliative chemotherapy	23.0	Stable disease Survived
3	81	Male	cT2N0	1-2	Unknown	pT3N0	No	Synchronous locoregional and distant	19.8	Palliative chemotherapy	32.7	Dead
4	82	Female	cT3N1	0-1	Moderately differentiated	ypT2N0	No	Synchronous locoregional	4.1	Palliative chemotherapy	12.2	Dead

Abbreviations: cT = clinical tumour; N = nodal; p = pathological; T = tumour; yp = posttreatment pathological.
* From start of treatment.
† Up to last follow-up date from start of treatment.

irradiation. Among the 81 patients who did not receive elective inguinal irradiation, five (6.2%) experienced intestinal obstruction and one (1.2%) developed rectovaginal fistula. No chronic gastrointestinal toxicities have been reported in patients with elective inguinal irradiation, though the abovementioned differences were not statistically significant. Table 6 shows the chronic toxicities profile (the Radiation Therapy Oncology Group and the European Organisation for Research and Treatment of Cancer Grade ≥3).

DISCUSSION

For rectal cancer, determining optimal radiation targets based on their location and mode of spread is a challenge. Despite the theoretical risk that tumour cells in low rectal cancer with ACI could spread to the ILN region, there has been no consensus on whether to include the inguinal nodal region in CTV for this patient subgroup. More clinical evidence is needed to optimise the CTV for these patients in order to reduce irradiation of normal tissue.

The low ILN failure rate (4.9%) in our study, which mirrored the findings of other retrospective studies,[8-10] showed that most patients with low rectal cancer with ACI would not benefit from elective inguinal

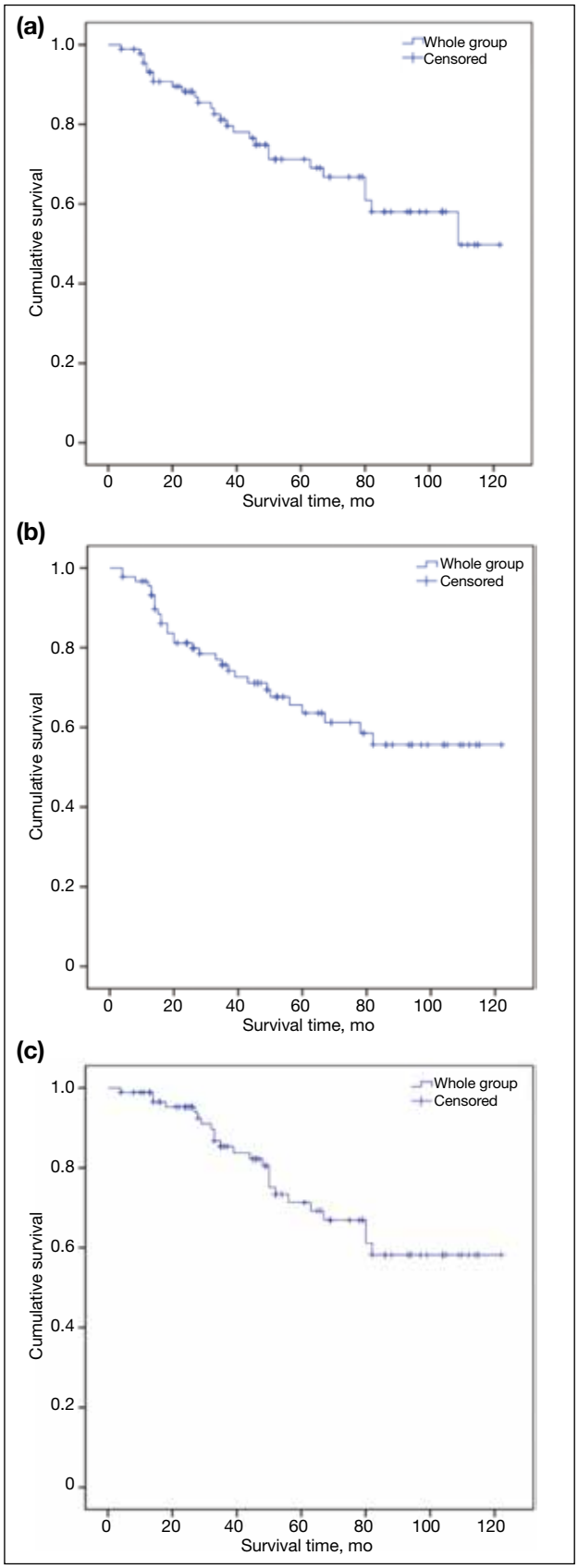

Figure. Kaplan-Meier survival curves for (a) locoregional recurrence-free survival, (b) distant metastasis recurrence-free survival, and (c) overall survival.

irradiation during neoadjuvant or adjuvant (chemo)RT. Some experts, however, still recommend elective ILN irradiation based on acceptable morbidities.[14] In our study, the acute toxicity associated with inguinal irradiation cannot be neglected. There were more acute grade 3 perineal dermatitis among patients who received elective inguinal irradiation (33.3% vs. 14.8%), though none required a treatment break. Meanwhile, the reported chronic complications of elective inguinal irradiation appeared relatively minor in our study. Only 1 out of 9 patients (11.1%) who had elective inguinal irradiation developed a protracted gap wound after perineal recurrence.

Measures were developed to identify patients who were at a higher risk of developing inguinal nodal metastasis. Firstly, Song et al[8] created a nomogram to predict the probability of ILN failures according to tumour location, histological grade, and presence of perineural invasion. It can be used as a guide to select patients for elective inguinal irradiation at high risk of ILN failure, but the presence of perineural invasion may not be known until postoperatively. Shiratori et al[15] have also noted that dentate line involvement and ILNs >8 mm may predict the development of inguinal nodal metastasis. PET/CT has been suggested to detect abnormal inguinal uptake for inguinal nodal region irradiation. Although up to 17% of patients with distal rectal cancer, especially those ultra-low tumours, had inguinal nodes showing fluorodeoxyglucose uptake on PET/CT, the false positivity rate was high, as nearly half of these nodes no longer demonstrated uptake after CRT despite the fact that the inguinal region is not included in the radiation field. Moreover, none of these patients in that study developed inguinal recurrence after 22 months of follow-up.[16] A review of sentinel nodes in anal cancer revealed that 44% of all node metastases located in lymph nodes measured <5 mm in diameter.[17] The spatial resolution of PET/CT is limited to a few millimetres, suggesting it may not have sufficient sensitivity and specificity to select outpatients for inguinal irradiation.[18] The sentinel node technique was also studied in rectal cancer with ACI. A small prospective study of 15 patients showed no recurrence in the groin for patients whose sentinel lymph nodes were determined to be negative for metastatic adenocarcinoma.[19] However, a systematic review indicated that the sentinel lymph node procedure showed only a fair sensitivity rate of 82% (95% CI = 60%-93%), regardless of tumour stage, localisation or pathological technique.[20] Due to the relatively low sensitivity, technically demanding procedures, risk of surgical

Table 4. Simple and multivariable Cox regression models for locoregional recurrence-free survival (LRFS), distant metastasis recurrence-free survival (DMRFS), and overall survival (OS).

Variable	LRFS				DMRFS				OS			
	Simple OR (95% CI)	p Value	Multivariable OR (95% CI)	p Value	Simple OR (95% CI)	p Value	Multivariable OR (95% CI)	p Value	Simple OR (95% CI)	p Value	Multivariable OR (95% CI)	p Value
Age	1.031 (0.991-1.072)	0.136			1.018 (0.982-1.055)	0.339			1.028 (0.986-1.072)	0.191		
Sex (male vs. female)	1.291 (0.758-2.199)	0.346			1.820 (0.743-4.454)	0.190			1.675 (0.625-4.490)	0.305		
ECOG performance status score												
0-1	1				1				1			
2	3.138 (1.081-9.113)	0.035	1.762 (0.314-9.878)	0.520	2.500 (0.869-7.188)	0.089	1.065 (0.175-6.470)	0.946	3.917 (1.328-11.551)	0.013	1.744 (0.278-10.957)	0.553
Baseline serum CEA level, ng/mL (≥4.7 vs. <4.7)	1.319 (0.605-2.876)	0.486			1.886 (0.876-4.059)	0.105			1.530 (0.661-3.538)	0.320		
cT stage												
1-2	1				1				1			
3	0.999 (0.335-2.984)	0.999			1.023 (0.348-3.012)	0.967			0.832 (0.273-2.531)	0.746		
4	1.291 (0.321-5.185)	0.719			1.375 (0.343-5.502)	0.653			1.374 (0.343-5.506)	0.654		
cN (positive vs. negative)	1.389 (0.547-3.528)	0.490			1.472 (0.588-3.690)	0.409			1.195 (0.463-3.082)	0.713		
Distance of lower edge of tumour from anal verge, cm												
3	1				1				1			
0	1.535 (0.428-5.507)	0.511			1.257 (0.363-4.349)	0.718			1.090 (0.238-4.982)	0.912		
1	1.924 (0.611-6.053)	0.263			1.028 (0.297-3.559)	0.965			1.678 (0.461-6.106)	0.432		
2	1.552 (0.623-3.870)	0.346			1.070 (0.453-2.527)	0.877			1.683 (0.663-4.275)	0.274		
RT alone vs. CRT	12.185 (4.387-33.849)	<0.001	33.338 (4.525-245.633)	0.001	5.772 (2.145-15.527)	0.001	3.748 (0.557-25.199)	0.174	12.180 (4.146-35.786)	<0.001	13.917 (2.095-92.437)	0.006
SCRT vs. LCRT	20.460 (1.08×10^{11}–3.89×10^{13})	0.834			20.465 (8.1×10^{10}–5.18×10^{11})	0.805			20.451 (1.08×10^{19}–3.87×10^{21})	0.899		
CRT (adjuvant vs. neoadjuvant)	1.836 (0.732-4.606)	0.195			2.005 (0.852-4.715)	0.111			2.269 (0.886-5.815	0.088		
Without elective groin RT vs. with elective groin RT	1.802 (0.244-13.315)	0.564			2.097 (0.285-15.428)	0.467			1.537 (0.207-11.411)	0.675		
Tumour histological grade												
Low	1				1				1			
High	1.020 (0.349-2.976)	0.972			1.117 (0.387-3.226)	0.838			1.212 (0.358-4.106)	0.757		
LVI (positive vs. negative)	1.106 (0.567-2.156)	0.768			3.864 (1.827-8.171)	<0.001	1.203 (0.302-4.787)	0.793	3.741 (1.601-8.744)	0.002	2.144 (0.344-13.363)	0.414
PNI (positive vs. negative)	2.029 (0.660-6.243)	0.217			2.820 (1.020-7.795)	0.046	2.822 (0.699-11.389)	0.145	1.585 (0.446-5.633)	0.477		
Resection margin (R1 vs. R0)	6.130 (2.081-18.061)	0.001	27.296 (5.592-133.241)	<0.001	2.914 (0.873-9.727)	0.082			5.004 (1.466-17.079)	0.010	49.982 (4.561-547.759)	0.001
pT stage												
1-2	1				1				1			
3-4	39.396 (0.044-35181)	0.289			39.783 (0.075-21206)	0.250			40.216 (0.48-34015)	0.283		

Abbreviations: CEA = carcinoembryonic antigen; CI = confidence interval; cN = clinical nodal; CRT = chemoradiotherapy; cT = clinical tumour; ECOG = Eastern Cooperative Oncology Group; LCRT = long-course radiotherapy; LVI = lymphovascular invasion; OR = odds ratio; pCR = pathological complete remission; pN = pathological nodal; PNI = perineural invasion; pT = pathological tumour; RT = radiotherapy; SCRT = short-course radiotherapy; ypN = posttreatment pathological nodal; ypT = posttreatment pathological tumour.

Table 4. (cont'd)

Variable	LRFS				DMRFS				OS			
	Simple OR (95% CI)	p Value	Multivariable OR (95% CI)	p Value	Simple OR (95% CI)	p Value	Multivariable OR (95% CI)	p Value	Simple OR (95% CI)	p Value	Multivariable OR (95% CI)	p Value
pN status (positive vs. negative)	1.474 (0.284-7.661)	0.645			1.368 (0.270-6.940)	0.705			1.259 (0.243-6.521)	0.784		
ypT stage												
0	1				1				1			
1	1.004 (0.063-16.1104)	0.998			2.236 (0.202-24.728)	0.512			1.057 (0.066-16.950)	0.969		
2	2.441 (0.283-21.053)	0.417			2.336 (0.272-20.070)	0.439			1.999 (0.222-18.041)	0.537		
3	3.149 (0.402-24.683)	0.275			3.148 (0.407-24.363)	0.272			2.488 (0.312-19.861)	0.390		
4	4.547 (0.411-50.261)	0.217			7.290 (0.657-80.841)	0.106			4.649 (0.420-51.418)	0.210		
ypN stage												
0	1				1				1			
1-2	7.072 (2.828-17.682)	<0.001	9.066 (3.291-24.972)	<0.001	5.557 (2.368-13.044)	<0.001	6.426 (1.944-21.244)	0.002	5.617 (2.124-14.857)	<0.001	11.750 (3.583-38.526)	<0.001
pCR (no vs. yes)	2.687 (0.357-20.195)	0.337			2.851 (0.382-21.284)	0.307			2.214 (0.291-16.814)	0.442		
Adjuvant chemotherapy (no vs. yes)	1.389 (0.547-3.528)	0.490			1.444 (0.686-3.038)	0.333			1.950 (0.866-4.392)	0.107		

Table 5. Comparison of grade 3 or above acute radiotherapy (RT) toxicities with and without elective inguinal RT.*

	Without elective inguinal RT (n = 81)	With elective inguinal RT (n = 9)	p Value
General adverse events			
Radiation dermatitis	12 (14.8%)	3 (33.3%)	0.347
Weight loss	0	0	
Fatigue/lethargy	0	0	
Hand-foot syndrome	0	0	
Haematologic	0	0	
Cardiac disorder	0	0	
Infection	0	0	
Gastrointestinal toxicity			
Mucositis	0	0	
Nausea and vomiting	0	0	
Diarrhoea	3 (3.7%)	0	
Abdominal pain	0	0	
Obstruction/constipation	1 (1.2%)	0	
Proctitis and rectal bleeding	0	0	
Total	4 (4.9%)	0	1.000

* Data are shown as No. (%), unless otherwise specified.

Table 6. Comparison of grade 3 or above chronic radiotherapy (RT) toxicities with and without elective inguinal RT.*

	Without elective inguinal RT (n = 81)	With elective inguinal RT (n = 9)	p Value
Perineal skin reaction	0	1 (11.1%)	0.100
Chronic gastrointestinal toxicities	6 (7.4%)	0	0.521

* Data are shown as No. (%), unless otherwise specified.

morbidity, and doubtful impact on subsequent clinical management, this is not currently a standard practice for low rectal cancer with ACI.

Only one patient (25%) developed isolated ILN metastases among all the four patients with inguinal recurrence. Salvage treatment for isolated ILN recurrence can provide long-term ILN control in our study. As a result, prophylactic treatment of the inguinal region may not be necessary. The other three patients (75%) who experienced inguinal recurrence had synchronous locoregional and/or distant recurrences. One may question whether early detection and treatment of occult inguinal nodal metastases can help prevent subsequent distant metastases. Damin et al[18] observed that despite inguinal dissection, 75% of sentinel ILN–positive cases developed hepatic or pulmonary metastases within 6 months of the surgery. Thus, localised treatment of the inguinal region may not affect the final clinical outcome, which is determined mainly by the occurrence of metastasis to distant organs.[19] In this context, a sentinel lymph node metastasis could represent a potential marker for systemic dissemination of the disease.[19]

From our results, patients who had positive pathological lymph node(s) following neoadjuvant therapy and/or a positive resection margin had an inferior rate of 3-year LRFS and OS, implying that more aggressive neoadjuvant treatment is needed to shrink the tumour before surgery, such as the addition of an induction or consolidation chemotherapy regimen. Several recently published large-scale randomised controlled trials consistently showed that total neoadjuvant treatment can improve disease-free survival, pathological complete remission rate, and the risk of disease-related treatment failure in patients with high-risk rectal cancer.[20-23] Among them, the phase 3 STELLAR trial was the first trial to demonstrate OS benefit, which found that short-course RT followed by perioperative chemotherapy resulted in better 3-year OS rates than CRT followed by postoperative chemotherapy, with 86.5% vs. 75.1% (OR = 0.67, 95% CI = 0.46-0.97; p = 0.033).[23] Furthermore, in our study, as compared to radiation alone, concomitant chemotherapy was linked with a superior LRFS and OS. A Cochrane review found that preoperative CRT improved local control (OR = 0.56, 95% CI = 0.42-0.75; p < 0.0001) in resectable stage III rectal cancer but did not increase OS (OR = 1.01, 95% CI = 0.85-1.20; p = 0.88).[24] The STELLAR OS benefit may be attributable to different patient selection criteria as our included patient population was restricted to low rectal cancer with ACI. This high-risk group may derive more benefit from concurrent chemotherapy. Additional studies are encouraged to validate the OS benefit of preoperative CRT against RT alone in resectable low rectal cancer with ACI.

Song et al[8] also investigated the impact of excluding irradiation of ILNs during neoadjuvant (chemo)RT in low rectal cancer with ACI. Their 3-year ILN failure rate was 3.7%. Our 3-year RFS rate (76.6% vs. 77.7%) is comparable to their disease-free survival rate, but our 3-year OS rate (86.8% vs. 91.9%) outcome appeared slightly inferior. Reasons for our relatively inferior OS may be multifactorial. Our research population had an older median age (67 years vs. 57 years). Our study also covered a small number of patients with worse Eastern Cooperative Oncology Group performance status (a score of 2) [6.7%], whereas their study only included individuals with a score of 0 to 1. Almost all of our patients (93.3%) received bolus 5-FU as concurrent chemotherapy, with the exception of one patient who received oral capecitabine, compared to 78.1% of capecitabine patients in their study.[8] Patients receiving prolonged 5-FU infusion had a significantly longer time to relapse and improved survival compared with bolus 5-FU.[11] Two randomised controlled trials have shown that patients with rectal cancer who received neoadjuvant or adjuvant capecitabine CRT had non-inferior disease-free and OS when compared to continuous 5-FU.[12,13] Therefore, concurrent chemotherapy with oral capecitabine should produce better outcomes compared with bolus 5-FU. In addition, induction (7.0%) and consolidation chemotherapy (30.8%) were used in their research, which might further improve treatment outcomes.[8]

Limitations

Our study had several limitations. First, it was a retrospective study based on data from a single centre, and this may add selection and information bias. Second, our small sample size reduced the power of the study. Despite a trend towards lower acute and chronic skin toxicity rates without inguinal RT, it did not reach statistical significance. In light of the small number of patients with inguinal RT and the retrospective nature of the study, these results should be interpreted with caution. Moreover, the elective inguinal RT group's small sample size may make it difficult to statistically compare survival rates with those who did not receive inguinal RT. Third, some baseline characteristics (i.e., baseline carcinoembryonic antigen level, clinical tumour staging, and proportion of patients receiving neoadjuvant vs. adjuvant radiation/chemoradiation therapy between

patients with or without elective inguinal irradiation) were imbalanced, and this might create bias to the interpretation of results. Lastly, as there was no uniform follow-up imaging in our study population, survival outcomes may have been overstated.

CONCLUSION

Omission of elective inguinal irradiation resulted in a low inguinal failure rate and similar survival outcomes for low rectal cancer patients with ACI. This study demonstrated that the majority of inguinal recurrences also had synchronous locoregional recurrence and/or distant failure, while isolated inguinal recurrences were uncommon and could be salvaged by inguinal dissection. These findings added to the body of evidence supporting the omission of elective ILN irradiation for this patient subgroup. Better-designed randomised studies are warranted to define the role of elective inguinal irradiation and to elucidate the best strategy for treatment escalation.

REFERENCES

1. Li Y, Wang J, Ma X, Tan L, Yan Y, Xue C, et al. A review of neoadjuvant chemoradiotherapy for locally advanced rectal cancer. Int J Biol Sci. 2016;12:1022-31.
2. Kachnic LA. Adjuvant chemoradiation for localized rectal cancer: current trends and future directions. Gastrointest Cancer Res. 2007;1(4 Suppl 2):S64-72.
3. Lee IK. The Lymphatic Spread of the Rectal Cancer. In: Kim NK, Sugihara K, Liang JT, editors. Surgical Treatment of Colorectal Cancer: Asian Perspectives on Optimization and Standardization. Singapore: Springer; 2018. p 47-53.
4. Glynne-Jones R, Wyrwicz L, Tiret E, Brown G, Rödel C, Cervantes A, et al. Rectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2017;28(suppl_4):iv22-40.
5. Valentini V, Gambacorta MA, Barbaro B, Chiloiro G, Coco C, Das P, et al. International consensus guidelines on clinical target volume delineation in rectal cancer. Radiother Oncol. 2016;120:195-201.
6. Wo JY, Anker CJ, Ashman JB, Bhadkamkar NA, Bradfield L, Chang DT, et al. Radiation therapy for rectal cancer: executive summary of an ASTRO Clinical Practice Guideline. Pract Radiat Oncol. 2021;11:13-25.
7. Myerson RJ, Garofalo MC, El Naqa I, Abrams RA, Apte A, Bosch WR, et al. Elective clinical target volumes for conformal therapy in anorectal cancer: a Radiation Therapy Oncology Group consensus panel contouring atlas. Int J Radiat Oncol Biol Phys. 2009;74:824-30.
8. Song M, Li S, Zhang Y, Geng J, Wang H, Zhu X, et al. Is elective inguinal or external iliac irradiation during neoadjuvant (chemo) radiotherapy necessary for locally advanced lower rectal cancer with anal sphincter invasion? Pract Radiat Oncol. 2022;12:125-34.
9. Taylor N, Crane C, Skibber J, Feig B, Ellis L, Vauthey JN, et al. Elective groin irradiation is not indicated for patients with adenocarcinoma of the rectum extending to the anal canal. Int J Radiat Oncol Biol Phys. 2001;51:741-7.
10. Yeo SG, Lim HW, Kim DY, Kim TH, Kim SY, Baek JY, et al. Is elective inguinal radiotherapy necessary for locally advanced rectal adenocarcinoma invading anal canal? Radiat Oncol. 2014;9:296.
11. O'Connell MJ, Martenson JA, Wieand HS, Krook JE, Macdonald JS, Haller DG, et al. Improving adjuvant therapy for rectal cancer by combining protracted-infusion fluorouracil with radiation therapy after curative surgery. N Engl J Med. 1994;331:502-7.
12. Allegra CJ, Yothers G, O'Connell MJ, Beart RW, Wozniak TF, Pitot HC, et al. Neoadjuvant 5-FU or capecitabine plus radiation with or without oxaliplatin in rectal cancer patients: a phase III randomized clinical trial. J Natl Cancer Inst. 2015;107:djv248.
13. Hofheinz RD, Wenz F, Post S, Matzdorff A, Laechelt S, Hartmann JT, et al. Chemoradiotherapy with capecitabine versus fluorouracil for locally advanced rectal cancer: a randomised, multicentre, non-inferiority, phase 3 trial. Lancet Oncol. 2012;13:579-88.
14. Lee WR, McCollough WM, Mendenhall WM, Marcus RB Jr, Parsons JT, Million RR. Elective inguinal lymph node irradiation for pelvic carcinomas. The University of Florida experience. Cancer. 1993;72:2058-65.
15. Shiratori H, Nozawa H, Kawai K, Hata K, Tanaka T, Kaneko M, et al. Risk factors and therapeutic significance of inguinal lymph node metastasis in advanced lower rectal cancer. Int J Colorectal Dis. 2020;35:655-64.
16. Perez RO, Habr-Gama A, São Julião GP, Proscurshim I, Ono CR, Lynn P, et al. Clinical relevance of positron emission tomography/computed tomography–positive inguinal nodes in rectal cancer after neoadjuvant chemoradiation. Colorectal Dis. 2013;15:674-82.
17. Damin DC, Rosito MA, Schwartsmann G. Sentinel lymph node in carcinoma of the anal canal: a review. Eur J Surg Oncol. 2006;32:247-52.
18. Damin DC, Tolfo GC, Rosito MA, Spiro BL, Kliemann LM. Sentinel lymph node in patients with rectal cancer invading the anal canal. Tech Coloproctol. 2010;14:133-9.
19. van der Pas MH, Meijer S, Hoekstra OS, Riphagen II, de Vet HC, Knol DL, et al. Sentinel-lymph-node procedure in colon and rectal cancer: a systematic review and meta-analysis. Lancet Oncol. 2011;12:540-50.
20. Bahadoer RR, Dijkstra EA, van Etten B, Marijnen CA, Putter H, Kranenbarg EM, et al. Short-course radiotherapy followed by chemotherapy before total mesorectal excision (TME) versus preoperative chemoradiotherapy, TME, and optional adjuvant chemotherapy in locally advanced rectal cancer (RAPIDO): a randomised, open-label, phase 3 trial. Lancet Oncol. 2021;22:29-42.
21. Bujko K, Wyrwicz L, Rutkowski A, Malinowska M, Pietrzak L, Kryński J, et al. Long-course oxaliplatin-based preoperative chemoradiation versus 5 × 5 Gy and consolidation chemotherapy for cT4 or fixed cT3 rectal cancer: results of a randomized phase III study. Ann Oncol. 2016;27:834-42.
22. Conroy T, Bosset JF, Etienne PL, Rio E, François É, Mesgouez-Nebout N, et al. Neoadjuvant chemotherapy with FOLFIRINOX and preoperative chemoradiotherapy for patients with locally advanced rectal cancer (UNICANCER-PRODIGE 23): a multicentre, randomised, open-label, phase 3 trial. Lancet Oncol. 2021;22:702-15.
23. Jin J, Tang Y, Hu C, Jiang LM, Jiang J, Li N, et al. Multicenter, randomized, phase III trial of short-term radiotherapy plus chemotherapy versus long-term chemoradiotherapy in locally advanced rectal cancer (STELLAR). J Clin Oncol. 2022;40:1681-92.
24. McCarthy K, Pearson K, Fulton R, Hewitt J. Pre-operative chemoradiation for non-metastatic locally advanced rectal cancer. Cochrane Database Syst Rev. 2012;12:CD008368.