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Original Article

Outcome of neoadjuvant chemoradiation in MRI staged locally advanced rectal cancer: Retrospective analysis of 123 Chinese patients

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KEYWORDS
Chemoradiotherapy;
Magnetic resonance imaging;
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Survival

Background: For advanced rectal cancer with involved or threatened mesorectal fascia (MRF), current standard is pre-operative long course chemoradiotherapy (PLCRT) with either capecitabine or 5-fluorouracil (5-FU). However, few Chinese data on its clinical outcome are available, especially for those with pelvic MRI staging.
Methods: Between Jan-2009 and Oct-2014, 123 consecutive patients with biopsy proven adenocarcinoma of rectum, all with pelvic MRI staging, selected for PLCRT after multidisciplinary team discussion were recruited. Their clinical records were retrospectively reviewed.
Results: Median follow-up was 1392 days (range: 48–2886) MRI defined poor risk factors as follows: MRF threatened or involved ≤1 mm 61.8% ($n = 76$), cT4 13.8% ($n = 17$), cN2 26.8% ($n = 33$) and low-lying tumor (≤5 cm from anal verge) 24.4% ($n = 30$). Five year OS and DFS were 63.9% and 68.3% respectively. Among 112 patients who received TME, 108 (96.4%) had microscopic clear resection (R0). Twelve and 32 individuals had pathological complete response and ypT0-2N0, respectively. Five local recurrences (4.5%) were detected. The incidence of grade 3 or above acute and late radiotherapy toxicity was 8.1% and 12.2% respectively. After multivariate adjustment, positive circumferential resection margin (CRM) status on pathology report was found to be significant factor for worse OS and DFS.

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Conclusion: The clinical outcomes of PLCRT in our institution are comparable with those in western literature. Our MRI staging lends support to the validity of data. CRM status is the most significant prognostic factor in OS and DFS, after multivariate adjustment.

Introduction

In the last two decades we have witnessed the evolution in the management of rectal cancer. Though surgery is still the most important treatment, the management has changed profoundly and is more relied on the contributions from other colleagues, like oncologists, radiologists and pathologists. Best clinical management is nowadays increasingly delivered by an expert multidisciplinary team (MDT).

Surgery is the primary treatment of localized rectal cancer, but conventional resections had been associated with local recurrence rate up to 25—40%. Local relapse has been much reduced after introduction of total mesorectal excision (TME), which is currently the gold standard procedure that reduced the rate of local relapse to less than 10% and increased the overall survival.[1,2]

Multiple randomized studies and meta-analyses have confirmed adding neo-adjuvant[3—8] or adjuvant radiotherapy[1,9—12] will improve the local control rate. Historically, some argued post-operative radiation is better as better selection of patients is possible according to the final pathological stage. However, in the Germany trial (CAO/ARO/AIO 94)[5] that compared the preoperative and post-operative chemo-irradiation, the preoperative group had a significant decrease in local failure, acute toxicity, late toxicity, significant increase in sphincter preservation and no difference in five year survival. Since then, pre-operative treatment is preferred in cT3/4 N+ rectal cancer that required combined modality treatment.

For locally advanced rectal cancer (T3/4 or N+), there are two commonly used strategies: pre-operative short course radiation (PSCRT) (5 Gy per fraction, 5 fractions per week) followed by immediate surgery that usually carried out in around 1 week, and pre-op long course chemo-radiotherapy (PLCRT) (1.8 Gy per fraction, 5 fractions per week, to a total dose of 45—50 Gy) and surgery was performed after 6—8 weeks of waiting time. Neither approach is superior in direct comparison, in terms of local control and overall survival. However, subgroup analyses have suggested that PSCRT is less effective individuals with predictive of positive circumferential resection margin (CRM) or low-lying tumor. In fact PSCRT followed by immediate surgery rarely induced tumor regression. Therefore, most authorities[13—16] have recommended PLCRT, either concurrent with 5-fluorouracil (5-FU) or capecitabine,[17] in patients with threatened or involved mesorectal fascia (MRF), tumor with adjacent organ invasion (cT4 stage) and low-lying tumor. Other high risk factors of local recurrence would also be taken into consideration, like cN2 disease (≥four lymph nodes), lateral pelvic lymph node (internal iliac or obturator lymph nodes) involvement and extra-mural vascular invasion (EMVI).

Magnetic resonance imaging (MRI) now becomes the impeccable tool for local staging. It defines the location of tumor and its relationship with MRF and adjacent structure. Nodal status and EMVI can also be assessed. Multiple studies have confirmed MRI is highly reliable in predicting CRM.[18—20] On the contrary, multi-slice computed tomography (CT) is inferior to MRI in local staging and CRM prediction. Therefore, pre-operative MRI assessment is now the gold standard in management of rectal cancer. Despite PLCRT is now the standard treatment of advanced rectal cancer worldwide, most series reported outcomes based on rectal cancer variably staged with MRI or CT; few local data is available, especially for those with MRI staging. Therefore, we set up a study to report the clinical outcomes of the 123 Chinese patients with locally advanced rectal cancer all confirmed with MRI and were treated with PLCRT.

Methods

Patients

For all biopsy proven rectal adenocarcinoma (≤15 cm from anal verge) in our hospital, we used high-resolution thin-slice magnetic resonance imaging (MRI) of pelvis to assess its local staging; contrast computed tomography (CT) of thorax, abdomen and pelvis to look for any distant metastasis. All patients had advanced rectal cancer (T3/4 or N+) without distant metastasis (M0) was then referred to MDT clinic for discussion.

Our institutional protocol defined poor risk factors as follows: tumor extending to within 1 mm MRF (i.e. anticipated CRM threatened or involved); cT3 low lying tumor (within 5 cm from anal verge); tumor has adjacent organ involvement (cT4 stage) or cN2 disease (≥four lymph nodes). Patients possess one or more risk factors would be treated with PLCRT. The MDT assessed all patients' physical condition and organ function to confirm their fitness for treatment.

Data were collected retrospectively by performing review of medical records (hard copy and electronic patient records, pre- and post-treatment radiology, radiotherapy documentation, surgical notes, pathological reports and follow-up clinic records). The research ethics committee of our hospital approved our study.

Treatment

All individuals were scheduled to start chemo-irradiation in around 2 weeks after MDT clinic. Patients were simulated in the treatment position (lied prone with a full bladder) using the belly-board. Target volume was defined using the clinical and radiological information. All patients underwent CT

planning and the gross tumor volume (GTV) included the primary tumor and any significant surrounding lymphadenopathy. Clinical target volume (CTV) includes GTV plus 2 cm margin and high-risk nodal area includes mesorectal, pre-sacral, internal iliac and obturator lymph nodes. Planning target volume defined as CTV + 1 cm margin to account for the setup error and organ motion. Patients were planned using conformal technique in a four to five fields arrangement to include the PTV within the 95% isodose. A dose of 45–50.4 Gy in 25–28 fractions over 5–6 week was prescribed to the 95% isodose line; dose was escalated to 54–56 Gy by means of simultaneous integrated boost (SIB) in selected bulky T3 and T4 disease.

Concurrent chemotherapy regime, either in form of 5-fluorouracil (5-FU) intravenous bolus (500 mg/m^2 in Day 1–3 and Day 29–31) or capecitabine (825 mg/m^2 twice daily from first day till last day of radiotherapy), was selected according to patients' preference. Patients were monitored weekly for symptoms, performance status, peripheral blood cell counts, biochemistry and toxicities during the treatment.

We repeated MRI exam in around 6 weeks after the completion of chemo-radiation to evaluate treatment response. Then, we performed TME surgery (either anterior resection, or abdominoperineal resection at the discretion of surgeons) at around 8–12 weeks after completion of PLCRT.

MDT clinic will review patients' recovery and their pathology report within 4 weeks after operation. We started adjuvant chemotherapy after patients recovered from surgery. Regime of choice includes capecitabine (2500 mg/m^2 twice daily for 2 weeks) or CAPOX (oxaliplatin 130 mg/m^2 day 1 and capecitabine 2000 mg/m^2 twice daily for 2 weeks), both repeated every 3 weeks for 6 cycles. Patients' age, comorbidities, performance status, recovery from surgery, and final pathology stage were taken into consideration. According to our institutional protocol, combination chemotherapy CAPOX was offered to patients with ypN+ disease based on the subgroup analysis result of ADORE trial,[21] while capecitabine or 5-FU alone for patients with ypN0 disease.

Post-treatment follow-up included measurement of carcinoembryonic antigen (CEA) at every clinic visit. Patients were reviewed every three months for the two years, and then every four to six months in the third to fifth years. We arranged imaging if there was clinical suspicious of recurrence or increasing trend of CEA. Colonoscopic exam was performed once within three years and repeated another within five years. For those with incomplete colonoscopy before operation, we carried out first endoscopy within first year after surgery. Acute and late radiotherapy side effects were assessed according to according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0, and the Toxicity criteria of the Radiation Therapy Oncology Group and the European Organization for Research and Treatment of Cancer. Perioperative complications represented by rate of 30-day postoperative mortality and morbidity were also reported.

Statistical analysis

Data were analyzed using SPSS version 22.0. Survival data was calculated using the Kaplan–Meier method. Overall survival (OS) was defined as the time of radiotherapy begins to death for any reason or the day of last follow-up. Disease free survival (DFS) was defined as time of commencement of radiotherapy to date of disease recurrence (distant metastasis or locoregional recurrence) or death from any cause, whichever occurred first or the day of last follow-up. Cox proportional hazards regression model was used to adjust for various factors.[22]

Results

Between 1st Jan 2009 to 30th Oct 2014, 123 consecutive rectal cancer patients who had pelvic MRI staging and had been selected for PLCRT were recruited. Table 1 presents patients' baseline characteristics. Median follow-up time was 1392 days (range: 48–2886). Median age of patients was 59 years (range from 27 to 79 years). Imaging defined high risk factors were as follows: total 76 patients (61.8%) with either threatened or involved MRF (≤1 mm); 17 patients (13.8%) were staged as cT4 disease with adjacent organ(s) invasion; 30 patients (24.4%) had low lying tumor; and 33 patients (26.8%) had cN2 disease (≥4 lymph nodes).

All but only two patients completed the planned course of chemo-radiation. Both of them refused treatment at

Table 1 Baseline patient characteristics.

Characteristics	Patients (n = 123)
Age, years	
Median (range)	59 (27–79)
Sex, n (%)	
Male	95 (77.2)
Female	28 (22.8)
Performance status (ECOG), n (%)	
0	14 (11.4)
1	98 (79.7)
2	11 (8.9)
CEA level, n (%)	
>5	63 (51.2)
≤5	60 (48.8)
Distance from anal verge (cm), n (%)	
0 to ≤5 (lower)	34 (27.6)
>5 to 10 (mid)	84 (68.3)
>10 (upper)	5 (4.1)
Clinical T stage, n (%)	
T3	106 (86.2)
T4	17 (13.8)
Clinical N stage, n (%)	
N0	35 (28.5)
N1	57 (46.3)
N2	31 (25.2)
Mesorectal fascia, n (%)	
Involved or threatened (≤1 mm)	110 (89.4)
>1 mm	13 (10.6)
Lateral pelvic lymph nodes, n (%)	
Yes	20 (16.3)
No	103 (83.7)

Abbreviations: CEA = carcinoembryonic antigen; ECOG = Eastern Cooperative Oncology Group.

27 Gy and 39 Gy due to toxicity respectively. Median time from the end of chemo-radiotherapy to surgery was 77 days (interquartile range: 32 days) with 117 individuals proceed to surgical operation. Total 110 patients with total mesorectal excision done (78 anterior resections, 25 abdominal-perineal resection and nine with other operations). Seven were found to have inoperable disease at laparotomy. Kaplan–Meier estimates of survival probabilities for patients who received TME exhibited a better OS and DFS rates compared with no TME (see Supplementary Fig. 1). Quality of TME was available in 49 patients, of which 47 (95.9%) had mesorectal fascia plane excision and two (4.1%) had intramesorectal plane dissection. Among 34 patients with tumor $\leq$5 cm from anal verge, 32 had surgery (two had inoperable disease at laparotomy). 15 (46.9%) patients had anterior resection and 17 (53.1%) had abdominal-perineal resection. But whether sphincter preservation surgery was performed also depended on age, co-morbidities, tumor bulkiness and surgical expertise.

The combined incidence of grade 3 or above acute radiotherapy toxicity to the skin, bowel, and urinary toxicity was 8.1%. The combined incidence of grade 3 or above late radiotherapy toxicity to the bowel, and urinary tract was 12.2%. For grade 3 or above acute chemotherapy-related toxicity, the incidences of neutropenia, anemia, and thrombocytopenia were 8.9%, 2.4%, and 0%, respectively. The most common non-hematological grade 3 or above acute toxicity was diarrhea (5.7%). With regard to surgical complications, 13 (10.6%) patients had delayed wound healing, 12 (9.8%) had anastomotic leakages of different grades, six (4.9%) had post-operative ileus. There was no 30-day postoperative mortality reported.

Among patients who had TME, 96 (87.3%) received adjuvant chemotherapy. For 14 (12.7%) patients without initiation of adjuvant systemic treatment, two due to patients' refusal, seven due to poor post-operative recovery or complications, three were medically unfit, one developed rapid disease progression, one due to both poor recovery and rapid disease progression. 96.4% (106/110) of the population undergoing TME surgery achieved microscopic clear resection (R0) and 90.6% (106/117) including for all who underwent operation. Four patients with involved CRM $<$1 mm (R1) at pathological specimen.

Among the 110 patients who had TME, 68 patients had information of their pathological grading of regression, 10.9% (12 out of 110) patients had pathological complete response (pCR). 25.5% (28 out of 110) had only microscopic foci, while the remaining 28 (25.5%) reported with no tumor regression.

The distribution of MRI radiological and pathological response is highlighted in Table 3. 67.3% (74 out of 110) patients had T- and/or N-downstaging, and 43.2% (32 out of 74) of them had significant downstaging after PLCRT, with pathological stage I disease (ypT0-2N0) (see Table 4). Around 46.4% (51/110) of tumors was over-staged when comparing post-PLCRT MRI re-staging versus final pathological staging.

33 of 110 patients who had received TME have had recurrent cancer and 26 have died of recurrence. One patient died of small cell carcinoma. One patient died of post-operative complication. Another two individuals died without proven cancer recurrence (cerebrovascular accident $n = 1$, pneumonia $n = 1$); causes of death were unknown in two patients.

Distant relapse was the commonest mode of failure, it occurred in 32 patients. Most common site of first recurrence was lung metastasis ($n = 20$). Other sites of distant recurrence include liver metastases ($n = 12$), peritoneal disease ($n = 5$), para-aortic lymph nodes metastasis ($n = 8$). Multiple sites of relapse were detected in 10 individuals. Five patients developed local pelvic recurrence, three patients presented with synchronous distant recurrence; one patient had peritoneal disease beforehand and developed metastasis at the pouch of Douglas; only one patient had isolated local relapse. Most of the recurrences were asymptomatic ($n = 25$), which was detected by rising trend of CEA followed by subsequent imaging.

Kaplan–Meier curves were performed to evaluate OS and DFS. Univariate and multivariate analysis using Cox regression model were used to adjust for different factors (Table 2). Three year and five year OS were 77.2% and 63.9% respectively. Three year and five year DFS were 69.4% and 68.3% respectively (Fig. 1). For CRM positive patients, the OS was significantly compromised and no long term survivor, while for CRM negative patients, three year OS was 88.3% (95% CI 0.80, 0.93). Univariate analyses for OS have shown that age, Eastern Cooperative Oncology Group (ECOG) status, time from PLCRT completion to surgery, histological tumor grading, tumor regression grade, presence of threatened CRM on final pathology, pathological T and N stage had p-values $\leq$ 0.100, but after multivariate adjustment, only threatened CRM (hazard ratio [HR] 18.51, 95% CI 1.29–264.52, p-value = 0.032) and histological grade (hazard ratio [HR] 27.72, 95% CI 1.96–392.88, p-value = 0.014) remained significant (Fig. 2A). Univariate analysis revealed that the time from RT completion to surgery, presence of threatened CRM on final pathology, pathological T and N stage, and number of histologically involved lymph node could potentially influence DFS, but only threatened CRM (HR 8.36, 95% CI 2.31–30.24, p-value = 0.001) and pathological N stage (HR 1.83, 95% CI 1.11–3.01, p-value = 0.018) remained significant after multivariate adjustment (Fig. 2B).

Discussion

pCR rate was 10.9% and five year OS was 63.9%, though slightly less favorable but still is comparable to local[23] and international data.[6,24–26] All of our patients underwent pelvic MRI as part of their staging investigations, while other international and local series did not, or only offered to a portion of patients. Since MRI is standard in determining locoregional disease status now, we postulated that our data reflect prognosis more accurately in patients with T3 with risk factors, T4 and/or N2 disease, treated with neoadjuvant chemoradiation. Also, our cohort contained patients with advanced diseases, the inclusion criteria is also the reason for the different survival figures. Patients who received TME had better OS and DFS rates. It is likely that the number of patients who did not receive TME was too small to draw definitive conclusions from these findings. Nevertheless, our result showed that the importance of good TME surgery that is compatible with current evidence.

Table 2 Univariate and multivariate analysis[a] for OS and DFS.

Factors	Univariate HR	95% CI	*p*-Values	Multivariate HR	95% CI	*p*-Values
For OS						
Age (per 1 year increase)	1.04	1.00, 1.07	0.049	1.03	0.95, 1.12	0.495
Sex (female vs. male)	0.92	0.44, 1.94	0.828			
ECOG (per 1 score increase)	3.33	1.72, 6.45	<0.001	2.46	0.53, 11.38	0.248
Pretreatment T stage	1.62	0.75, 3.54	0.222			
Pretreatment N stage	1.28	0.84, 1.97	0.255			
Time from nCRT completion to surgery (continuous variable)	0.99	0.98, 1.00	0.016	1.00	0.99, 1.01	0.892
MRF involved or threatened (<1 mm) on baseline MRI staging (yes vs. no)	1.21	0.37, 3.93	0.757			
Histological grade (per 1 grade increase)	19.98	2.86, 139.80	0.003	27.72	1.96, 392.88	0.014
Tumor regression grade[b] (per 1 grade increase)	2.52	0.99, 6.45	0.053	0.98	0.27, 3.50	0.971
Presence of threatened CRM on final pathology (yes vs. no)	21.77	6.51, 72.79	<0.001	18.51	1.29, 264.52	0.032
Pathological T stage	1.37	0.98, 1.93	0.068	1.93	0.34, 10.19	0.440
Pathological N stage	1.63	1.10, 2.44	0.017	2.01	0.55, 7.31	0.288
Number of involved nodes[c] (continuous variable)	1.13	1.00, 1.29	0.058			
Completion of adjuvant chemotherapy at full dose (yes vs. no)	0.57	0.20, 1.58	0.280			
Pathological response reported (yes vs. no)	0.79	0.36, 3.79	0.765			
DFS						
Age (per 1 year increase)	0.99	0.95, 1.02	0.420			
Sex.(female vs. male)	1.66	0.80, 3.42	0.173			
ECOG (per 1 score increase)	1.53	0.70, 3.32	0.286			
Pretreatment T stage	2.15	0.93, 4.96	0.073	2.17	0.86, 5.46	0.100
Pretreatment N stage	1.07	0.67, 1.71	0.782			
Time from nCRT completion to surgery (continuous variable)	0.99	0.98, 1.00	0.003	0.99	0.99, 1.00	0.103
MRF involved or threatened (<1 mm) on baseline MRI staging (yes vs. no)	1.09	0.33, 3.56	0.892			
Histological grade (per 1 grade increase)	1.84	0.40, 8.43	0.434			
Tumor regression grade[b] (per 1 grade increase)	0.83	0.44, 1.58	0.578			
Presence of threatened CRM on final pathology (yes vs. no)	14.74	4.94, 44.01	<0.001	8.36	2.31, 30.24	0.001
Pathological T stage	1.43	0.97, 2.11	0.072	1.17	0.74, 1.84	0.505
Pathological N stage	2.22	1.47, 3.38	0.001	1.83	1.11, 3.01	0.018
Number of involved nodes[c] (continuous variable)	1.18	1.06, 1.32	0.003			
Completion of adjuvant chemotherapy at full dose (yes vs. no)	0.71	0.29, 1.74	0.456			
Pathological response reported (yes vs. no)	1.68	0.21, 13.69	0.628			

Abbreviations: CRM = circumferential resection margin; DFS = disease free survival; ECOG = Eastern Cooperative Oncology Group; HR = hazard ratio; nCRT = neoadjuvant chemoradiotherapy; OS = overall survival.

[a] Factors having *p*-value $\leq$ 0.100 were selected into the multivariate model.

[b] Tumor regression grade: 0 = no viable cancer cell; 1 = single cells or small groups of cancer cells; 2 = residual cancer outgrown by fibrosis; 3 = minimal or no tumor kill and extensive residual cancer.

[c] Number of involved nodes was not included in multivariate analysis of DFS to avoid collinearity with pathological N stage.

Together with the downstaging effects, the completion resection rate was high (96.4%), which is most important for cure in rectal cancer. CRM status is prognostic factors for OS and DFS, it remains significant after multivariate adjustment. Studies have shown CRM involvement is an independent prognostic factor, it not only predicts local recurrence, but also distant metastasis and overall survival.[27] In our cohort, local recurrence was low in both groups, however, patients with CRM involvement were more commonly associated with distant metastases and

Table 3 Responses after PLCRT.

MRI radiological responses		
Responses	*n*	Proportions (*n* = 123)
CR	0	0%
PR	63	51.2%
Stable	56	45.5%
PD	4	3.3%
Objective response rate	63	51.2%

Pathological responses							
Baseline MRI clinical staging	Pathological T staging					Pathological node negative	Pathological node positive
	ypT0	ypT1	ypT2	ypT3	ypT4		
cT3	13	4	15	66	1	–	–
cT4	2	0	0	7	5	–	–
Node negative	–	–	–	–	–	24	8
Node positive	–	–	–	–	–	54	26

Table 4 Pathological downstaging after PLCRT.

Pathological downstaging	*n*	Proportion (total = 110)
T-downstaging only	17	15.5%
N-downstaging only	34	30.9%
Both T- and Ndownstaging	23	20.9%
Significant downstaging (ypT0-2N0)	32	29.1%

that is accounted for poorer DFS & OS. It is in line with the current literature. We could not find association between time from chemoradiation completion to surgery and outcome, likely due to the sample size.

The benefit of adjuvant chemotherapy in rectal cancer is controversial, especially after PLCRT and definitive rectal operation. The long term result from EORTC 22921[28] showed that adjuvant chemotherapy with 5-fluorouracil (5-FU) and folinic acid after preoperative radiotherapy (with or without chemotherapy) did not affect DFS or OS in cT3-4 resectable rectal cancer. Similar findings were detected in other trials, using 5-FU based[29] or oxaliplatin based adjuvant chemotherapy.[30] However, studies have shown that adding oxaliplatin to adjuvant[21] and/or neo-adjuvant[31] treatment can improve DFS. In our study, completion of adjuvant chemotherapy at full dose was not a prognostic factor. This highlights the importance of future research, preferably in prospective manner, to assess the benefit of adjuvant chemotherapy in this context.

Pelvic MRI is standard staging modality in rectal cancer. In our series, all our patients underwent MRI as part of

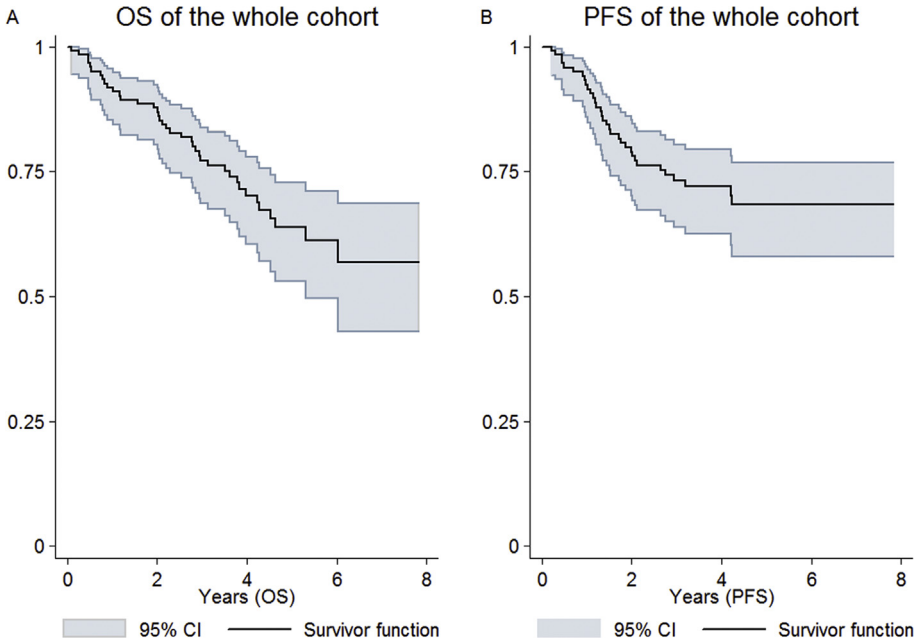

Fig. 1 Kaplan–Meier curves. Kaplan–Meier estimate for (A) OS and (B) DFS of the whole study cohort (*n* = 123). OS = overall survival; DFS = disease free survival.

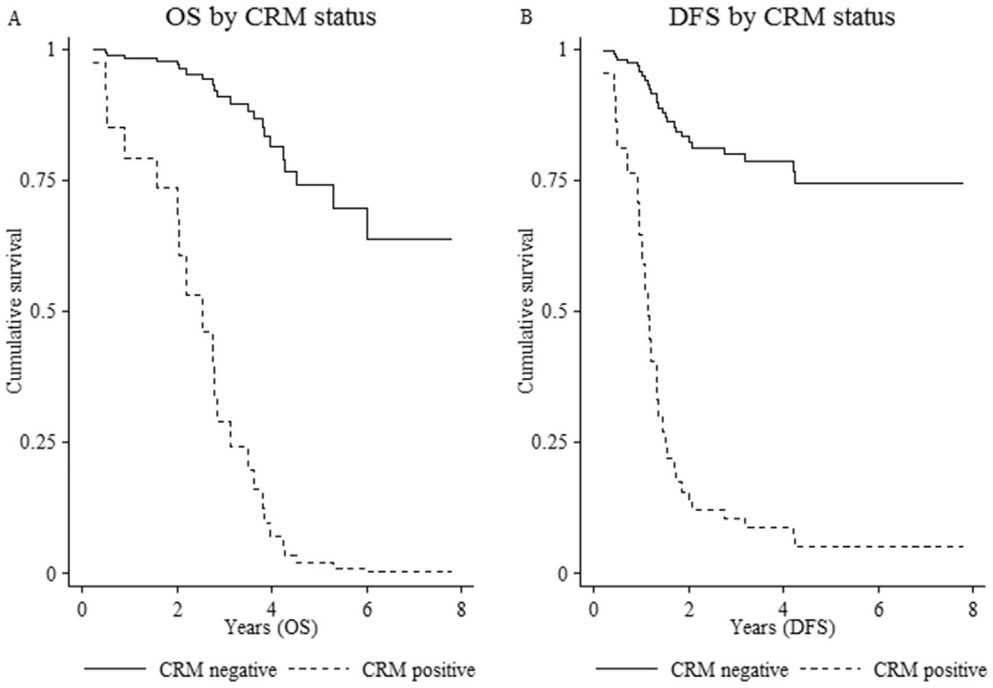

Fig. 2 Kaplan–Meier curves according to CRM status. Kaplan–Meier estimate for (A) OS and (B) DFS (n = 123). CRM = circumferential resection margin; OS = overall survival; DFS = disease free survival.

initial staging, this ensured the accuracy of our staging. However, it was not uncommon we encountered the problem of over-staging in the post-PLCRT MRI. There are reports suggesting that post-PLCRT MRI is often unable to differentiate between viable tumor, residual fibrotic non-tumor tissue, and desmoplastic reaction, resulting in poor agreement between post-PLCRT MRI and pathologic staging in both T and N stages.[32] In our data, a significant portion of patients were over-staged by post-PLCRT MRI re-staging. On the other hand 67.3% patients responded to PLCRT by RECIST criteria (T-downstaging, N-downstaging and T-/N-downstaging). These figures are compatible with modern series. However, our follow up time was long, we could reliably report late toxicity. Our study had certain limitations. Our data were collected retrospectively, there could be selective bias and other unknown confounding factors. Toxicity data and comorbidities were not systematically recorded, this may lead to inadequate statistical adjustment. Our sample size limited the ability to adjust for potential confounding factors and long term toxicity requires longer follow up to conclude.

Conclusion

The clinical outcomes of PLCRT in our institution are comparable with those in western literature. Our MRI staging lends support to the validity of data. CRM status is the most significant prognostic factor in OS and DFS, after multivariate adjustment.

Conflicts of interest

None to declare.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jfma.2017.10.002.

References

1. Kapiteijn E, Marijnen CA, Nagtegaal ID, Putter H, Steup WH, Wiggers T, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. *N Engl J Med* 2001;**345**:638–46.
2. Martling AL, Holm T, Rutqvist LE, Moran BJ, Heald RJ, Cedemark B. Effect of a surgical training programme on outcome of rectal cancer in the County of Stockholm. Stockholm Colorectal Cancer Study Group, Basingstoke Bowel Cancer Research Project. *Lancet* 2000;**356**:93–6.
3. Cedermark B, Dahlberg M, Glimelius B, Pahlman L, Rutqvist LE, Wilking N. Improved survival with preoperative radiotherapy in resectable rectal cancer. Swedish Rectal Cancer Trial. *N Engl J Med* 1997;**336**:980–7.
4. Pahlman L, Glimelius B. Pre- or postoperative radiotherapy in rectal and rectosigmoid carcinoma. Report from a randomized multicenter trial. *Ann Surg* 1990;**211**:187–95.
5. Sauer R, Liersch T, Merkel S, Fietkau R, Hohenberger W, Hess C, et al. Preoperative versus postoperative chemoradiotherapy for locally advanced rectal cancer: results of the German CAO/ARO/AIO-94 randomized phase III trial after a median follow-up of 11 years. *J Clin Oncol* 2012;**30**:1926–33.
6. Sauer R, Becker H, Hohenberger W, Rodel C, Wittekind C, Fietkau R, et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. *N Engl J Med* 2004;**351**:1731–40.
7. Cedermark B, Johansson H, Rutqvist LE, Wilking N. The Stockholm I trial of preoperative short term radiotherapy in operable rectal carcinoma. A prospective randomized trial.

Stockholm Colorectal Cancer Study Group. *Cancer* 1995;**75**:2269—75.
8. Martling A, Holm T, Johansson H, Rutqvist LE, Cedermark B, Stockholm Colorectal Cancer Study G. The Stockholm II trial on preoperative radiotherapy in rectal carcinoma: long-term follow-up of a population-based study. *Cancer* 2001;**92**:896—902.
9. van Gijn W, Marijnen CA, Nagtegaal ID, Kranenbarg EM, Putter H, Wiggers T, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer: 12-year follow-up of the multicentre, randomised controlled TME trial. *Lancet Oncol* 2011;**12**:575—82.
10. Douglass Jr HO, Moertel CG, Mayer RJ, Thomas PR, Lindblad AS, Mittleman A, et al. Survival after postoperative combination treatment of rectal cancer. *N Engl J Med* 1986;**315**:1294—5.
11. Krook JE, Moertel CG, Gunderson LL, Wieand HS, Collins RT, Beart RW, et al. Effective surgical adjuvant therapy for high-risk rectal carcinoma. *N Engl J Med* 1991;**324**:709—15.
12. Fisher B, Wolmark N, Rockette H, Redmond C, Deutsch M, Wickerham DL, et al. Postoperative adjuvant chemotherapy or radiation therapy for rectal cancer: results from NSABP protocol R-01. *J Natl Cancer Inst* 1988;**80**:21—9.
13. Maeng CH, Ahn SW, Ryu SY, Han S, Ko YH, Ji JH, et al. Treatment outcomes and clinical relevance of the Follicular Lymphoma International Prognostic Index in Korean follicular lymphoma patients treated with chemotherapy. *Korean J Intern Med* 2016;**31**:560—9.
14. Glimelius B, Tiret E, Cervantes A, Arnold D, Group EGW. Rectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2013;**24**(Suppl 6):vi81—8.
15. Minsky BD. Counterpoint: long-course chemoradiation is preferable in the neoadjuvant treatment of rectal cancer. *Semin Radiat Oncol* 2011;**21**:228—33.
16. Moureau-Zabotto L, Farnault B, de Chaisemartin C, Esterni B, Lelong B, Viret F, et al. Predictive factors of tumor response after neoadjuvant chemoradiation for locally advanced rectal cancer. *Int J Radiat Oncol Biol Phys* 2011;**80**:483—91.
17. 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.
18. Group MS. Diagnostic accuracy of preoperative magnetic resonance imaging in predicting curative resection of rectal cancer: prospective observational study. *BMJ* 2006;**333**:779.
19. Wibe A. Magnetic resonance imaging for rectal cancer. Nature clinical practice. *Oncology* 2007;**4**:222—3.
20. Sizer BF, Arulampalam T, Austin R, Lacey N, Menzies D, Motson R. MRI in predicting curative resection of rectal cancer: defining a "window of opportunity" for laparoscopic surgery. *BMJ* 2006;**333**:808—9.
21. Hong YS, Nam BH, Kim KP, Kim JE, Park SJ, Park YS, et al. Oxaliplatin, fluorouracil, and leucovorin versus fluorouracil and leucovorin as adjuvant chemotherapy for locally advanced rectal cancer after preoperative chemoradiotherapy (ADORE): an open-label, multicentre, phase 2, randomised controlled trial. *Lancet Oncol* 2014;**15**:1245—53.
22. Cox DR. Regression models and life-tables. *J Roy Stat Soc Ser B Methodol* 1972;**34**:187—220.
23. Yeung WW, Ma BB, Lee JF, Ng SS, Cheung MH, Ho WM, et al. Clinical outcome of neoadjuvant chemoradiation in locally advanced rectal cancer at a tertiary hospital. *Hong Kong Med J* 2016;**22**:546—55.
24. Bujko K, Nowacki MP, Nasierowska-Guttmejer A, Michalski W, Bebenek M, Kryj M. Long-term results of a randomized trial comparing preoperative short-course radiotherapy with preoperative conventionally fractionated chemoradiation for rectal cancer. *Br J Surg* 2006;**93**:1215—23.
25. Gerard JP, Conroy T, Bonnetain F, Bouche O, Chapet O, Closon-Dejardin MT, et al. Preoperative radiotherapy with or without concurrent fluorouracil and leucovorin in T3-4 rectal cancers: results of FFCD 9203. *J Clin Oncol* 2006;**24**:4620—5.
26. Zeng WG, Liang JW, Wang Z, Zhang XM, Hu JJ, Hou HR, et al. Clinical parameters predicting pathologic complete response following neoadjuvant chemoradiotherapy for rectal cancer. *Chin J Cancer* 2015;**34**:468—74.
27. Wibe A, Rendedal PR, Svensson E, Norstein J, Eide TJ, Myrvold HE, et al. Prognostic significance of the circumferential resection margin following total mesorectal excision for rectal cancer. *Br J Surg* 2002;**89**:327—34.
28. Bosset JF, Calais G, Mineur L, Maingon P, Stojanovic-Rundic S, Bensadoun RJ, et al. Fluorouracil-based adjuvant chemotherapy after preoperative chemoradiotherapy in rectal cancer: long-term results of the EORTC 22921 randomised study. *Lancet Oncol* 2014;**15**:184—90.
29. Sainato A, Cernusco Luna Nunzia V, Valentini V, De Paoli A, Maurizi ER, Lupattelli M, et al. No benefit of adjuvant Fluorouracil Leucovorin chemotherapy after neoadjuvant chemoradiotherapy in locally advanced cancer of the rectum (LARC): Long term results of a randomized trial (I-CNR-RT). *Radiother Oncol* 2014;**113**:223—9.
30. Glynne-Jones R, Counsell N, Quirke P, Mortensen N, Maraveyas A, Meadows HM, et al. Chronicle: results of a randomised phase III trial in locally advanced rectal cancer after neoadjuvant chemoradiation randomising postoperative adjuvant capecitabine plus oxaliplatin (XELOX) versus control. *Ann Oncol* 2014;**25**:1356—62.
31. Rodel C, Graeven U, Fietkau R, Hohenberger W, Hothorn T, Arnold D, et al. Oxaliplatin added to fluorouracil-based preoperative chemoradiotherapy and postoperative chemotherapy of locally advanced rectal cancer (the German CAO/ARO/AIO-04 study): final results of the multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol* 2015;**16**:979—89.
32. Chen CC, Lee RC, Lin JK, Wang LW, Yang SH. How accurate is magnetic resonance imaging in restaging rectal cancer in patients receiving preoperative combined chemoradiotherapy? *Dis Colon Rectum* 2005;**48**:722—8.