Clinical outcome of neoadjuvant chemoradiation in locally advanced rectal cancer at a tertiary hospital

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A B S T R A C T

Objectives: To review the clinical outcome of locally advanced rectal cancer treated with neoadjuvant chemoradiation followed by definitive surgery with or without adjuvant chemotherapy and to elucidate the prognostic factors for treatment outcome.

Methods: This historical cohort study was conducted at a tertiary public hospital in Hong Kong. All patients who had undergone neoadjuvant chemoradiation for locally advanced rectal cancer in our department from November 2005 to October 2014 were recruited. Local recurrence–free survival, distant metastasis–free survival, disease-free survival, and overall survival of patients were documented.

Results: A total of 135 patients who had received neoadjuvant chemoradiation during the study period were reviewed. There were 130 patients who had completed neoadjuvant chemoradiation and surgery. The median follow-up time was 35.1 months. The 3- and 5-year local recurrence–free survival, distant metastasis–free survival, disease-free survival, as well as overall survival rates were 91.8% and 86.7%, 73.9% and 72.1%, 70.1% and 64.6%, as well as 86.5% and 68.4%, respectively. The rate of pathological complete response was 13.8%. The T and N downstaging rate was 49.2% and 63.1%, respectively. The rate of conversion from threatened circumferential resection margin to clearance of margin was 90.6%. Of the 42 cases that were initially deemed to require abdominal perineal resection, 15 (35.7%) were converted to sphincter-sparing surgery.

Conclusions: The treatment outcome of neoadjuvant chemoradiation for locally advanced rectal cancer was comparable with overseas data in terms of local control rate and overall survival. This strategy may increase the chance of achieving a clear surgical margin by downstaging the tumour, especially in patients who presented with threatened circumferential margin.

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New knowledge added by this study

- This is a local study from a tertiary oncology centre on the clinical outcome of neoadjuvant chemoradiation in the treatment of locally advanced rectal cancer.

Implications for clinical practice or policy

- Neoadjuvant chemoradiation is effective in downstaging advanced rectal cancers, especially those with threatened circumferential resection margin, facilitating definitive surgery to achieve a clearance of the final pathological margin.

Introduction

According to the Hong Kong Cancer Registry,[1] there were 1797 new cases of rectal/anal cancer in 2013. The incidence rate per 100 000 persons was 25.0 (crude rate) and 13.3 (age-standardised rate). The total number of deaths from rectal/anal cancer was 597, and the mortality rate was 8.3 (crude rate) or 3.7 (age-standardised rate) per 100 000 persons. In Hong Kong, colorectal cancer is the first most common cancer in incidence and the second in mortality rate for both sexes.

Conventional treatment of rectal cancer is mainly surgery. In locally advanced cancer, adjuvant therapy with concurrent chemoradiation has been

shown to improve local control and disease-free survival (DFS) in phase III clinical trials.[2-5] The major indication for adjuvant chemoradiation is pathological T3 or T4 and/or regional nodal disease without distant metastasis.

Preoperative radiotherapy with or without concurrent chemotherapy has been shown to reduce the local recurrence rate of locally advanced rectal cancer.[6-12] Preoperative radiotherapy comprises a short or long course.

Short-course preoperative radiotherapy was given in 5 Gy per fraction for five fractions over 1 week, followed by surgery about 1 week after completion of radiotherapy. Since the introduction of total mesorectal excision (TME), the local recurrence rate has been significantly reduced. In the new era of TME surgery, a Dutch rectal trial confirmed that a short course of preoperative radiotherapy, followed by TME surgery, was also beneficial in reducing local recurrence rate from 8.2% to 2.4% over 2 years compared with TME surgery alone in locally advanced rectal cancer.[13,14]

Long-course preoperative radiotherapy involves a conventional fractionation of 1.8 Gy per fraction, five fractions per week, up to a total dose of 45 to 50 Gy. It is given with concurrent chemotherapy consisting of mostly a fluoropyrimidine-containing regimen. Surgery is usually performed approximately 4 to 10 weeks after completion of chemoradiation.

A randomised German trial (CAO/ARO/AIO 94)[10] compared preoperative long-course chemoradiation with postoperative chemoradiation. At a median follow-up of 4 years, no significant difference was reported in the 5-year overall survival (OS). Nonetheless, treatment compliance, grade 3/4 acute and late toxicity profile, tumour and nodal downstaging, and rates of pelvic recurrence all favoured the preoperative chemoradiation arm. In addition, the sphincter preservation rate in the 194 patients with low-lying tumours declared by the surgeon prior to randomisation requiring an abdominoperineal resection (APR) was enhanced with preoperative treatment (39% vs 19%; P=0.004).

Since 2005, our hospital has adopted a treatment policy of long-course neoadjuvant (or preoperative) chemoradiation (nCRT) for selected cases of locally advanced rectal cancer. The objective of this study was to review the clinical outcome of these patients with locally advanced rectal cancer treated with nCRT in our department from November 2005 to October 2014 and to elucidate the prognostic factors for treatment outcome retrospectively.

一間三級公立醫院以新輔助放射化療法醫治局部晚期直腸癌的臨床研究結果

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目的：回顧利用新輔助放射化療和隨後的確定性手術，不論術後是否加上輔助化療，用於局部晚期直腸癌的臨床療效；並闡明對治療結果的預後因素。

方法：這歷史性隊列研究於香港一間三級公立醫院內進行。於2005年11月至2014年10月在本部門接受新輔助放射化療的所有局部晚期直腸癌病人均被列入研究範圍，並記錄病人的無局部復發生存率、無遠處轉移生存率、無病生存率和總體生存率。

結果：研究期間接受新輔助放射化療的患者共有135人。其中已完成新輔助放射化療及手術的有130例。中位隨訪時間為35.1個月。3年和5年的無局部復發生存率、無遠處轉移生存率、無病生存率，以及總體生存率分別為91.8%和86.7%、73.9%和72.1%、70.1%和64.6%，以及86.5%和68.4%。病理完全緩解率為13.8%。腫瘤T分期和N分期的降期率相應為49.2%和63.1%。從環週切緣受威脅到乾淨切緣（即切緣組織沒有癌細胞）的轉化率為90.6%。原本需要腹會陰切除術的42例中，15例（35.7%）被轉換了成保肛手術。

結論：運用新輔助放化療針對局部晚期直腸癌之療法，在局部控制率和總體生存率方面與國際研究的臨床結果相若。這療法有利於腫瘤降期，尤其是在那些環週切緣受威脅情況下，有利於手術達至乾淨切緣的效果。

Methods

Eligible patients included those without distant metastasis and who were staged preoperatively on radiological grounds with T3 or T4 disease and/or having nodal involvement. There might have been other extra specific reasons for recommending nCRT, including threatened circumferential resection margin (CRM), sphincter-sparing surgery, avoidance of pelvic exenteration, and unresectability (Table 1). Patients were required to be medically fit and agree to the nCRT.

TABLE 1. Other reasons for recommending neoadjuvant chemoradiation

Reason	Description
Threatened circumferential margin	Less than 2 mm of the shortest distance from the tumour or node to the mesorectal fascia
Sphincter-sparing surgery	Indication for APR: consider APR if the distal visible margin of the tumour is less than 1 cm from the palpable anal sphincter complex
Avoiding pelvic exenteration	Indication for exenteration: if the tumour is found to be densely adhering to adjacent pelvic structure with loss of anatomical plane in the preoperative imaging, exenteration type of resection is performed

Abbreviation: APR = abdominoperineal resection

The nCRT scheme adopted in our department consisted of the following.

Radiotherapy

Simulation procedure was done in an immobilised prone position with full bladder, using simulation computed tomography (CT) scan. The three-dimensional conformal radiotherapy planning was performed on the simulation CT scan imaging, using three coplanar fields with shielding conformal to the target volume. The radiotherapy was given in two phases. Phase 1 included the whole pelvis. A total dose of 45 Gy was delivered at 1.8 Gy per day, five fractions per week over 5 weeks. Phase II included only the gross tumour and the enlarged pelvic nodes with margins. A booster dose of 5.4 Gy was administered in the same fractionation as phase 1.

Chemotherapy

Concurrent chemotherapy was given in the first and fifth weeks of radiation. It comprised an intravenous (IV) bolus of 5-fluorouracil (5-FU; 400 mg/m^2) and leucovorin (20 mg/m^2) on days 1 to 4.

The surgery was scheduled about 4 to 10 weeks after completion of nCRT. Adjuvant chemotherapy with four cycles of 5-FU and leucovorin was administered to most patients. In some selected cases with pathological node-positive disease following surgery, four cycles of capecitabine and oxaliplatin ('XELOX' regimen) were given.

In this study, clinical data were collected retrospectively from the medical records of all patients who had undergone nCRT for locally advanced rectal cancer in the Department of Clinical Oncology at the Prince of Wales Hospital, Hong Kong from November 2005 to October 2014. The surgery was performed either at Prince of Wales Hospital or the referring hospital. There was variation in practice for pretreatment staging method, re-staging on completion of nCRT (follow-up CT scan was arranged to exclude distant metastasis at least 2 weeks after nCRT; optional magnetic resonance imaging [MRI] was considered at least 4 weeks after nCRT), and follow-up among different hospitals. The patients' demographic information, tumour characteristics, and treatment details were retrieved. The initial type of surgery recommended by the referring surgical team at presentation and any extra specific reasons (intentions) for referral for nCRT were reviewed. The final pathology at the definitive surgery (the pathological T and N staging, the tumour size, any pathological complete response [pCR], the resection margins), the treatment-related toxicity (radiation- or chemotherapy-related, surgical complications), recurrence (local, regional, distant relapse), and disease status at follow-up were reviewed.

The key study endpoints included loco-regional recurrence–free survival, distant metastasis–free survival, DFS, and OS. Other secondary endpoints included the rate of pCR, tumour downstaging (T and N staging), conversion of threatened CRM to clearance of margins (R0), conversion to sphincter-sparing surgery for lower rectal cancers, conversion from a potential pelvic exenteration to non-exenterating surgery, and the rate of conversion from unresectable to resectable tumour. For toxicity endpoints, the rate of grade 3 or above acute toxicity according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0, and the rate of grade 3 or above late radiation toxicity according to the Toxicity criteria of the Radiation Therapy Oncology Group and the European Organization for Research and Treatment of Cancer, and perioperative complications as represented by rate of 30-day postoperative mortality and morbidity (delayed wound healing, anastomotic complication, reoperation) were also assessed.

Statistical analysis

Descriptive statistics were used to report the incidence rates of secondary endpoints that were calculated directly. The survival rates and time-to-event rates were estimated with the Kaplan-Meier method. Univariate analysis based on the proportional hazard model was performed to investigate the relationship between different outcome (survival) and prognostic factors. The hazard ratio and the corresponding 95% confidence interval were shown. The prognostic factors included pretreatment T stage, pretreatment N stage, histological grade, threatened CRM, completion of nCRT, time from nCRT to surgery, pathological T stage, pathological N stage, pathological group stage, pCR, pathological margin, number of involved nodes, and completion of adjuvant chemotherapy. For those significant prognostic factors, multivariate analysis using Cox regression with stepwise selection was performed.

This study was approved by the Joint Chinese University of Hong Kong–New Territories East Cluster Clinical Research Ethics Committee with informed consent waived. The principles outlined in the Declaration of Helsinki have also been followed.

Results

A total of 135 patients who had received nCRT in our department from November 2005 to October 2014 were reviewed, of whom 130 had completed nCRT and surgery with or without adjuvant chemotherapy. Of the five patients who did not have surgery, two refused surgery after nCRT and three progressed after nCRT without undergoing surgery.

Patient characteristics are shown in Table 2. The mean age was 60.9 (standard deviation [SD],

9.23) years. The male-to-female ratio was 3.2:1. For the pretreatment stage, 80% and 20% were T3 and T4 respectively, while 13.8%, 40.0% and 45.4% were N0, N1 and N2 stage, respectively. For the overall group stage, the incidences of stage IIA, IIB/C, and III were 8.5%, 6.1%, and 85.4%, respectively. A total of 65.4% cases had threatened CRM at pretreatment imaging.

Of the 130 patients who had surgery, 128 (98.5%) completed nCRT. For the radiotherapy-related toxicities, the combined incidence of grade 3 or above acute toxicity to the skin, bowel, and urinary toxicity was 6.2%. Similarly, the radiotherapy-related grade 3 or above late toxicity to the bowel and urinary tract was 6.2%. For chemotherapy-related grade 3 or above acute toxicity, the incidences of neutropenia, anaemia, and thrombocytopenia were 14.6%, 1.5%, and 1.5%, respectively. The most common non-haematological grade 3 or above acute toxicities were hand-foot-mouth syndrome (0.8%), mucositis (1.5%), and diarrhoea (0.8%). Adjuvant chemotherapy was given to 103 (79.2%) patients, of whom 92 (89.3%) received the regimen of IV bolus 5-FU and leucovorin. With regard to surgical complications, 22 (16.9%) patients had delayed wound healing (>30 days after operation), six (4.6%) had anastomotic complication, and six (4.6%) required reoperation. There was no 30-day postoperative mortality reported (Table 3).

Of the 130 cases, 124 (95.4%) underwent TME surgery and 114 (87.7%) had laparoscopic surgery. The mean time from the date of completion of nCRT to surgery was 7.2 (SD, 4.8) weeks. Comparing the type of surgery recommended before starting nCRT and those finally carried out after nCRT, the rate of anterior resection/low anterior resection increased to 65.4% from 50.8%, and the rate of APR/pelvic exenteration decreased to 27.7%/3.8% from 32.3%/12.3% respectively. The overall rate of surgical conversion was reported in several clinical contexts: (1) percentage achieving a R0 resection, (2) percentage undergoing sphincter-sparing surgery, and (3) percentage avoiding pelvic exenteration. First, of the total number of patients who were found to have threatened CRM before treatment, 90.6% finally achieved a R0 resection. Of the 42 patients who were initially deemed on presentation to require an APR, 35.7% underwent sphincter-sparing surgery. In a subgroup of the 15 patients who had received nCRT with the intention of sphincter preservation, 86.7% (n=13) underwent sphincter-sparing surgery rather than APR. Among these 13 cases with successful sphincter-sparing surgery, one had pCR and all had clear resection margins. They remained alive and free of loco-regional and distant recurrence at the end of this study. Of the 16 patients who were initially assessed to require pelvic exenteration, 62.5% (n=10) underwent non-exenterating surgery.

TABLE 2. Patient characteristics (n=130)

Clinical characteristic	Data*
Age (years)	
Mean ± SD	60.9 ± 9.23
Median (range)	61 (36-82)
Gender	
Male	99 (76.2)
Female	31 (23.8)
Pretreatment staging†	
T stage	
T3	104 (80.0)
T4	26 (20.0)
N stage	
N0	18 (13.8)
N1	52 (40.0)
N2	59 (45.4)
N+(N1-2)	1 (0.8)
Overall stage‡	
Stage IIA	11 (8.5)
Stage IIB/IIC	8 (6.1)
Stage III	111 (85.4)
Pretreatment staging method	
CT	33 (25.4)
MRI	86 (66.1)
PET/CT	11 (8.5)
Site of primary tumour‡	
Upper	9 (6.9)
Mid	71 (54.6)
Lower	50 (38.5)
Lowest border of tumour from anal verge (cm)	
Mean ± SD	5.5 ± 2.4
Median (range)	5 (0-11)
Tumour length by imaging (cm)	
Mean ± SD	5.4 ± 1.8
Median (range)	5.0 (2-12)
Histology	
WD	5 (3.9)
MD	115 (88.4)
PD	9 (6.9)
Uncertain	1 (0.8)
Pretreatment CEA (μg/L)	
Mean ± SD	17.6 ± 27.3
Median (range)	6.5 (1-130)
Threatened CRM	
Yes	85 (65.4)
No	45 (34.6)
Extra specific reason for nCRT	
Threatened CRM	59 (45.4)
Sphincter-sparing surgery	15 (11.5)
Avoid exenteration	16 (12.3)
Unresectable	6 (4.6)
None of the above	34 (26.2)

Abbreviations: CEA = carcinoembryonic antigen; CRM = circumferential resection margin; CT = computed tomography; MD = moderately differentiated; MRI = magnetic resonance imaging; nCRT = neoadjuvant chemoradiation; PD = poorly differentiated; PET = positron emission tomography; SD = standard deviation; TNM = tumour node metastasis staging; UICC = Union for International Cancer Control; WD = well differentiated

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

† Stage IIA (T3N0M0), stage IIB (T4aN0M0), Stage IIC (T4bN0M0), Stage III (TxN1-2M0) according to TNM UICC 7th edition

‡ Site of tumour: distance of the lowest border of tumour measured from anal verge (AV); lower: 0-5 cm from AV, mid: >5-10 cm from AV, upper: >10 cm from AV

TABLE 3. Toxicity and treatment compliance

	No. (%) of patients (n=130)
Radiotherapy toxicity – acute grade 3/4 toxicity*	
Skin	4 (3.1)
Bowel	2 (1.5)
Urinary	1 (0.8)
Other	1 (0.8)
Total No. of patients	8 (6.2)
Radiotherapy toxicity – late grade 3/4 toxicity*	
Bowel	4 (3.1)
Urinary	1 (0.8)
Total No. of patients	8 (6.2)
Chemotherapy toxicity – acute grade 3/4 toxicity*	
Vomiting	0
Hand-foot-mouth syndrome	1 (0.8)
Oral mucositis	2 (1.5)
Diarrhoea	1 (0.8)
Anaemia	2 (1.5)
Thrombocytopenia	2 (1.5)
Neutropenia	19 (14.6)
Other	2 (1.5)
Chemotherapy toxicity – late grade 3/4 toxicity*	0
No. of patients received adjuvant chemotherapy	103 (79.2)
Regimen	
5-Fluorouracil/folinic acid	92 (89.3)
XELOX or its modification	11 (10.7)
No. of patients completed adjuvant chemotherapy	88/103 (85.4)
Reason of incomplete adjuvant chemotherapy	
Toxicity	6
Patient refusal	1
Other	8
30-Day surgical morbidity	
Delayed wound healing†	22 (16.9)
Anastomotic‡	6 (4.6)
Reoperation	6 (4.6)
30-Day surgical-related mortality	0

Abbreviation: XELOX = capecitabine and oxaliplatin

* Number of patients who ever had 1 or more grade 3/4 toxicity

† Wound healing was delayed by more than 30 days after operation

‡ Complication related to anastomosis included leakage, dehiscence, and infection

There were six patients in whom tumour was deemed unresectable and who were referred for nCRT to improve resectability. Complete resection with negative margins was subsequently achieved in four (66.7%) of the six patients while the other two had a positive margin in the palliative surgery.

The final pathological staging in the surgical specimen is reported (Table 4). The rates of pCR and clear resection margin were 13.8% and 89.2%, respectively. The rate of T downstaging was 49.2% and that for N stage was 63.1% (Table 3).

The median follow-up time was 35.1 months. Of the 130 patients, local recurrence, loco-regional recurrence, distant metastasis, disease recurrence, and death occurred in 10 (crude rate, 7.7%), 15 (11.5%), 30 (23.1%), 34 (26.2%), and 23 (17.7%) patients, respectively. The Kaplan-Meier estimates of the 3-year local recurrence–free survival, regional recurrence–free survival, loco-regional recurrence–free survival, distant metastasis–free survival, DFS, and OS were 91.8%, 92.6%, 87.9%, 73.9%, 70.1%, and 86.5%, respectively. The respective 5-year survival rates were 86.7%, 85.3%, 81.0%, 72.1%, 64.6%, and 68.4%. The corresponding Kaplan-Meier curves for local recurrence-free survival and OS is also shown in the Figure (the curves for loco-regional recurrence–free survival, distant metastasis–free survival, and DFS are shown in the Appendix).

Analysis of prognostic factors

The variables (factors including age and gender were tested but not significant in univariate model) in the univariate analysis included the pretreatment T stage, pretreatment N stage, histological grade, presence of threatened CRM, completion of nCRT, time from nCRT to surgery (continuous variable), pathological T stage, pathological N stage, pathological group stage, pCR, pathological margin, number of involved nodes (continuous variable), and completion of adjuvant chemotherapy. Those significant prognostic factors were studied by multivariate analysis.

In the multivariate analysis, the pathological clear margin, completion of nCRT, and the number of involved nodes were significantly associated with local recurrence–free survival. The number of involved nodes, pathological clear margin, and time from nCRT to surgery were significantly associated with loco-regional recurrence–free survival. The number of involved nodes, the pretreatment T4, pathological stage III/IV, and completion of adjuvant chemotherapy were significantly associated with distant metastasis–free survival. The number of involved nodes, pathological stage III/IV, and completion of adjuvant chemotherapy were significantly associated with DFS. Finally, the number of involved nodes, the pretreatment T4, and pathological stage III/IV were significantly associated with OS (Table 5).

Discussion

Although the current study was retrospective, survival data were comparable with figures reported in international studies. In the major randomised trials, 5-year local recurrence rate in the arm with

TABLE 4. Surgical and pathological outcomes

Outcome	No. (%) of patients
Time from completion of nCRT to surgery (months)	
Mean ± SD	1.8 ± 1.2
Median (range)	1.8 (0.3-13.3)
Type of surgery claimed before surgery	
AR/LAR	66 (50.8)
APR	42 (32.3)
Pelvic exenteration	16 (12.3)
Unresectable	6 (4.6)
Type of surgery performed after nCRT	
AR/LAR	85 (65.4)
APR	36 (27.7)
Pelvic exenteration	5 (3.8)
Palliative surgery	4 (3.1)
Surgery technique	
Total mesorectal excision	124 (95.4)
Laparoscopic surgery	114 (87.7)
Conversion of close/threatened CRM to R0	
No. of cases with conversion/total No. of cases of threatened CRM	77/85 (90.6)
Conversion to sphincter-sparing surgery	
No. of cases with conversion/total No. of cases of APR claimed before nCRT	15/42 (35.7)
No. of cases with conversion/total No. of cases with sphincter preservation as main reason (intent) of nCRT	13/15 (86.7)
Conversion of exenteration to AR/APR	
No. of cases with conversion/total No. of cases of pelvic exenteration claimed before CRT	10/16 (62.5)
Conversion to resectable (R0) from unresectable	
No. of cases with conversion/total No. of cases deemed unresectable before nCRT	4/6 (66.7)
Pathological T stage	
T0	18 (13.9)
T1	3 (2.3)
T2	25 (19.2)
T3	77 (59.2)
T4	7 (5.4)
Pathological N stage	
N0	86 (66.2)
N1	29 (22.3)
N2	15 (11.5)
Pathological overall stage	
Stage 0	18 (13.8)
Stage I	24 (18.5)
Stage IIA	38 (29.2)
Stage IIB/IIC	4 (3.1)
Stage III	45 (34.6)
Stage IVA/IVB	1 (0.8)
Pathological complete response	18 (13.8)
Pathological margin	
Clear	116 (89.2)
Closed	3 (2.3)
Involved	11 (8.5)
Pathological T downstaging	64 (49.2)
Pathological N downstaging	82 (63.1)
No. of LN resected	
Mean ± SD	13.0 ± 5.2
Median (range)	12 (0-28)
No. of LN pathologically involved	
Mean ± SD	1.3 ± 3.1
Median (range)	0 (0-19)
Pathological residual size (cm)	
Mean ± SD	2.5 ± 3.3
Median (range)	2 (0-35)

Abbreviations: APR = abdominal perineal resection; AR/LAR = anterior resection or low anterior resection; CRM = circumferential resection margin; LN = lymph nodes; nCRT = neoadjuvant chemoradiation; R0 = clear resection margin; SD = standard deviation

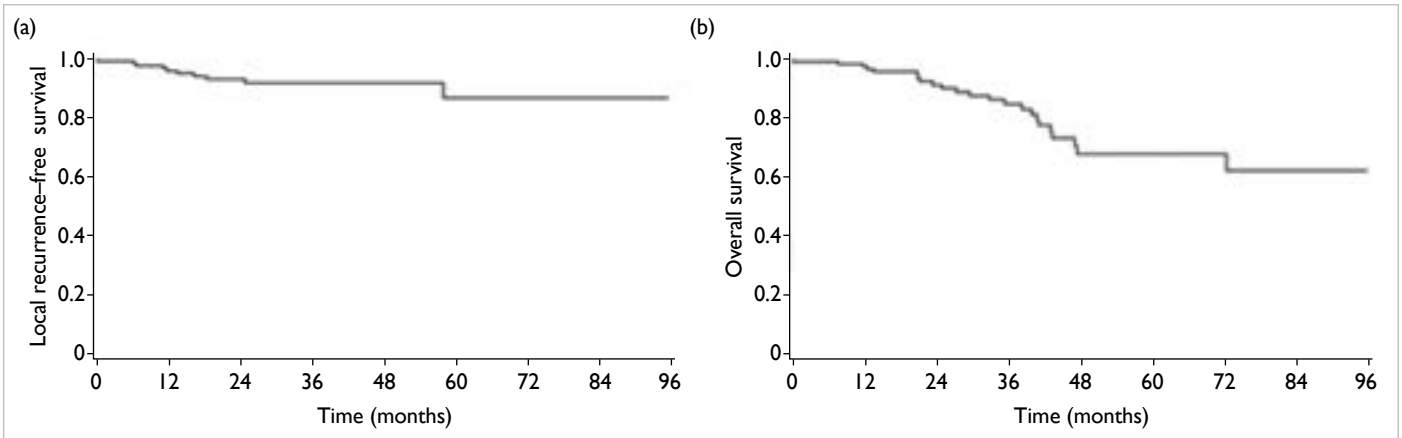

FIG. (a) Local recurrence–free and (b) overall survival curves

TABLE 5. Significant prognostic factors for various survival categories in both univariate and multivariate analysis

Factor	Univariate analysis			Multivariate analysis		
	P value	HR	95% CI	P value	HR	95% CI
Local recurrence–free survival						
Completion of nCRT	0.0191	0.083	0.010-0.665	0.0013	0.019	0.002-0.210
Pathological margin (clear)	0.0002	0.098	0.028-0.339	0.0002	0.075	0.019-0.291
No. of involved nodes	0.0079	1.153	1.038-1.281	0.0046	1.190	1.055-1.343
Loco-regional recurrence–free survival						
Time from nCRT to surgery	0.0026	1.362	1.114-1.665	0.0052	1.348	1.093-1.663
Pathological margin (clear)	0.0002	0.140	0.050-0.395	0.0004	0.147	0.051-0.422
No. of involved nodes	0.0002	1.170	1.079-1.269	0.0013	1.166	1.061-1.280
Distant metastasis–free survival						
Pretreatment T4	0.0002	3.984	1.945-8.163	0.0220	2.402	1.134-5.087
Pathological stage III/IV	0.0023	3.103	1.499-6.423	0.0100	6.891	1.586-29.942
No. of involved nodes	<0.0001	1.181	1.099-1.268	0.0027	1.126	1.042-1.217
Completion of adjuvant chemotherapy	0.0176	0.418	0.203-0.859	0.0267	0.428	0.202-0.907
Disease-free survival						
Pathological stage III/IV	0.0040	2.704	1.373-5.326	0.0023	9.498	2.231-40.428
No. of involved nodes	<0.0001	1.184	1.106-1.268	0.0006	1.139	1.058-1.227
Completion of adjuvant chemotherapy	0.0101	0.411	0.209-0.809	0.0025	0.345	0.173-0.688
Overall survival						
Pretreatment T4	0.0256	2.565	1.122-5.864	0.0093	3.115	1.323-7.331
Pathological stage III/IV	0.0002	5.046	2.126-11.978	0.0334	3.135	1.094-8.987
No. of involved nodes	<0.0001	1.221	1.134-1.316	0.0034	1.160	1.050-1.280

Abbreviations: CI = confidence interval; HR = hazard ratio; nCRT = neoadjuvant chemoradiation

preoperative short-course radiotherapy was in the range of 11% to 14%, and OS was in the range of 42% to 76%.[6-9] In the randomised trials that had an arm with nCRT, the 4- or 5-year local recurrence rates were 5.7% to 15.6% and the OS were 66.2% to 76%.[10,15-18] In this study, the 5-year local recurrence rate and loco-regional recurrence rate was 13.3% and 19%, respectively. These were close to the reported figures from randomised studies.[10,15-18] The 5-year OS in this study was 68.4% and is comparable with

international studies.[10,15-18]

The pCR rate was 13.8% in this study, again comparable with randomised trials[10,15-18] and reviews.[19] Together with the favourable down-staging effects, the completion resection rate was high (89.2%). This is the primary aim of nCRT in advanced rectal cancer. The role of nCRT in sphincter preservation for low-lying tumours has been a controversial issue in some randomised trials,[10,11,15,16] and critical reviews.[20,21] In a German study,[10] among the 194 patients with tumours that were determined by the surgeon before randomisation to require an APR, a statistically significant increase in sphincter preservation was achieved among patients who received nCRT compared with those who received postoperative chemoradiation (39% vs 19%; P=0.004). Although long-course nCRT is expected to result in tumour downsizing, a Polish trial[11] did not find that long-course chemoradiation was superior to short-course preoperative radiotherapy in reducing the APR rate. The possible explanations for this finding include the possibility that the degree of downsizing was not sufficient to alter the surgical approach, due to surgeon's concern about residual microscopic disease despite an apparently good response after nCRT, or the surgeons had made their clinical decision based on the pretreatment staging information. In our study the overall rate of conversion from APR to sphincter-sparing surgery was 35.7% and was comparable with that (39%) in the German trial[10]; and for the subgroup of patients with an intention to spare the sphincter, the conversion rate was even higher, up to 86.7%, with a good clinical outcome.

The extent of extramural tumour spread and lymph node and CRM status are powerful predictive factors for local recurrence, distant metastases, and OS in patients with rectal cancer.[22-28] From our study, it was evident that the number of involved nodes in the final pathology was an independent factor in OS, DFS, local or loco-regional recurrence–free survival, and distant metastasis–free survival. For local or loco-regional recurrence, the pathological clear margin, the completion of nCRT, and the time from nCRT to surgery were independent prognostic factors. Although in this study there was an attempt to find the optimal cut-off time for surgery after the completion of nCRT, this was not possible because of the small sample size. Increasing the time interval from completion of nCRT to surgery was associated with a detrimental effect on loco-regional recurrence (hazard ratio=1.348).

In this study, completion of adjuvant chemotherapy was a prognostic factor for distant metastasis. This implies that adjuvant chemotherapy might be important in reducing distant metastasis. It remains controversial whether adjuvant chemotherapy should be given after nCRT and surgery. A 2x2 factorial randomised trial (EORTC trial 22921)[29-32] that assessed the value of pre-operative chemo-radiotherapy versus preoperative radiotherapy and postoperative chemotherapy versus no postoperative chemotherapy in patients with cT3-4 disease could not demonstrate any prolonged progression-free or OS from adjuvant chemotherapy in patients with resectable T3-T4 rectal cancer. Its follow-up report of 785 eligible patients who underwent R0 resection showed that patients with a good prognosis (ypT0-2) seemed to benefit from adjuvant chemotherapy, especially if the tumour was located in the mid-rectum.[33] Nonetheless, an updated analysis of the EORTC 22921 trial[18] recently failed to confirm the benefit of adjuvant chemotherapy for ypT0-2 patients after a median follow-up of 10.4 years. In the I-CNR-RT phase III randomised trial,[34] there was no benefit of adjuvant chemotherapy (6 cycles of 5-FU and folinic acid) compared with observation only after nCRT. The result may be partly attributed to the low compliance to complete the planned number of chemotherapy cycles. The British Chronicle trial[35] is unique in comparing XELOX postoperatively against observation alone in locally advanced rectal cancer treated with nCRT. After a median follow-up of 44.8 months, there was no statistically significant benefit of adjuvant XELOX in the 3-year DFS rate. A Korean study reported the results of ADORE phase II study in which 321 patients of ypT3-4/ypN0 or ypTx/ypN1-2 after nCRT with 5-FU alone were randomised to receive adjuvant chemotherapy with 5-FU or FOLFOX.[36,37] After a median follow-up of 38.2 months, the 3-year DFS rate was better in the FOLFOX arm (P=0.047). Although adjuvant treatment of patients with rectal cancer remains controversial, the National Comprehensive Cancer Network guidelines recommend 5-FU–based chemotherapy with oxaliplatin as the preferred adjuvant treatment for all patients with rectal cancer, who receive neoadjuvant 5-FU–based chemoradiation, regardless of surgical pathology results. The recently reported German CAO/ARO/AIO-04 trial also revealed the benefit of adding oxaliplatin to both neoadjuvant and adjuvant treatment with significant improvement in DFS of patients with clinically staged cT3-4 or cN1-2 rectal cancer compared with conventional 5-FU–based combined modality regimen.[38]

There were limitations to this study. The data were collected retrospectively and there was no blinding during data collection. It is possible that potential confounding factors like smoking and co-morbidity were inadequately controlled for. Toxicity data were not collected systematically and thus could be underreported. If the data can be collected prospectively, a tailor-made toxicity form will be designed and more toxicity can be captured.

The median follow-up time was relatively short. Magnetic resonance imaging is now a standard staging tool in rectal cancer. The use of MRI as initial staging was only 66.1% in this cohort. Therefore, pre-treatment staging might not accurately reflect the true staging at presentation. In this study, there was limited reporting of late toxicity of radiation such as sexual and sphincter dysfunction. The full extent of the late toxicity of radiation requires longer follow-up. Due to the small sample size, the adjustment of the potential confounding factors for survival was a limitation of the study.

Conclusions

The treatment outcome following nCRT for locally advanced non-metastatic rectal cancer in our experience was comparable with overseas data in terms of local control rate and OS. The high conversion rate from having a threatened circumferential margin to clear resection margin, and the high T and N downstaging rates, suggest that this approach is effective in facilitating surgery to obtain complete surgical clearance. In the subgroup with an intention of sphincter preservation, the conversion rate from APR to sphincter-sparing surgery was high. The rate of acute toxicities was within expectations and manageable and there were no treatment-related deaths.

Appendix

Additional material related to this article can be found on the HKMJ website. Please go to <http://www.hkmj.org>, and search for the article.

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Declaration

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References

1. Hong Kong Cancer Registry. Statistics. Available from: http://www3.ha.org.hk/cancereg/statistics.html. Accessed Aug 2016.
2. Prolongation of the disease-free interval in surgically treated rectal carcinoma. Gastrointestinal Tumor Study Group. N Engl J Med 1985;312:1465-72.
3. Douglass HO Jr, Moertel CG, Mayer R, et al. Survival after postoperative combination treatment of rectal cancer. N Engl J Med 1986;315:1294-5.
4. Krook JE, Moertel CG, Gunderson LL, et al. Effective surgical adjuvant therapy for high-risk rectal carcinoma. N Engl J Med 1991;324:709-15.
5. Fisher B, Wolmark N, Rockette H, 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.
6. Påhlman L, Glimelius B. Pre- or postoperative radiotherapy in rectal and rectosigmoid carcinoma. Report from a randomized multicenter trial. Ann Surg 1990;211:187-95.
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. Improved survival with preoperative radiotherapy in resectable rectal cancer. Swedish Rectal Cancer Trial. N Engl J Med 1997;336:980-7.
9. Martling A, Holm T, Johansson H, Rutqvist LE, Cedermark B, Stockholm Colorectal Cancer Study Group. The Stockholm II trial on preoperative radiotherapy in rectal carcinoma: long-term follow-up of a population-based study. Cancer 2001;92:896-902.
10. Sauer R, Becker H, Hohenberger W, et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. N Engl J Med 2004;351:1731-40.
11. Sauer R, Liersch T, Merkel S, 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.
12. Sebag-Montefiore D, Stephens RJ, Steele R, et al. Preoperative radiotherapy versus selective postoperative chemoradiotherapy in patients with rectal cancer (MRC CR07 and NCIC-CTG C016): a multicentre, randomised trial. Lancet 2009;373:811-20.
13. Kapiteijn E, Marijnen CA, Nagtegaal ID, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. N Engl J Med 2001;345:638-46.
14. Van Gijn W, Marijnen CA, Nagtegaal ID, 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.
15. 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.
16. Ngan SY, Burmeister B, Fisher RJ, et al. Randomized trial of short-course radiotherapy versus long-course chemoradiation comparing rates of local recurrence in patients with T3 rectal cancer: Trans-Tasman Radiation Oncology Group trial 01.04. J Clin Oncol 2012;30:3827-33.
17. Gérard JP, Conroy T, Bonnetain F, 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.
18. Bosset JF, Calais G, Mineur L, 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.
19. Damin DC, Lazzaron AR. Evolving treatment strategies for colorectal cancer: a critical review of current therapeutic options. World J Gastroenterol 2014;20:877-87.
20. Gerard JP, Rostom Y, Gal J, et al. Can we increase the chance of sphincter saving surgery in rectal cancer with

neoadjuvant treatments: lessons from a systematic review of recent randomized trials. Crit Rev Oncol Hematol 2012;81:21-8.
21. Bujko K, Kepka L, Michalski W, Nowacki MP. Does rectal cancer shrinkage induced by preoperative radio(chemo)-therapy increase the likelihood of anterior resection? A systematic review of randomised trials. Radiother Oncol 2006;80:4-12.
22. Dukes CE, Bussey JH. The spread of rectal cancer and its effect on prognosis. Br J Cancer 1958;12:309-20.
23. Gunderson LL, Sosin H. Areas of failure found at reoperation (second or symptomatic look) following "curative surgery" for adenocarcinoma of the rectum: clinicopathologic correlation and implications for adjuvant therapy. Cancer 1974;34:1278-92.
24. Rich T, Gunderson LL, Lew R, Galdibini JJ, Cohen AM, Donaldson G. Patterns of recurrence of rectal cancer after potentially curative surgery. Cancer 1983;52:1317-29.
25. Quirke P, Durdey P, Dixon MF, Williams NS. Local recurrence of rectal adenocarcinoma due to inadequate surgical resection. Histopathological study of lateral tumour spread and surgical excision. Lancet 1986;2:996-9.
26. Merkel S, Mansmann U, Siassi M, Papadopoulos T, Hohenberger W, Hermanek P. The prognostic inhomogeneity in pT3 rectal carcinomas. Int J Colorectal Dis 2001;16:298-304.
27. Birbeck KF, Macklin CP, Tiffin NJ, et al. Rates of circumferential resection margin involvement vary between surgeons and predict outcomes in rectal cancer surgery. Ann Surg 2002;235:449-57.
28. Wibe A, Rendedal PR, Svensson E, et al. Prognostic significance of the circumferential resection margin following total mesorectal excision for rectal cancer. Br J Surg 2002;89:327-34.
29. Bosset JF, Collette L, Calais G, et al. Chemotherapy with preoperative radiotherapy in rectal cancer. N Engl J Med 2006;355:1114-23.
30. Bosset JF, Calais G, Mineur L, et al. Enhanced tumorocidal effect of chemotherapy with preoperative radiotherapy for rectal cancer: preliminary results—EORTC 22921. J Clin Oncol 2005;23:5620-7.
31. Bosset JF, Calais G, Mineur L, et al. Preoperative radiation (Preop RT) in rectal cancer: effect and timing of additional chemotherapy (CT) 5-year results of the EORTC 22921 trial. Proc Am Soc Clin Oncol 2005;23:247S (abstract no. 3505).
32. Bosset JF, Calais G, Daban A, et al. Preoperative chemoradiotherapy versus preoperative radiotherapy in rectal cancer patients: assessment of acute toxicity and treatment compliance. Report of the 22921 randomised trial conducted by the EORTC Radiotherapy Group. Eur J Cancer 2004;40:219-24.
33. Collette L, Bosset JF, den Dulk M, et al. Patients with curative resection of cT3-4 rectal cancer after preoperative radiotherapy or radiochemotherapy: does anybody benefit from adjuvant fluorouracil-based chemotherapy? A trial of the European Organisation for Research and Treatment of Cancer Radiation Oncology Group. J Clin Oncol 2007;25:4379-86.
34. Sainato A, Cernusco Luna Nunzia V, Valentini V, 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.
35. Glynne-Jones R, Counsell N, Quirke P, 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.
36. Hong YS, Nam B, Kim K, et al. Adjuvant chemotherapy with oxaliplatin/5-fluorouracil/leucovorin (FOLFOX) versus 5-fluorouracil/leucovorin for rectal cancer patients whose postoperative yp stage 2 or 3 after preoperative chemotherapy: updated results of 3-year disease-free survival from a randomized phase II study (The ADORE). J Clin Oncol 2014;32(5 Suppl):abstract no. 3502.
37. Hong YS, Nam BH, Kim KP, 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.
38. Rödel C, Graeven U, Fietkau R, 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.