Original Article

Oncologic Outcomes of Neoadjuvant Chemoradiation for Locally Advanced Rectal Cancer: A Single-institution Experience

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Abstract

Introduction: This study reports the outcomes of patients with locally advanced rectal cancer treated with neoadjuvant chemoradiation followed by surgery in a local population of Singapore. Materials and Methods: The records of 85 patients who underwent neoadjuvant chemoradiation for locally advanced rectal cancer followed by surgery at the Tan Tock Seng Hospital (TTSH) between November 2002 and January 2012 were reviewed. The treatment protocol comprised radiotherapy to a total dose of 50.4 Gy concurrent with 5-fluorouracil-based chemotherapy. Patients underwent total mesorectal excision surgery following the completion of neoadjuvant chemoradiation. Local control, disease-free survival and overall survival were analysed using Kaplan-Meier methods. Results: Median age of the patients was 61 years. All of them completed radiotherapy. One patient did not complete neoadjuvant chemotherapy. The median time to surgery was 52 days. Fifty-five percent (47 of 85) of patients achieved pathological downstaging and 13% (11 of 85) of patients had a pathologic complete response to preoperative treatment. The neoadjuvant chemoradiation was well tolerated. Four percent of patients had grade 3 diarrhoea and 4% of them had grade 3 dermatitis. There were no grade 4 toxicities. With a median follow-up of 41 months, the 5-year actuarial local recurrence, disease-free survival and overall survival rates were 7%, 71.9%, and 83.2% respectively. Univariate analysis showed that patients with positive surgical margins had significantly worse disease-free survival and overall survival ($P = 0.012$ and $P < 0.001$ respectively) and a trend towards a higher rate of local recurrence ($P = 0.08$). Conclusion: Our study provides evidence that neoadjuvant chemoradiation is an effective treatment for locally advanced rectal cancer. Our outcomes are comparable with internationally published data and demonstrate the reproducibility of the neoadjuvant approach in an Asian population.

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Key words: Chemoradiotherapy, Preoperative, Rectal carcinoma

Introduction

In Singapore, colorectal cancer is the most common cancer in males and second most common cancer in females, with rectal cancers accounting for 30% to 40% of all colorectal cancers.[1] Local recurrence after treatment of rectal cancer results in significant morbidity and mortality and poses significant management challenges.[2,3] Advances in surgical techniques with the adoption of total mesorectal excision (TME) surgery and improvement in chemoradiation strategies have led to better outcomes but local recurrence remains difficult to manage.[4] The optimal management of locally advanced rectal cancer consists of a combined modality approach with surgery as the cornerstone of cure. Randomised trials in the 1990s have shown that for patients with locally advanced cancer, postoperative chemoradiotherapy improves local control and overall survival.[5,6] Further efforts to improve local control and preserve the function of the anal sphincter have led to the consideration of neoadjuvant approaches.[7,8] The results of a large randomised trial comparing neoadjuvant versus adjuvant chemoradiation clearly demonstrated that toxicity

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is reduced and local control is improved with a neoadjuvant approach, thus representing the prevailing paradigm for treatment at this time.[9]

Since 2002, our institution has adopted neoadjuvant chemoradiation for patients with locally advanced rectal cancer. The purpose of this study is to report the outcomes of patients with locally advanced rectal cancer treated with neoadjuvant chemoradiation followed by surgery in our institution.

Materials and Methods

Patients

The medical records of 102 patients with locally advanced rectal cancer who were planned for neoadjuvant chemoradiation at the Tan Tock Seng Hospital (TTSH) in Singapore from January 2002 to January 2012 were reviewed. The patients were first identified from the radiation oncology department electronic database and further clinical information was obtained from hospital-wide medical records. Patients must have had biopsy-confirmed rectal adenocarcinoma. The tumours must have been locally advanced, defined as T3 or T4 and/or node positive disease and within 15 cm from the anal verge, with (only oligometastasis) or without distant metastases.[10] Low, mid and high rectal tumours were defined as tumours that were ≤5 cm, 5.1 cm to 10 cm and 10.1 cm to 15 cm from the anal verge respectively.[11] Patients who did not undergo surgery, who received previous radiotherapy or those who were treated with palliative intent were excluded. Seventeen patients were excluded from analysis (1 declined radiotherapy, 10 declined surgery, 2 had surgery upfront, 3 had progression of disease after radiation, 1 died of unrelated pneumonia before surgery). Eighty-five patients were eligible for analysis.

Pre-treatment Evaluation

Local tumour and nodal stages were established using magnetic resonance imaging (MRI) or computed tomography (CT) of the pelvis or transrectal ultrasound (TRUS). Distant stage was established with CT of the thorax and abdomen. The 7th edition of the American Joint Committee on Cancer (AJCC) TNM (tumour, node, metastases) staging criteria was used.[10]

Radiotherapy

Three-dimensional conformal radiotherapy was delivered using high energy 6 or 10 MV photons from a linear accelerator. A 3- or 4-beam arrangement was used. The field borders were defined as follows: the superior border was the L5-S1 intervertebral space, the inferior border was the inferior obturator foramen or 2 cm below the inferior edge of the tumour, the lateral border was 1 to 1.5 cm lateral to the pelvic brim, the anterior border was the posterior edge of the pubic symphysis and the posterior border was 1 cm posterior to the sacrum. Boost clinical target volumes (CTV) extended to the entire mesorectum and presacral regions at involved levels, including 2 cm cephalad and caudad in the mesorectum and 2 cm on the gross tumour within the anorectum. Planning target volumes (PTV) included the clinical target volume (CTV) with a 0.5 to 1 cm expansion. All patients received a total pelvic dose of 45 Gy in 25 fractions in 1.8 Gy daily fractions over a period of 5 weeks plus a PTV boost of 5.4 Gy in 3 fractions in 1.8 Gy daily fractions to a total dose of 50.4 Gy. Attempts were made to exclude small bowel from the fields using multileaf collimators and bladder distension. The following dose constraints were applied: whole small bowel <45 Gy, whole bladder <65 Gy, femoral heads V45 Gy (volume that receives 45 Gy) <50%.

Chemotherapy

Seventeen patients received intravenous 5-fluorouracil (5-FU) at a dose of 225 mg/m^2/day as a continuous infusion for 6 weeks. Sixty-seven patients received oral capecitabine at a dose of 825 mg/m^2 twice a day for 5 days a week during the course of radiation. One patient declined neoadjuvant chemotherapy. Seventy-eight (92%) patients received adjuvant chemotherapy in the form of 5-FU or capecitabine for a further 4 to 8 cycles. The reasons for not giving adjuvant chemotherapy were as follows: 2 patients declined, 1 had renal failure, 4 unknown.

Toxicity

Toxicities were recorded using version 3.0 of the Common Terminology Criteria for Adverse Events (CTCAE).[12]

Surgery

Surgery was planned to take place 4 to 8 weeks after completion of chemoradiation. Preoperative imaging was obtained where possible. Total mesorectal excision (TME) was performed for low and mid rectal tumours and wide mesorectal excision (WME) with preservation of the distal rectum for high rectal tumours. Surgery included low anterior resection, ultra low anterior resection and abdominoperineal resection. Postoperative complications were recorded. Pathologic response to neoadjuvant treatment was assessed and recorded. The circumferential resection margin was deemed involved if on histopathological examination, there was tumour at a distance of 1 mm or less from the margin.[13]

Follow-up

Patients were followed-up with 3-monthly history and physical examination for 2 years, then 6-monthly up to 5 years and annually thereafter. Full blood count, renal panel, liver function and carcinoembryonic antigen (CEA) tests were performed every 3 to 6 months for the first 2 years and 6-monthly CEA obtained till at least 5 years. CT of the thorax, abdomen and pelvis were performed yearly for at least the first 2 years from treatment. Colonoscopy was performed within a year from surgery for patients who had anterior resection. Local recurrence was determined either via colonoscopy plus biopsy or radiologically. Distant recurrence was determined radiologically.

Statistics

Recurrence and survival were analysed according to the Kaplan-Meier method. Univariate analysis was carried out on factors that potentially might influence the outcomes. The Cox regression model was used to compare survival estimates and to calculate *P* values and hazard ratios, with a *P* value of <0.05 considered statistically significant. The IBM SPSS version 19.0 software (SPSS Inc., Illinois, USA) was used for generating the statistical values and curves.

Results

Patients

Between 2002 and 2012, 85 patients with locally advanced rectal cancer received neoadjuvant chemoradiation followed by surgery. Median follow-up was 41 months (range, 4 to 120 months). The patient characteristics are summarised in Table 1.

Surgery

The median time from completion of chemoradiation to surgery was 52 days (range, 19 to 179 days). The upper limit of this range was 179 days due to 1 patient's delay in surgery because of concurrent coronary artery disease. Sixty-three percent of patients had preoperative imaging in the form of CT, while 16% of them had MRI, 1% had TRUS and 20% did not have any. The median time to performing preoperative imaging was 30 days (range, 13 to 120 days) from the completion of radiation. One patient had preoperative imaging done 13 days prior to completion of radiotherapy as part of the inpatient investigations for grade 3 diarrhoea. Twenty-six patients had abdominoperineal resection, 51 had low anterior resection, 6 had Hartmann's procedure, 1 had total proctectomy and 1 had exenteration. Sphincter preservation rate was 60%. TME was performed in 81 patients with low to mid rectal tumours and WME on 4 patients with high rectal tumours. Clear resection margins were achieved in 85% of patients. There was no perioperative mortality. The median time from surgery to hospital discharge was 6 days (range, 2 to 27 days). One patient had anastomotic leak, 2 had wound infection, 2 had postoperative sepsis, 3 had postoperative ileus that were conservatively managed and 1 had high stoma output.

Pathologic Response and Downstaging

Table 2 shows the downstaging effects of chemoradiation on the tumour and lymph nodes. Histopathological examination was performed on all the surgical specimens. Eleven patients (13%) achieved pathological complete response (pCR), of which 8 had a preoperative TNM stage of III and 3 had a preoperative stage of II. For T stage, 34% of cT2, 28% of cT3 and 55% of cT4 tumours were downstaged by chemoradiation. For N stage, 62% of cN1 tumours and 83% of cN2 tumours were downstaged. Overall, taking into account both T and N stages, 55% of patients were downstaged.

Table 1. Patient Characteristics

Characteristics	**n = 85 (%)**	
Sex	M	66 (78)
	F	19 (82)
Age (years)	Median	61
	Range	29 – 82
Race	Chinese	72 (84)
	Malay	7 (8)
	Indian	3 (4)
	Others	3 (4)
ECOG performance score	0 – 1	83 (98)
	2	2 (2)
Pre-chemoradiation staging modality	MRI	39 (46)
	CT	40 (47)
	TRUS	6 (7)
Pre-chemoradiation TNM stage	II	19 (22)
	III	62 (73)
	IVA	4 (5)
Rectal tumour location	Low	48 (56)
	Mid	33 (39)
	High	4 (5)
Chemotherapy regimen	Capecitabine	Capecitabine
	5FU	5FU
	None	None
Type of resection	Abdominoperineal	26 (31)
	Low anterior	51 (60)
	Hartmann	6 (7)
	Others	2 (2)

5FU: 5-Fluorouracil; CT: Computed tomography; ECOG: Eastern Cooperative Oncology Group; MRI: Magnetic resonance imaging; TNM: Tumour, node, metastasis; TRUS: Transrectal ultrasonography

Table 2. Preoperative TNM Staging and Tumour Downstaging After Neoadjuvant Chemoradiation

Preoperative Stage (Clinical and/or Radiological)	n = 85 (% of Study Population)	Postoperative Stage (Pathological)	n (% of Preoperative Stage)
T2	6 (7%)	T0	1 (17%)
		T1	1 (17%)
		T2	2 (33%)
		T3	2 (33%)
T3	69 (81%)	T0	8 (12%)
		T1	3 (4%)
		T2	8 (12%)
		T3	49 (71%)
		T4	1 (1%)
T4	9 (11%)	T0	1 (11%)
		T1	0 (0%)
		T2	2 (22%)
		T3	2 (22%)
		T4	4 (45%)
Tx	1 (1%)	T3	1 (100%)
N0	19	N0	14 (74%)
		N1	5 (26%)
N1	48	N0	30 (62%)
		N1	10 (21%)
		N2	8 (17%)
N2	18	N0	8 (44%)
		N1	7 (39%)
		N2	3 (17%)
M0	81	-	-
M1 (oligometastases)	4	-	-

TNM: Tumour, node, metastases

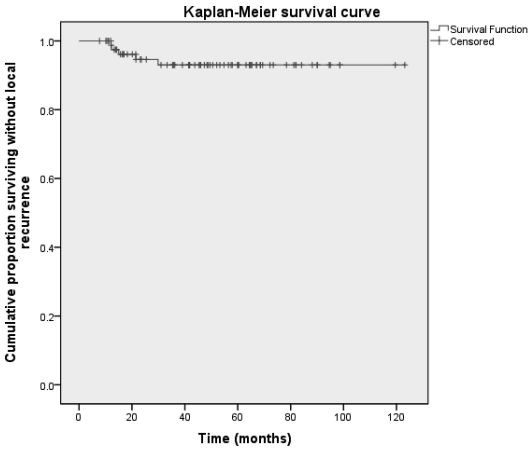

Fig.1. Local recurrence-free survival in 85 patients who received neoadjuvant chemoradiation.

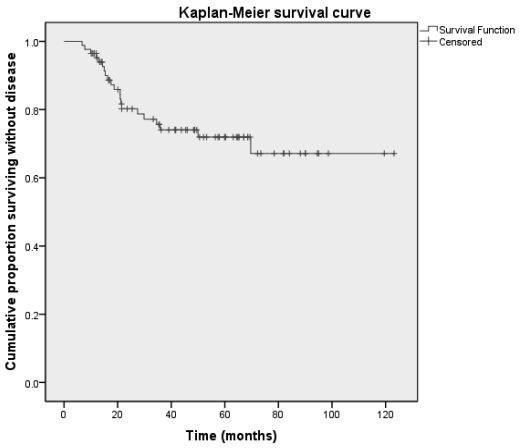

Fig. 2. Disease-free survival in 85 patients who received neoadjuvant chemoradiation.

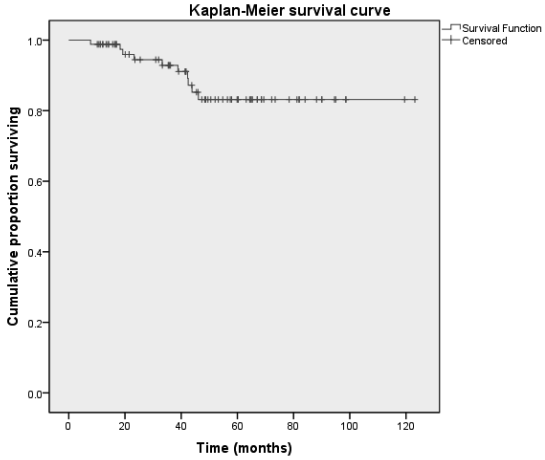

Fig. 3. Overall survival in 85 patients who received neoadjuvant chemoradiation.

Local Recurrence and Survival

Only one patient was lost to follow-up. Five patients developed local recurrence. The actuarial 5-year local recurrence rate was 7% (Fig. 1). Twenty patients developed distant metastasis. The main sites of metastases were lung, liver and bone. At the end of the follow-up period, 10 patients have died. The 5-year actuarial disease-free survival and overall survival rates were 71.9 % and 83.2% respectively (Figs. 2 and 3).

Univariate Analysis

Cox regression analysis was performed on factors that might potentially have an impact on local recurrence and survival. Factors analysed were age, gender, pre-chemoradiation carcinoembryonic antigen (CEA) level, chemotherapy regimen, pathologic node positivity, surgical margins and presence of tumour downstaging (Table 3). Age and gender were found to have no influence on local recurrence and survival (data not shown). A raised CEA

level prior to chemoradiation did not have an impact on local recurrence and survival. For chemotherapy regimen, patients who were treated in the earlier years (from 2002 to 2007) received intravenous 5-FU while patients who were treated from 2007 to 2012 received oral capecitabine. Our analysis did not demonstrate any statistical difference in local recurrence and survival between patients who received the 2 regimens. Patients with positive circumferential margins had significantly worse disease-free survival and overall survival, with a trend towards higher rate of local recurrence. For T-stage, downstaging by neoadjuvant chemoradiation resulted in statistically significant improved overall survival and a trend towards improved local control and disease-free survival. Pathologic node positivity did not have an influence on local recurrence and survival. Pathologic complete remission, which was achieved in 11 patients, was not associated with improved local control and survival.

Toxicity

All patients completed the prescribed course of radiotherapy. One patient declined neoadjuvant chemotherapy. Table 4 shows the acute toxicities of the patients. The neoadjuvant regimen was well tolerated with no grade 4 acute toxicities recorded. Three (4%) patients had grade 3 diarrhoea. Three (4%) patients had grade 3 dermatitis. Four (5%) patients had grade 3 haematological toxicities. Overall, grade 3 acute toxicities were found in 8 patients (9%). For late toxicities, 4 (5%) patients had grade 3 toxicities (2 anastomotic strictures, 1 urethrorectal fistula, 1 small bowel adhesions). No patients had grade 4 late toxicities.

Discussion

This is the first paper to date to report the oncologic results of neoadjuvant chemoradiation for rectal cancer in a local

Table 3. Factors Affecting Local Recurrence and Survival by Univariate Analysis

Variable	Local Recurrence		Disease-free Survival		Overall Survival	
	P Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)
Raised CEA	0.628	1.72 (0.19 – 15.42)	0.978	0.99 (0.37 – 2.60)	0.647	0.74 (0.21 – 2.65)
Chemotherapy regimen	0.214	NA*	0.128	2.87 (0.74 – 11.14)	0.050	NA*
Margin positivity	0.080	4.76 (0.79 – 28.61)	0.012	3.36 (1.30 – 8.72)	<0.001	12.80 (3.54 – 46.32)
T-downstaging	0.076	NA*	0.054	0.34 (0.11 – 1.02)	0.012	NA*
Node positivity	0.302	2.56 (0.42 – 15.35)	0.476	1.37 (0.58 – 3.26)	0.710	1.27 (0.36 – 4.52)
Pathological complete response	0.369	NA*	0.564	0.65 (0.15 – 2.80)	0.219	NA*

CEA: Carcinoembryonic antigen; CI: Confidence interval; HR: hazard ratio; NA: Not applicable
*Hazard ratio is not applicable as there was no event in one category of the analysed variable.

Table 4. Acute Toxicities Associated with Neoadjuvant Chemoradiation*

	Grade n (%)				
	0	1	2	3	4
Nausea/vomiting	84 (99)	1 (1)	0 (0)	0 (0)	0 (0)
Diarrhoea	23 (27)	45 (53)	14 (16)	3 (4)	0 (0)
Cystitis	40 (47)	39 (46)	6 (7)	0 (0)	0 (0)
Dermatitis	20 (23)	38 (45)	24 (28)	3 (4)	0 (0)
Haematological	45 (53)	22 (26)	14 (16)	4 (5)	0 (0)

*Multiple toxicities in the same patient scored as separate events

population in Singapore. Following the conclusive results of the landmark German Rectal Cancer Trial, neoadjuvant chemoradiation for locally advanced rectal cancer has become increasingly accepted in our institution and today, it is the standard of care. This trend has been paralleled by a decrease in the number of patients who received upfront surgery and adjuvant chemoradiation.

The results from our study are consistent with internationally published data. The German Rectal Cancer Trial reported a 5-year local relapse rate of 6% in the preoperative arm and the 5-year overall survival rate was 76%. In that same arm, grade 3 or 4 toxicities occurred in 27% of patients. We treated patients with similar a regimen consisting of 50.4 Gy of radiation delivered in fractions of 1.8 Gy per day with concurrent 5-FU based chemotherapy. The median time from completion of chemoradiation to surgery in our study was 52 days, which was similar to the duration of 6 weeks in the German Rectal Cancer Trial. All patients underwent TME or WME surgery. Median follow-up was also similar. We report a comparable local recurrence rate of 7% and 5-year overall survival rate (83.2%) and lower rates of acute and long term grade 3 toxicities (9% and 5% respectively). The preoperative regimen was well tolerated and the compliance rate in our study was 99%.

The number of patients that had MRI staging was 47%. Before 2008, the majority of patients had staging with CT or EUS. The ability of MRI in staging rectal cancer is now well established.[14] The use of MRI for staging is now the standard of care in our institution.

The favourable influence of tumour downstaging has been demonstrated in various studies.[15,16] In our subgroup analysis, we found a statistically significant improvement in survival rates with T-downstaging. Nodal positivity on surgical specimens has been shown to be a significant predictor of long-term oncologic outcomes.[17] However, we were not able to demonstrate this. This could be due to the small number of patients in our subgroup analysis to demonstrate an effect. We demonstrated that patients with positive margins had significantly worse disease-free survival and overall survival, with a trend towards higher rate of local recurrence. This is in line with results from various large studies which have shown the influence of circumferential resection margins as an independent determinant of local recurrence and survival.[18,19] Although preoperative radiotherapy has been shown to reduce local recurrence, the benefit of radiotherapy has not been proven to be significantly greater in patients with positive circumferential margins.[20] This implies that radiotherapy does not make up for the poorer outcomes associated with having positive resection margins.

The pCR rate in our study was 13%. This was consistent with the results from Sauer et al.[9] Although we did not demonstrate better local control and survival in patients with pCR likely because of a small sample size, other studies have raised the prospect of cure from just chemoradiation alone and whether patients with pCR can be spared the surgical procedure.[20,21] However, there is currently no conclusive evidence for eliminating surgery from the management of patients with pCR. The determination of complete clinical responders from clinical assessment is a complex issue and studies are needed to look at standardisation of clinical assessment of response. Future research will need to explore radiological or molecular markers to predict which group of patients is likely to be complete responders to neoadjuvant treatment.

Another area of research potential is on dose escalation in preoperative radiation to locally advanced rectal cancers. Some studies have demonstrated encouraging results in using a higher dose by employing intensity-modulated radiotherapy (IMRT) methods.[22,23] There are ongoing trials addressing the issue of dose escalation and the results are awaited. Favourable results from these dose escalation trials will further improve local control of rectal cancers, the recurrence of which remains a difficult management issue for both physicians and patients.

The chemotherapy regimen used by the German Rectal Cancer Group was infusional 5-FU. Capecitabine has been shown to be equivalent to intravenous 5-FU in terms of local recurrence rates and was non-inferior to 5-FU for 5-year overall survival rates.[24] There was also less leucopenia with capecitabine. As capecitabine gained popularity on the background of evidence for its efficacy and safety profile, coupled with the relative ease of its administration, its use in our patients increased. In our study, 17 patients (20%) had intravenous 5-FU while 67 (79%) patients had oral capecitabine. Our subgroup analysis did not demonstrate any difference in outcomes between intravenous 5-FU and capecitabine use.

The German Rectal Cancer Trial highlighted the lack of effect on survival with neoadjuvant chemoradiation, highlighting the need for better systemic therapy. Five-FU based regimens given concurrent with radiotherapy is the current standard of care. The addition of oxaliplatin during radiotherapy did not show any benefit, nor did the addition of irinotecan.[25,26] There are no phase III randomised studies demonstrating the efficacy of targeted agents. In the adjuvant setting, 5-FU-based regimens are widely used based on recommendations by the National Cancer Comprehensive Network (NCCN) guidelines, although the optimal adjuvant regimen is still yet to be determined.[27] With excellent local control rates using neoadjuvant chemoradiation, the search for better systemic therapy to address the issue of micrometastases and distant failure has become important and future research will have to focus on this.

Conclusion

In conclusion, our study confirmed that neoadjuvant chemoradiation with single agent chemotherapy with 5-FU or capecitabine is an effective treatment for locally advanced rectal cancer. A high rate of local control was shown with low rates of toxicities. The outcomes of our study are comparable to internationally published data. This study also shows the reproducibility of the results in a local population of Singapore, thus lending credence for its widespread adoption worldwide. For these reasons, we advocate and have adopted the neoadjuvant approach for the management of locally advanced rectal cancer.

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