Hong Kong J Radiol. 2014;17:255-66 | DOI: 10.12809/hkjr1414235

ORIGINAL ARTICLE

Five-year Treatment Outcomes for Stage II to III Rectal Cancer in a Single Cancer Institution

KC Lee[1], ATY Chang[1], ALY Law[1], LK Chan[1], HYS Cheung[2], WT Ng[1]

Departments of [1]Clinical Oncology and [2]Surgery, Pamela Youde Nethersole Eastern Hospital, Chai Wan, Hong Kong

ABSTRACT

Objective: *This study aimed to find out the survival and recurrence rates following curative treatments for stage II and III rectal adenocarcinoma.*

Methods: *Between 1 January 2002 and 31 December 2007, 344 patients with stage II or III rectal cancer treated with curative intent were retrospectively reviewed in our institution. Treatment methods, survival outcomes, and the patterns of failure were analysed.*

Results: *Among this patient cohort, 193 patients received total mesorectal excision (TME) surgery and 146 had non-TME surgery. Of the patients, 83 underwent neoadjuvant radiotherapy or chemoradiotherapy, whereas 261 received surgery without neoadjuvant treatment. The overall survival rate and local recurrence rate of the entire group at 5 years was 66.1% and 14.4%, respectively. Patients with TME surgery had significantly lower local recurrence rate (9.7%) than those with non-TME surgery (20.1%; p = 0.01). There was a trend for superior 5-year overall survival (70.6% vs. 61.9%; p = 0.09). The 5-year disease-free survival (61.4% vs. 48.2%; p = 0.025) was significantly improved in the TME versus non-TME groups. Clear surgical margins and the use of adjuvant therapy were associated with better overall survival. Routine preoperative local staging of patients was inadequate, with only 31.7% of patients having received endorectal ultrasound or pelvic magnetic resonance imaging before operation.*

Conclusion: *Increased adoption of TME surgery, clear surgical margins, and the use of adjuvant therapy are important factors for improving the treatment outcomes for stage II and III rectal cancer. An adequate preoperative local staging is also recommended.*

Key Words: *Chemotherapy, adjuvant; Prognosis; Rectal neoplasms; Rectum/surgery; Treatment outcome*

中文摘要

單中心二、三期直腸癌五年治療結果報導

李建忠、張天怡、羅麗柔、陳麗君、張睿珊、吳偉棠

目的：探討二、三期直腸腺癌根治性治療的生存率和復發率。

方法：回顧性分析2002年1月1日至2007年12月31日本中心二、三期直腸癌根治性治療，患者共344例。分析其治療方法、生存結果和失敗模式。

Correspondence: *Dr Amy TY Chang, Department of Clinical Oncology, Pamela Youde Nethersole Eastern Hospital, 3 Lok Man Road, Chai Wan, Hong Kong.*
Tel: (852) 2595 4175; Fax: (852) 2904 4526; Email: changty@ha.org.hk

Submitted: 6 Mar 2014; Accepted: 26 Jun 2014.

© 2014 Hong Kong College of Radiologists

結果：患者中，193例進行全直腸系膜切除術（TME），146例未行TME；83例接受新輔助放療或放化療，261例行單純手術，未接受新輔助治療。全組五年總生存率和局部復發率分別為66.1%和14.4%。接受TME的患者局部復發率明顯降低（TME組9.7%，非TME組20.1%，p = 0.01）。接受TME的患者五年總生存率有提高的趨勢（TME組70.6%，非TME組61.9%，p = 0.09），五年無病生存率也明顯改善（TME組61.4%，非TME組48.2%，p = 0.025）。手術切緣淨和輔助治療可提高總生存率。患者術前的常規局部分期不足，僅31.7%的患者術前曾接受直腸內超聲或盆腔磁共振成像檢查。

結論：推廣TME、手術切緣淨及聯合輔助治療是提高二、三期直腸腺癌療效的重要因素。建議完善術前局部分期。

INTRODUCTION

Colorectal carcinoma is a major malignancy in developed countries. In Hong Kong, colorectal carcinoma is the commonest cancer, accounting for 16.5% of all cancers. There were 4450 new cases in 2011, and the incidence has been rising in the past 10 years. This disease also ranked second in terms of cancer mortality in Hong Kong, accounting for 14.4% of cancer deaths in 2011.[1] The Hong Kong Cancer Registry does not have separate statistics for colon cancer and rectal cancer. However, around one-third of colorectal carcinoma arises from the rectum.[2] Definition of rectal cancer is controversial; some define it as tumour lying below the peritoneal reflection, while others define it by adopting a specific distance from the anal verge.[3] Compared with colon cancer, local recurrence is more common in rectal cancer and, hence, poses a real concern following its treatment. Radiotherapy (RT), before or after operation, is an important adjunctive treatment in the management of rectal cancer. Multiple clinical trials have demonstrated that neoadjuvant RT / chemo-radiotherapy (CRT) or adjuvant CRT improves local control and survival.[4-9] However, the treatment philosophy and pattern of care have changed dramatically during the last decade since the introduction of total mesorectal excision (TME).[10] Multiple studies have subsequently produced impressive results in achieving low local failure rates following TME, and this has become a widely adopted surgical technique.[11-13] The clinical data in Hong Kong based on these approaches are sparse.

The objective of this article was to report the clinical outcomes of patients with stage II and III rectal carcinoma treated with a curative intent at the Department of Clinical Oncology, Pamela Youde Nethersole Eastern Hospital, Hong Kong. The roles of TME, neoadjuvant / adjuvant therapy, and impact of surgical margins on the treatment outcome were also evaluated.

METHODS

All patients with stage II or III rectal carcinoma referred to the Department of Clinical Oncology, Pamela Youde Nethersole Eastern Hospital, between 1 January 2002 and 31 December 2007, and who received treatment with curative intent were included and retrospectively analysed. These included patients who had already received curative surgery and were referred to us for consideration of adjuvant therapy, and also those who were referred for neoadjuvant therapy before operation. All patients had histologically confirmed rectal adenocarcinoma.

Following curative resection, pathological staging was reported according to the 6th edition of American Joint Committee on Cancer Staging System.[14] For patients who were referred for neoadjuvant treatment, apart from assessing the mobility of the primary tumour, clinical T and N stages were assessed using endorectal ultrasound (ERUS), computed tomography (CT), magnetic resonance imaging (MRI), and / or physical findings. However, for those who underwent surgery without neoadjuvant therapy, there was no consistent policy on preoperative local staging investigation.

Tumour locations were classified as low, middle, and high lying for 0-5 cm, >5-10 cm, and >10 cm from the anal verge, respectively, according to the measurement at colonoscopy or during operation. There is no definite cutoff for the upper limit of high rectal cancer. In our study, among the 85 patients with upper rectal cancer, 52 were within 11-15 cm from the anal verge; 23 patients had tumours of >15 cm from the anal verge, although they were defined by the surgeon as rectal cancer due to its location below the peritoneal

reflection. Ten patients were defined as having upper rectal cancer from surgical and consultation notes, but with insufficient detail regarding the exact location of the tumour.

Surgical procedures included anterior resection (AR) or low anterior resection (LAR) with TME, AR or LAR without TME, abdominoperineal resection (APR) with TME, APR without TME, and other miscellaneous resections (others). Circumferential resection margins on pathology report were classified as either clear (>1 mm margin) or involved (≤1 mm margin).

Treatment Methods

There was no consistent referral policy for neoadjuvant therapy during the study period; the indication of neoadjuvant therapy was largely determined by the referring surgeon. Our preferred neoadjuvant therapy was CRT if patients were medically fit, and the commonest indication for requesting neoadjuvant therapy was unresectable disease. Therefore, the majority of these patients had clinically advanced T3 / T4 and / or node-positive disease.

For patients referred after surgery, adjuvant therapy was offered to all stage II and III patients if they were medically fit. CRT was our preferred adjuvant therapy at that time based on the National Cancer Institute Consensus Conference.[15] However, adjuvant chemotherapy alone was given if patients refused RT or if the patients had undergone TME surgery with clear margins. RT alone was given to a small number of patients with significant medical comorbidities or with advanced age, who were considered to have high risk of local relapse.

The standard chemotherapy during the study period was 5-fluorouracil/folinic acid (5FU/FA) which was based on treatment arm 3 of the US Intergroup 0144 trial.[16] We aimed at delivering 6 cycles of chemotherapy. The neoadjuvant and adjuvant CRT are shown in Figure 1.

Neoadjuvant or adjuvant pelvic RT was delivered using a conventional 3-field technique utilising one posterior and two lateral 6 MV photon beams. RT comprised whole-pelvic irradiation followed by boosting with smaller fields. Typically, the whole-pelvic field covered the upper border of L5 down to the obturator foramen and at least 3 cm below the primary tumour, or the

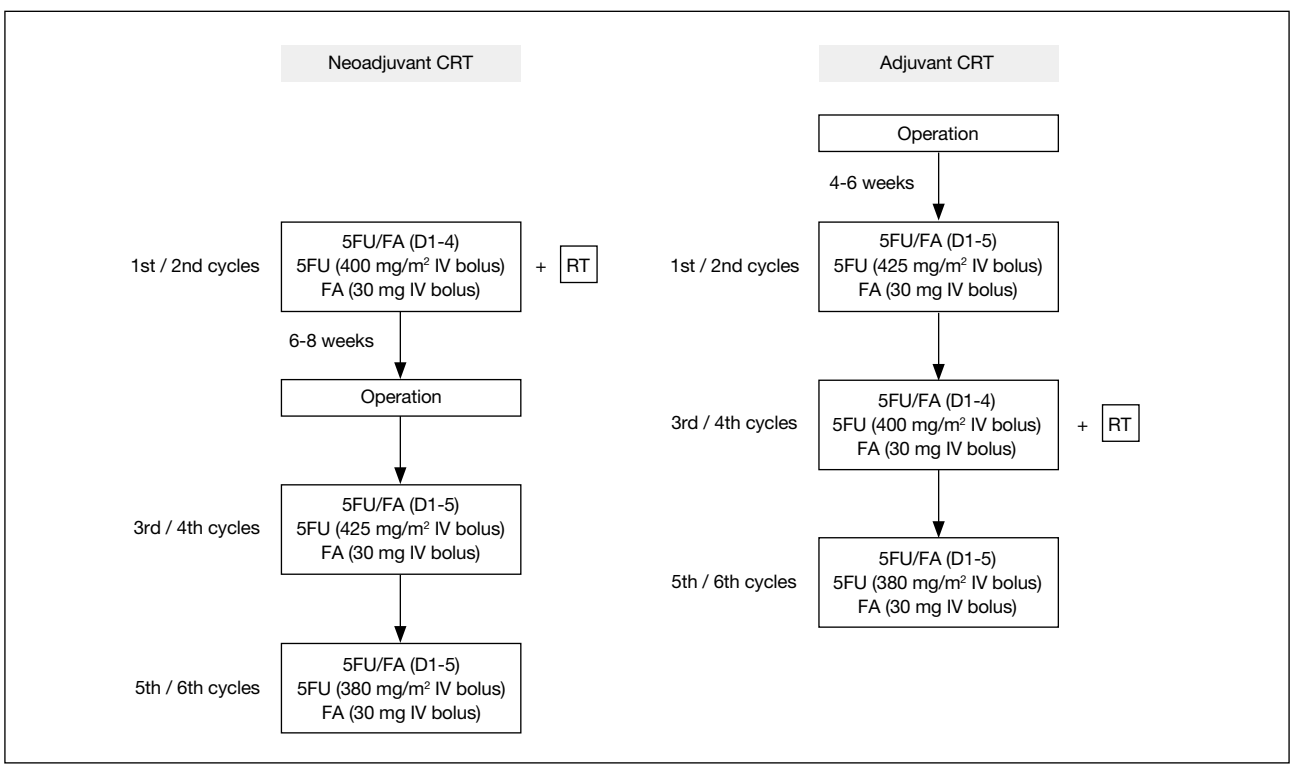

Figure 1. The neoadjuvant and adjuvant CRT.
Abbreviations: CRT = chemoradiotherapy; D = day; 5FU/FA = 5-fluorouracil/folinic acid; IV = intravenous; RT = radiotherapy.

whole perineal scar in patients who had undergone APR. The lateral border was 1.5 cm lateral to the widest bony margin of the true pelvic sidewall. The anterior border was put in front of the pubic symphysis (except for T3N0 tumour for which the anterior border was behind the pubic symphysis). The posterior border covered the whole sacrum. For the boost fields, the anterior border was moved posteriorly to cover the posterior vaginal wall in female patients, and to cover half of the acetabulum in male patients. The dose per fraction was 1.8 to 2.0 Gy. The whole pelvis received 45 to 50 Gy, and then the boosted region received up to 50.4 to 54 Gy.

Depending on application of RT, chemotherapy, and their orders in relation to surgery, oncological treatments were classified into the following types: neoadjuvant CRT, adjuvant CRT, neoadjuvant RT alone, adjuvant RT alone, adjuvant chemotherapy alone, and no adjuvant therapy.

Endpoints

Time to any recurrence was defined as the time from histological diagnosis to the date of any recurrent disease. The time to the first defining event was assessed for the following end-points: local recurrence rate (any recurrence within the anatomical pelvis), disease-free survival rate (DFS; recurrence at any site), and overall survival rate (OS; death due to any cause). The actuarial rates were calculated with the Kaplan Meier method, and the differences were compared with the log rank test. Cox proportional hazards model was used for multivariate analyses for significant factors.

All statistical tests used two-sided p values with alpha level of 0.05 as significant. All statistical analyses were performed with SPSS version 12.0 (SPSS Inc.).

RESULTS

Patient Characteristics

A total of 344 patients with stage II and III rectal cancer who received curative treatments in our department were included for analysis. The median age at the time of diagnosis was 63 (range, 27-88) years; 63% of patients were male. The median duration of follow-up was 5.2 (range, 0.1-10.4) years. Staging CT was performed prior to treatment in all patients. Only 102 (29.7%) patients from the whole cohort had preoperative ERUS, and only 7 (2.0%) patients had preoperative MRI of the pelvis. Among patients planning for neoadjuvant therapy, 48 (57.8%) out of 83 had undertaken ERUS.

Overall, 83 patients received neoadjuvant therapy. Clinical T3/T4 tumours accounted for 94% among this group of patients. Five patients with low-lying cT2 tumour were referred for sphincter preservation; 57.8% of these patients also had clinically node-positive disease (Table 1). Approximately 47% of these patients had low-lying tumours, 49.4% had middle-lying tumours, and 3.6% had high-lying tumours. Among this group of patients, two were referred to us for neoadjuvant therapy after attempted resections showed inoperable disease. Two patients in this group did not undergo subsequent definitive surgery: one of them died of pneumonia during neoadjuvant RT, and the

Table 1. Characteristics of patients receiving neoadjuvant therapy before surgery (n = 83).

	Data*
Mean (range) age (years)	60 (67-88)
Male gender	61 (73.5%)
cT stage	
2	5 (6.0%)
3	48 (57.8%)
4	30 (36.1%)
cN stage	
N-	35 (42.2%)
N+	48 (57.8%)
Level	
Upper	3 (3.6%)
Middle	41 (49.4%)
Low	39 (47.0%)
Neoadjuvant therapy	
Neoadjuvant RT	10 (12.0%)
Neoadjuvant CRT	73 (88.0%)
Surgery	
TME	53 (63.9%)
Non-TME	26 (31.3%)
Miscellaneous operation	2 (2.4%)
No surgery	2 (2.4%)
Margin	
Clear	73 (88.0%)
Positive	9 (10.8%)
Unknown	1 (1.2%)
yp T stage	
0	6 (7.2%)
1	2 (2.4%)
2	12 (14.5%)
3	52 (62.7%)
4	9 (10.8%)
Missing	2 (2.4%)
yp N stage	
0	44 (53.0%)
1	26 (31.3%)
2	11 (13.3%)
Missing	2 (2.4%)

Abbreviations: CRT = chemoradiotherapy; RT = radiotherapy; TME = total mesorectal excision; yp = pathological data following therapy be it prior to surgery or as a primary treatment.

* Because of rounding, not all percentages total 100.

other died of neutropenic sepsis just upon completion of neoadjuvant CRT. As the majority of these patients had advanced local disease on presentation, positive resection margins were relatively high (10%) despite neoadjuvant therapy. However, downstaging was also seen for some patients following neoadjvuant therapy. On pathological assessment of the resected tumours, the proportion of T4 disease decreased from 36.1% to 10.8%, and that of node-positive disease decreased from 57.8% to 45.7%. Six patients had pathologically complete response (Table 1).

Overall, 261 patients were referred to us from the surgeon after curative surgery (Table 2). The percentages of pathological T1, T2, T3 and T4 tumours were 0.8%, 8.8%, 75.9%, and 14.6%, respectively. Approximately 66% had pathological node-positive disease. Among this group of patients, 28.4%, 39.1%, and 31.4% had low-, middle- and high-lying tumours, respectively. The information on tumour location was not available for 3 (1.1%) patients. Although adjuvant therapy was routinely offered, 22% of the patients did not receive any form of adjuvant therapy. This was predominantly due to old age, suboptimal performance status, multiple medical comorbidities, or patient preference.

A comparison of patients receiving TME versus non-TME surgery after neoadjuvant therapy and upfront surgery is shown in Tables 3 and 4, respectively. Results

Table 2. Characteristics of patients receiving upfront surgery (n = 261).

	Data*
Mean age (range)	62.4 (28-85)
Male gender	154 (59.0%)
pT stage	
1	2 (0.8%)
2	23 (8.8%)
3	198 (75.9%)
4	38 (14.6%)
pN stage	
N0	89 (34.1%)
N1	99 (37.9%)
N2	73 (28.0%)
Level	
Upper	82 (31.4%)
Middle	102 (39.1%)
Low	74 (28.4%)
Missing	3 (1.1%)
Surgery	
TME	140 (53.6%)
Non-TME	120 (46.0%)
Miscellaneous operation	1 (0.4%)
Margin	
Clear	252 (96.6%)
Positive	7 (2.7%)
Unknown	2 (0.8%)
Adjuvant therapy	
Nil	58 (22.2%)
RT alone	19 (7.3%)
Chemo alone	101 (38.7%)
CRT	83 (31.8%)

Abbreviations: CRT = chemoradiotherapy; RT = radiotherapy; TME = total mesorectal excision.
* Because of rounding, not all percentages total 100.

Table 3. Comparison of patient and tumour characteristics in the TME and non-TME surgery groups after neoadjuvant therapy (n = 83).*

	Non-TME (n = 26)	TME (n = 53)	p Value
Mean (range) age (years)	58.3 (27-88)	60.6 (40-81)	0.36
Male gender	22 (84.6%)	36 (67.9%)	0.12
cT stage			0.18
cT1-2	3 (11.5%)	2 (3.8%)	
cT3-4	23 (88.5%)	51 (96.2%)	
cN stage			0.37
cN0	9 (34.6%)	24 (45.3%)	
cN+	17 (65.4%)	29 (54.7%)	
Level			0.77
Upper	14 (53.8%)	24 (45.3%)	
Middle	11 (42.3%)	27 (50.9%)	
Low	1 (3.8%)	2 (3.8%)	

Abbreviation: TME = total mesorectal excision.
* Two patients did not undergo operation after neoadjuvant treatment; one patient received pelvic exenteration, another total proctocolectomy, and hence not classified into TME or non-TME group.

Table 4. Comparison of patient and tumour characteristics in the TME and non-TME groups receiving upfront surgery (n = 261).

	Non-TME (n = 120)	TME (n = 140)	p Value
Mean age (range)	62.9 (28-85)	62.0 (20-82)	0.44
Male gender	69 (57.5%)	84 (60.0%)	0.68
pT stage*			0.195
T1-2	9 (7.5%)	16 (11.4%)	
T3-4	111 (92.5%)	124 (88.6%)	
pN stage*			0.15
N0	46 (38.3%)	42 (30.0%)	
N1	47 (39.2%)	52 (37.1%)	
N2	27 (22.5%)	46 (32.9%)	
Level†			<0.001
Upper	36 (30.3%)	38 (27.5%)	
Middle	30 (25.2%)	72 (52.2%)	
Low	53 (44.5%)	28 (20.3%)	
Missing	1	2	

Abbreviation: TME = total mesorectal excision.
* One patient had missing operation record after surgery in China, and therefore was not classified into TME or non-TME group.
† Three patients had missing information about the level of rectal tumour.

did not show any significant difference in patient and tumour characteristics among the two groups, except for the patients receiving upfront surgery (n = 261) in whom the level of tumour did correlate significantly with the type of surgery performed (p < 0.001). However, this particular finding may be due to selection bias and surgeon preference, and it should be treated as a limitation of this retrospective review.

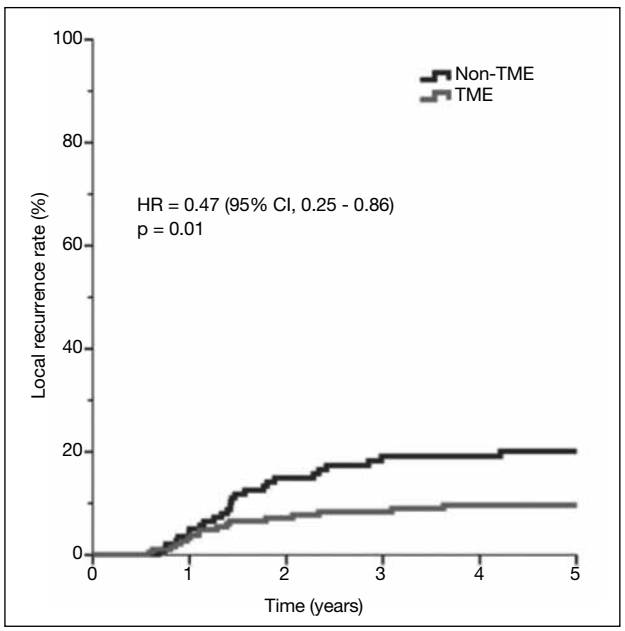

Figure 2. Local recurrence rate for the whole group according to the nature of surgery.
Abbreviations: CI = confidence interval; HR = hazard ratio; TME = total mesorectal excision.

Treatment Outcomes

Of all the 342 patients who underwent curative surgery, TME was performed in 56.4% (52% AR, 4.4% APR) while non-TME was performed in 42.7% (28.7% AR, 14.0% APR). Miscellaneous operations were carried out in three patients (pelvic exenteration in one, total proctocolectomy in one, and unknown operation in one patient in China) and these were not analysed according to the TME results. Sixteen (4.7%) patients showed involvement of the circumferential margin. No information on margin status was available for three patients.

At their last follow-up, 205 (59.6%) patients were alive. Recurrence of any type was identified in 135 (39.2%) patients — among them 46 (13.4%) developed local recurrence, and 111 (32.3%) developed distant recurrence. The 5-year OS and DFS rates were 66.1% and 55.2%, respectively. The 5-year local recurrence rate was 14.4%. Overall, after excluding the two patients who died during neoadjuvant therapy and three patients with miscellaneous operations, patients treated with TME had significantly lower local recurrence rate (9.7%) than those with non-TME surgery (20.1%; p = 0.01; Figure 2).

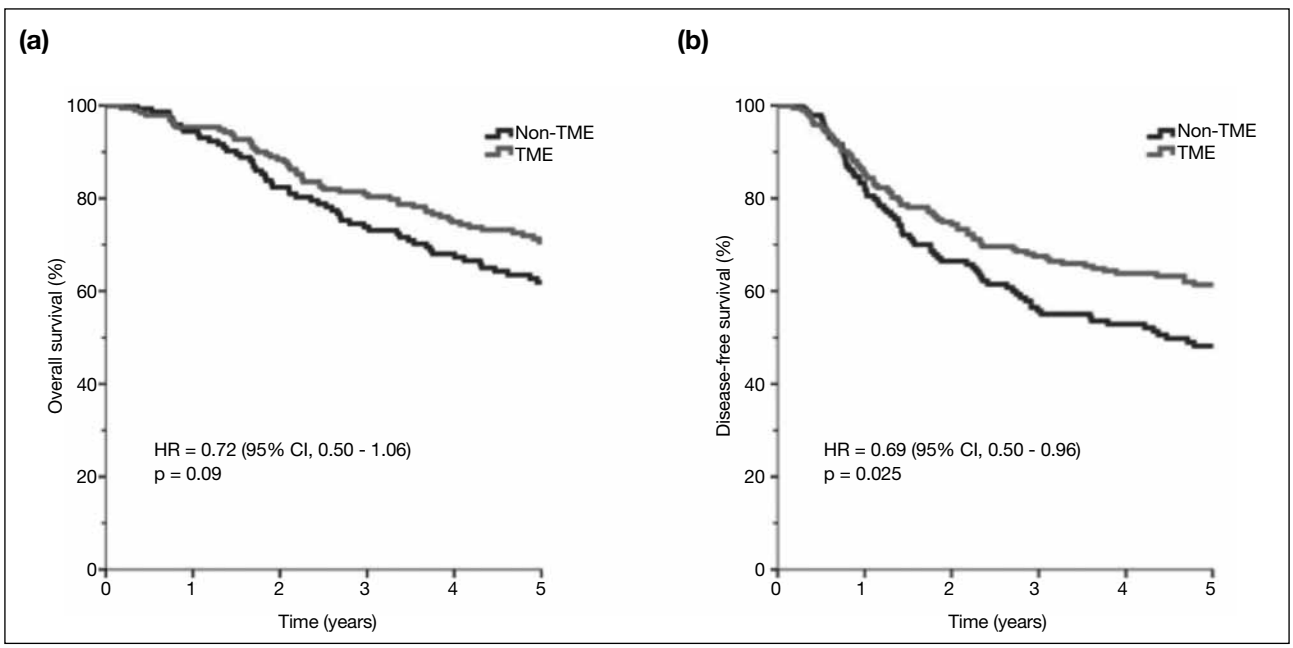

Figure 3. (a) Overall survival and (b) disease-free survival in the whole group according to the nature of surgery.
Abbreviations: CI = confidence interval; HR = hazard ratio; TME = total mesorectal excision.

There was a trend for superior 5-year OS in the TME group (70.6% vs. 61.9%; p = 0.09) compared with non-TME group. Furthermore, 5-year DFS was shown to be significantly better in the TME versus non-TME group (61.4% vs. 48.2%; p = 0.025; Figure 3).

For the 83 patients who were referred for neoadjuvant therapy, the 5-year OS rate was 56%. In view of the more advanced clinical stage of disease, a higher local recurrence rate (20%) was noted (Figure 4a). Both TME (p = 0.03) and clear resection margins (p < 0.01) were

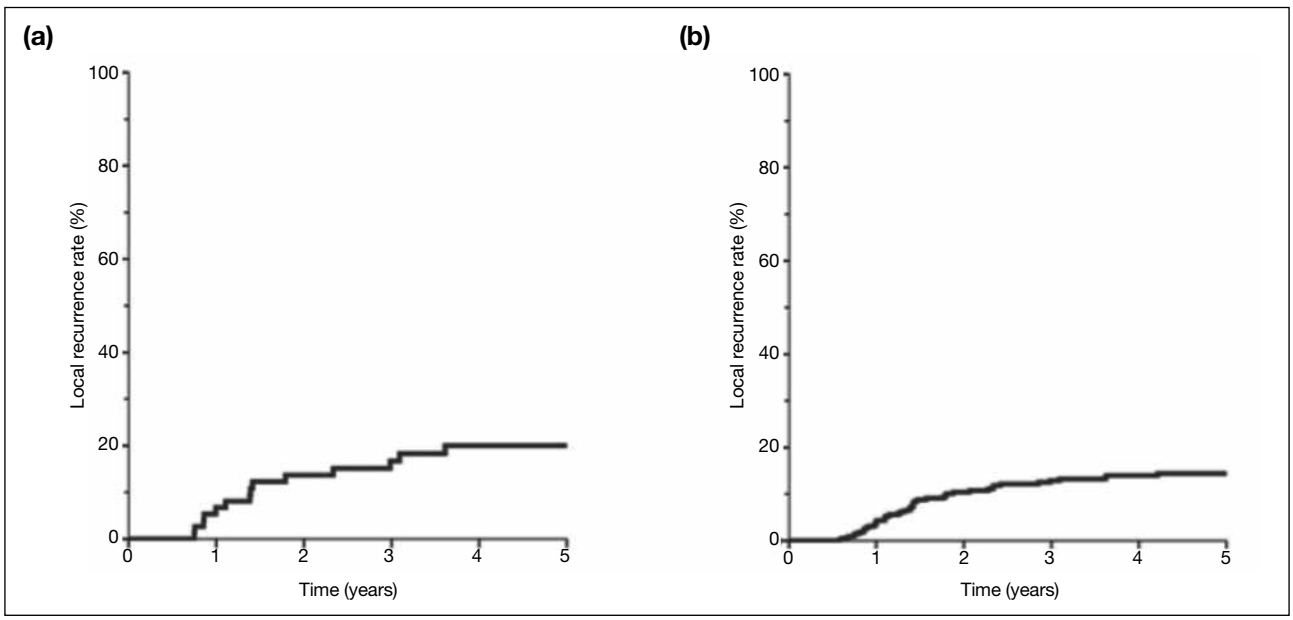

Figure 4. Local recurrence rates in patients receiving (a) neoadjuvant therapy and (b) upfront surgery.

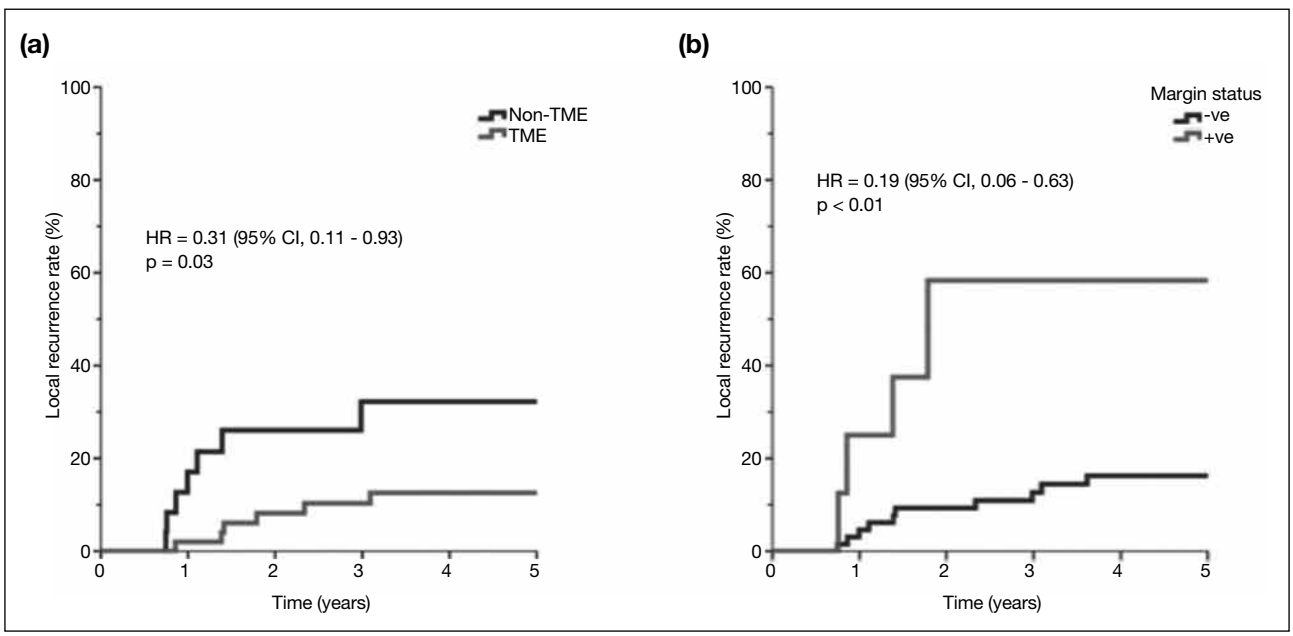

Figure 5. Local recurrence rates in patients receiving neoadjuvant therapy, stratified according to (a) the nature of surgery and (b) the margin status.
Abbreviations: CI = confidence interval; HR = hazard ratio; TME = total mesorectal excision.

associated with significantly better local control (Figure 5).

For the 258 patients who were referred after surgery, the 5-year OS and local recurrence rates were 70% and 13%, respectively (Figure 4b). On univariate analysis, both TME and clear resection margins were associated with better local control ($p = 0.05$ and $p < 0.01$, respectively; Figure 6). The use of adjuvant CRT or chemotherapy was associated with better OS ($p < 0.01$) and local control ($p < 0.01$) compared to those without adjuvant treatment or receiving RT alone (Figure 7). However,

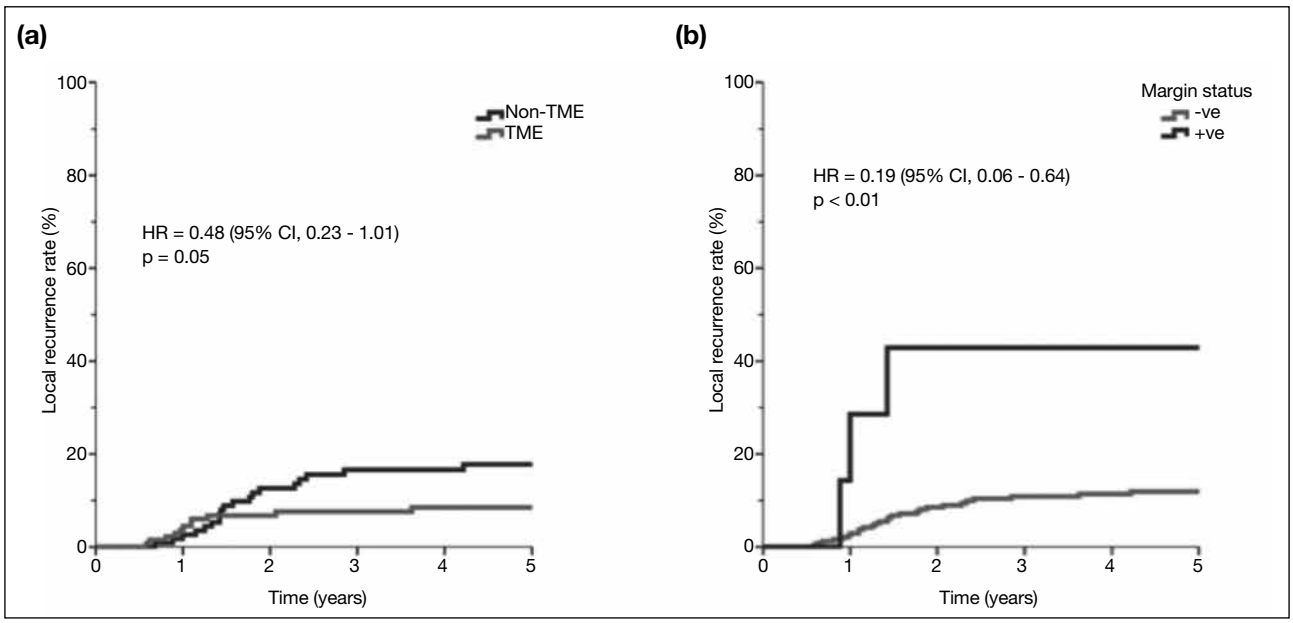

Figure 6. Local recurrences rate in patients receiving upfront surgery, stratified according to (a) the nature of surgery and (b) margin status.
Abbreviations: CI = confidence interval; HR = hazard ratio; TME = total mesorectal excision.

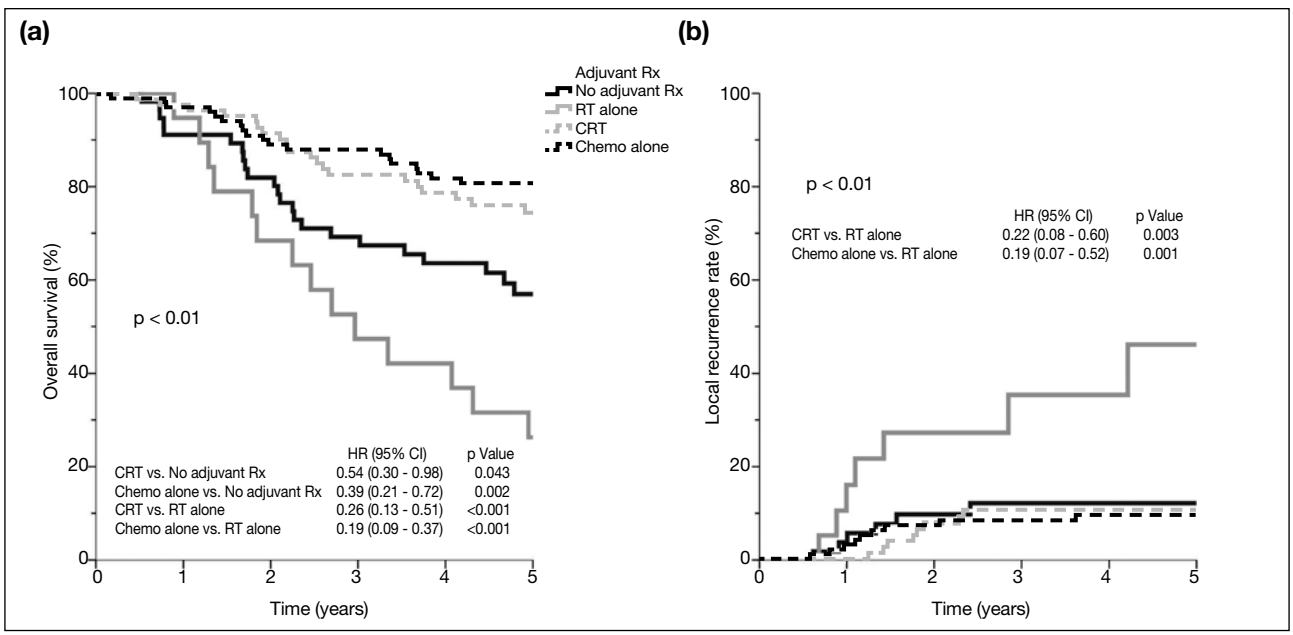

Figure 7. (a) Overall survival rate and (b) local recurrence rate in patients receiving upfront surgery, stratified according to the nature of adjuvant therapy.
Abbreviations: Chemo = chemotherapy; CI = confidence interval; CRT = chemoradiotherapy; HR = hazard ratio; RT = radiotherapy; Rx = treatment; TME = total mesorectal excision.

the statistical significance of local recurrence rate was mainly due to poor local control for patients receiving RT alone (Figure 7b). On multivariate analysis, nodal stage, location of tumour, margin status, and the use of adjuvant therapy were predictive of OS, while T stage, location of tumour, and adjuvant therapy were predictive of local recurrence (Tables 5 and 6). TME surgery for this particular group of patients failed to reach statistical significance (p = 0.08).

Treatment-related Mortality and Severe Late Complications Due To Neoadjuvant / Adjuvant Therapy

There were three treatment-related deaths in our group of patients. One patient died of pneumonia during neoadjuvant RT. This was an 81-year-old male patient with radiological T3N0 rectal cancer at 5 cm above the anal verge. He was referred to us for neoadjuvant RT. However, he died of pneumonia after 26 Gy/13 fractions. Another patient died of neutropenic sepsis upon completion of neoadjuvant CRT. This was a 54-year-old female patient referred to us for neoadjuvant therapy after intra-operative finding of inoperable T4 N+ rectal cancer at laparotomy. The third patient died of neutropenic sepsis after one cycle of adjuvant 5FU/FA. This was a 70-year-old male patient. He had stage pT3N2 rectal cancer with clear margins after AR and TME . Adjuvant chemotherapy alone was offered to him. Overall, the treatment-related death rate was 1.0%. Surgical mortality, however, cannot be assessed due to the nature of referral; there was no postoperative mortality for patients who underwent neoadjuvant treatment. Finally, two patients were documented with late complications after neoadjuvant CRT and TME surgery. One of them was a 59-year-old female who developed symptomatic radiation cystitis 2 years after CRT, and subsided spontaneously. The other was a 58-year-old male who had radiation proctitis 10 years after CRT. He required repeated treatments with argon plasma coagulation.

DISCUSSION

Before the introduction of TME, the results of surgery for rectal cancer were characterised by a 15% to 30% rate of local recurrence and a 5-year survival rate of <50%.[17,18] However, emerging data now indicate that surgeons who adopt the principles of TME can consistently achieve local recurrence rates of 4% to 10%.[11-13] This technique involving the sharp dissection of the mesorectum was introduced by Heald et al in 1982.[19] He first described the "holy plane", which is

Table 5. Multivariate analysis of factors affecting overall survival for patients undergoing upfront surgery (n = 258).*

	Hazard ratio (95% CI)	p Value
Age	-	0.98
Sex (F vs. M)	-	0.80
Pathological T stage		0.22
1 vs. 4	-	0.96
2 vs. 4	-	0.049
3 vs. 4	-	0.10
Pathological N stage		<0.001
1 vs. 0	1.63 (0.94-2.84)	0.08
2 vs. 0	4.36 (2.46-7.74)	<0.001
Surgery		
TME vs. non-TME	-	0.62
Level		0.034
Middle vs. low	0.55 (0.33-0.91)	0.021
Upper vs. low	0.52 (0.29-0.92)	0.024
Circumferential margin		
+ve vs. -ve	2.93 (1.13-7.66)	0.028
Adjuvant treatment		<0.001
RT alone vs. nil	1.08 (0.54-2.15)	0.83
CRT vs. nil	0.30 (0.16-0.54)	<0.001
Chemotherapy alone vs. nil	0.20 (0.11-0.37)	<0.001

Abbreviations: CI = confidence interval; CRT = chemoradiotherapy; RT = radiotherapy; TME = total mesorectal excision.
* Excluding 2 patients with unknown surgical margin and one patient with miscellaneous operation.

Table 6. Multivariate analysis of factors affecting local control in patients undergoing upfront surgery (n = 258).*

	Hazard ratio (95% CI)	p Value
Age	-	0.56
Sex (F vs. M)	-	0.89
Pathological T stage		0.05
1 vs. 4	0†	0.99
2 vs. 4	0†	0.94
3 vs. 4	0.46 (0.19-1.11)	0.006
Pathological N stage		0.17
1 vs. 0	-	0.56
2 vs. 0	-	0.06
Surgery		
TME vs. non-TME	-	0.08
Level		0.006
Middle vs. low	0.50 (0.23-1.08)	0.08
Upper vs. low	0.20 (0.08-0.53)	0.001
Circumferential margin		
+ve vs. -ve	-	0.52
Adjuvant Rx		0.014
RT alone vs. nil	2.00 (0.70-5.78)	0.20
CRT vs. nil	0.40 (0.15-1.08)	0.07
Chemotherapy alone vs. nil	0.87 (0.32-2.40)	0.79

Abbreviations: CRT = chemoradiotherapy; RT = radiotherapy; Rx = treatment; TME = total mesorectal excision.
* Excluding 2 patients with unknown surgical margin and one patient with miscellaneous operation.
† No event for T1 and T2.

an avascular interface between the mesorectal fascia and the parietal dorsolateral pelvic fascia. Dissection in this avascular cleavage allows complete removal of the mesorectal tissue, as well as affords good protection of the hypogastric nerves and the inferior hypogastric plexus, resulting in lower incidence of surgical margin involvement and disturbance of the bladder and sexual functions as opposed to blunt dissection.

One of the aims of this study was to assess the impact of TME when this surgical technique was being adopted during the last decade. Benchmark data in general are sparse in Hong Kong. Two recent studies from a local centre showed that the overall local recurrence rate was below 10%.[20,21] However, the primary aim of these two studies was to compare the outcomes according to open and laparoscopic approaches. The results based on TME have not been clearly addressed. Furthermore, the study by Ng et al[21] included a substantial proportion of subjects with stage I disease and this would, inevitably, have resulted in better overall local control, while the study by Day et al[20] did not include patients undergoing emergency operation. The strengths of this study included detailed comparison between TME and non-TME for almost all patients as well as assessing the impact of adjuvant therapy. Overall, our present study revealed a relatively higher local recurrence rate at 5 years (14.4%). However, when comparing the outcome data according to TME, the 5-year local recurrence rates for patients who underwent TME and non-TME surgery were 9.7% and 20.1%, respectively ($p = 0.01$).

Another interesting point in this study was the impact of adjuvant therapy after resection. Standard adjuvant therapy in that period was adjuvant CRT which was based on studies conducted in the 1980s when TME had never been practised.[15] However the exact contribution of CRT versus chemotherapy alone in the TME era was largely unknown. Due to the concern about increased morbidity related to the use of RT after TME, we did not routinely prescribe adjuvant CRT during this study period for patients having TME surgery with clear resection margins. Both univariate and multivariate analyses in our study showed that use of adjuvant therapy (either chemotherapy alone or CRT) was indeed associated with better OS.

We postulated that adjuvant chemotherapy alone might, in fact, be adequate for this particular group of patients. However, a properly conducted randomised trial is definitely needed in order to answer whether adjuvant CRT can be safely omitted after TME. It is also important to state that the current National Comprehensive Cancer Network and European Society for Medical Oncology guidelines[22,23] are indeed recommending the use of postoperative adjuvant CRT for ≥pT3 or node-positive patients (provided that no neoadjuvant therapy has been given). It should also be noted that the proportion of patients who did not receive adjuvant therapy after surgery may confoundingly bear poor prognostic factors (comorbidities, suboptimal performance status, old age), which is a limitation of this study.

On the other hand, the present series on neoadjuvant CRT was far from satisfactory. The likely explanation was that most of the treated patients in this group had unresectable disease. In fact, 36% of these patients had cT4 disease. This mandated the use of neoadjuvant therapy for the purpose of downstaging. The relatively high rate of circumferential margin involvement (10%) also reflected the advanced nature of their illnesses. In fact, Minsky et al[24] used a similar treatment approach for unresectable rectal cancer to reveal a 4-year actuarial local failure rate of only 30%. Other studies have shown local control rates of 80% to 85% for locally advanced, unresectable rectal cancers following neoadjuvant therapy.[25,26] These treatment results were in stark contrast to the excellent results of the Dutch and German trials where neoadjuvant therapy was employed for treating potentially resectable rectal cancer.[7,8] In the Dutch trial investigating the role of short-course preoperative RT combined with TME, the rate of local recurrence at 2 years was only 2.4% in the RT-plus-surgery group.[7] In this trial, only patients with resectable tumours were recruited while those with fixed tumours were excluded. Similarly, in the German trial comparing preoperative versus postoperative CRT, the 5-year cumulative incidence of local relapse was only 6% for patients assigned to preoperative CRT.[8] In this trial, only 6% of patients in the preoperative CRT group had stage T4 tumours. In fact, neoadjuvant treatment approach is now regarded as the standard of care for ≥cT3 and cN+ disease.[22,23] Whether similar results can be achieved in local patients having resectable rectal cancer cannot be answered in this study. However, the adoption of internationally recommended neoadjuvant therapy was relatively slow in Hong Kong, as upfront surgery was still offered in some situations.

One additional issue related to the limited adoption of neoadjuvant therapy is the under-utilisation

of preoperative imaging service. We found that preoperative local staging investigations were grossly inadequate during the study period. Only 102 (29.7%) patients of the whole cohort had preoperative ERUS, and only seven patients had preoperative MRI of the pelvis. Two patients were indeed found to have inoperable tumours at laparotomy who were then referred for neoadjuvant therapy. Adequate staging before definitive treatment is essential and it is particularly helpful in selecting patients who might benefit from neoadjuvant therapy. Nowadays MRI is the preferred modality for staging, and multiple studies have shown that margin status can be accurately predicted using high-resolution MRI.[27-30] The decision of offering neoadjuvant treatment is also best discussed in a multidisciplinary team, but this was unfortunately not a standard practice at that time.

Similar to many retrospective studies, several methodological limitations should also be borne in mind when interpreting the results of this study. One limitation is the possibly under-estimation of local failure especially in patients who had already developed distant metastasis during their course of illness, further assessment for local failure might not then be carried out. Secondly, there was no quality assessment of the TME specimen and we relied solely on the surgical record to see whether TME had been performed. This is an important issue as multiple studies have shown that the quality of TME was directly related to the treatment outcomes.[31,32] Lastly, pathological measurement of the distance between the surgical margin and invasive front of the tumour was seldom recorded during the study period and, hence, we cannot assess the impact of close surgical margins in this study.[33]

Currently, we routinely stage all newly diagnosed rectal cancer cases in our hospital with high-resolution MRI of the pelvis. All patients also received CT scan of the thorax, abdomen, and pelvis with or without ERUS. Each individual patient is jointly assessed by the surgeon, oncologist, and radiologist. We now follow international guidelines[22,23] to treat all patients with low-risk disease (including cT1 – cT3bN0 and tumours at least 5 mm from mesorectal fascia or cT1 low rectum) by upfront surgery while patients with more advanced disease are treated with a neoadjuvant approach. We also work very closely with our pathologists to ensure accurate assessment of the surgical margins. Future analyses of treatment outcomes based on this multidisciplinary approach are eagerly awaited.

CONCLUSION

We have demonstrated that TME surgery, ability to achieve clear resection margins, as well as adding adjuvant therapy can improve treatment outcomes in stage II and III rectal cancer. Ideally, we believe all patients with rectal cancer should receive proper staging work-up and be evaluated by a multidisciplinary team to determine the most optimal treatment strategy.

REFERENCES

1. Hong Kong Cancer Registry 2011. Available from: http://www3.ha.org.hk/cancereg/. Accessed 11 Apr 2014.
2. Glimelius B, Tiret E, Cervantes A, Arnold D; ESMO Guidelines Working Group. Rectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2013;24 Suppl 6:vi81-8. cross ref
3. McMullen TP, Easson AM, Cohen Z, Swallow CJ. The investigation of primary rectal cancer by surgeons: current pattern of practice. Can J Surg. 2005;48:19-26.
4. Prolongation of the disease-free interval in surgically treated rectal carcinoma. Gastrointestinal Tumor Study Group. N Engl J Med. 1985;312:1465-72. cross ref
5. Effective surgical adjuvant therapy for high-risk rectal carcinoma. N Engl J Med. 1991;325:519-20. cross ref
6. Improved survival with preoperative radiotherapy in resectable rectal cancer. Swedish Rectal Cancer Trial. N Engl J Med. 1997;336:980-7. cross ref
7. 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. cross ref
8. 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. cross ref
9. Sebag-Montefiore D, Stephens RJ, Steele R, Monson J, Grieve R, Khanna S, 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. cross ref
10. Heald RJ, Ryall RD. Recurrence and survival after total mesorectal excision for rectal cancer. Lancet. 1986;1:1479-82. cross ref
11. Ridgway PF, Darzi AW. The role of total mesorectal excision in the management of rectal cancer. Cancer Control. 2003;10:205-11.
12. Law WL, Chu KW. Anterior resection for rectal cancer with mesorectal excision: a prospective evaluation of 622 patients. Ann Surg. 2004;240:260-8. cross ref
13. Wibe A, Møller B, Norstein J, Carlsen E, Wiig JN, Heald RJ, et al. A national strategic change in treatment policy for rectal cancer — implementation of total mesorectal excision as routine treatment in Norway. A national audit. Dis Colon Rectum. 2002;45:857-66. cross ref
14. Page DL, Fleming ID, Fritz A. AJCC Cancer Staging Manual. 6th ed. Philadelphia: Lippincott-Raven; 2002.
15. NIH consensus conference. Adjuvant therapy for patients with colon and rectal cancer. JAMA. 1990;264:1444-50. cross ref
16. Smalley SR, Benedetti JK, Williamson SK, Robertson JM, Estes NC, Maher T, et al. Phase III trial of fluorouracil-based chemotherapy regimens plus radiotherapy in postoperative adjuvant rectal cancer: GI INT 0144. J Clin Oncol. 2006;24:3542-

7. cross ref
17. McCall JL, Cox MR, Wattchow DA. Analysis of local recurrence rates after surgery alone for rectal cancer. Int J Colorectal Dis. 1995;10:126-32. cross ref
18. Akyol AM, McGregor JR, Galloway DJ, Murray G, George WD. Recurrence of colorectal cancer after sutured and stapled large bowel anastomoses. Br J Surg. 1991;78:1297-300. cross ref
19. Heald RJ, Husband EM, Ryall RD. The mesorectum in rectal cancer surgery — the clue to pelvic recurrence? Br J Surg. 1982;69:613-6. cross ref
20. Day W, Lau PY, Li KM, Kwok SY, Yip AW. Clinical outcome of open and laparoscopic surgery in Dukes' B and C rectal cancer: experience from a regional hospital in Hong Kong. Hong Kong Med J. 2011;17:26-32.
21. Ng SS, Lee JF, Yiu RY, Li JC, Hon SS, Mak TW, et al. Long-term oncologic outcomes of laparoscopic versus open surgery for rectal cancer: a pooled analysis of 3 randomized controlled trials. Ann Surg. 2014;259:139-47. cross ref
22. National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology: Rectal Cancer. Version 4. Available from: http://www.nccn.org/; 2013. Accessed May 2013.
23. Schmoll HJ, Van Cutsem E, Stein A, Valentini V, Glimelius B, Haustermans K, et al. ESMO Consensus Guidelines for management of patients with colon and rectal cancer. A personalized approach to clinical decision making. Ann Oncol. 2012;23:2479-516. cross ref
24. Minsky BD, Cohen AM, Enker WE, Saltz L, Guillem JG, Paty PB, et al. Preoperative 5-FU, low-dose leucovorin, and radiation therapy for locally advanced and unresectable rectal cancer. Int J Radiat Oncol Biol Phys. 1997;37:289-95. cross ref
25. Ahmad NR, Nagle D. Long-term results of preoperative radiation therapy alone for stage T3 and T4 rectal cancer. Br J Surg. 1997;84:1445-8. cross ref
26. Nakfoor BM, Willett CG, Shellito PC, Kaufman DS, Daly WJ. The impact of 5-fluorouracil and intraoperative electron beam radiation therapy on the outcome of patients with locally advanced primary rectal and rectosigmoid cancer. Ann Surg. 1998;228:194-200. cross ref
27. Brown G, Daniels IR. Preoperative staging of rectal cancer: the MERCURY research project. Recent Results Cancer Res. 2005;165:58-74. cross ref
28. Beets-Tan RG, Beets GL, Vliegen RF, Kessels AG, Van Boven H, De Bruine A, et al. Accuracy of magnetic resonance imaging in prediction of tumour-free resection margin in rectal cancer surgery. Lancet. 2001;357:497-504. cross ref
29. Jones WE 3rd, Thomas CR Jr, Herman JM, Abdel-Wahab M, Azad N, Blackstock W, et al. ACR appropriateness criteria® resectable rectal cancer. Radiat Oncol. 2012;7:161. cross ref
30. Burton S, Brown G, Daniels IR, Norman AR, Mason B, Cunningham D; Royal Marsden Hospital, Colorectal Cancer Network. MRI directed multidisciplinary team preoperative treatment strategy: the way to eliminate positive circumferential margins? Br J Cancer. 2006;94:351-7. cross ref
31. Quirke P. Training and quality assurance for rectal cancer: 20 years of data is enough. Lancet Oncol. 2003;4:695-702.
32. Quirke P, Dixon MF. The prediction of local recurrence in rectal adenocarcinoma by histopathological examination. Int J Colorectal Dis. 1988;3:127-31. cross ref
33. Nagtegaal ID, Marijnen CA, Kranenbarg EK, van de Velde CJ, van Krieken JH; Pathology Review Committee; Cooperative Clinical Investigators. Circumferential margin involvement is still an important predictor of local recurrence in rectal carcinoma: not one millimeter but two millimeters is the limit. Am J Surg Pathol. 2002;26:350-7. cross ref