RESEARCH ARTICLE

Preoperative Long Course Chemoirradiation in a Developing Country for Rectal Carcinoma: Kuala Lumpur Hospital Experience

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Abstract

Background: The use of preoperative chemoirradiation is the commonest treatment strategy employed in Malaysia for locally advanced rectal cancer. We need to determine the local control and survival rates for comparison with established rates in the literature. Materials and Methods: This retrospective study analyzed all newly diagnosed patients with rectal adenocarcinoma who underwent long course preoperative radiotherapy (RT) at the Department of Radiotherapy and Oncology, Kuala Lumpur Hospital (HKL) between 1st January 2004 and 31st December 2010. The aim of the study was to determine the radiological response post radiotherapy, pathological response including circumferential resection margin (CRM) status, 3 years local control, 3 years overall survival (OS) and 3 years disease free survival (DFS). Statistical analysis was performed using the SPSS software. Kaplan-Meier and log rank analysis were used to determine survival outcomes. Results: A total of 507 patients with rectal cancer underwent RT at HKL. Sixty seven who underwent long course preoperative RT were eligible for this study. The median age at diagnosis was 60 years old with a range of 26-78 years. The median tumour location was 6 cm from the anal verge. Most patients had suspicion of mesorectum involvement (95.5%) while 28.4% of patients had enlarged pelvic nodes on staging CT scan. All patients underwent preoperative chemo-irradiation except for five who had preoperative RT alone. Only 38 patients underwent definitive surgery (56.7%). Five patients were deemed to be inoperable radiologically and 3 patients were found to have unresectable disease intraoperatively. The remaining 21 patients defaulted surgery (31.3%). The median time from completion of RT to surgery was 8 weeks (range 5.6 to 29.4 weeks). Fifteen patients (39.5%) had surgery more than 8 weeks after completion of RT. Complete pathological response was noted in 4 patients (10.5%). The pathological CRM positive rate after RT was 18.4%. With a median follow-up of 38.8 months, the 3 year local control rate was 67%. The 3 years rate for CRM positive (<2 mm), CRM clear (>2 mm) and pCR groups were 0%, 88.1% and 100% respectively (p-value of 0.007). The 3 year OS and DFS were 57.3% and 44.8% respectively. Conclusions: In conclusion, the approach of long course preoperative chemoirradiation for rectal cancer needs to be re-examined in our local setting. The high rate of local recurrence is worrying and is mainly due to patient defaulting post-preoperative chemoirradiation or delayed definitive surgery.

Keywords: Rectal cancer - preoperative chemoirradiation - local control

Asian Pacific J Cancer Prev, **14 (6)**, 3941-3944

Introduction

In Malaysia, cancer of the large bowel, which consists of cancer of the colon, rectum and anus, was the commonest cancer in males, accounting for 14.5% of all cancers. Among women, cancer of large bowel ranked third, accounting for 9.9% of all cancer (Gerald et al., 2006). Prior to the mid-80s, surgery alone was the cornerstone of curative treatment for patients with rectal cancer, with high rates of pelvic failure (ranges from 15 to 45%) and poor survival. Randomized studies in the era before total mesorectal resection (TME) demonstrated local recurrence rate of 15-35% and a 5 year overall survival (OS) rate of approximately 60% for Dukes B and only 25% for Dukes C after surgery alone (Wolmark et al., 1988). Refinement of surgical techniques in the 1980s to 1990s with the introduction of TME in Europe and subsequent standardization of rectal cancer surgery proved that surgery alone could result in good local control (LC). With TME, the positive radial margins can be reduced from 25% in conventional surgery to 7%. Adam and colleagues (1994) showed that patients with positive radial margins were 12 times more likely to have local recurrence (LR) than patients without radial margin involvement. In fact, it has been shown retrospectively that there was an improvement of 5 year OS rate from

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50 to 71% with the introduction of TME in a European study (Kockerling et al., 1998). Further improvement in survival may be obtained with the use of chemotherapy, radiotherapy (RT) or in combination. Dutch investigators conducted a large randomized trial investigating the value of preoperative short course RT for resectable rectal cancer in combination with TME versus TME alone. Initial results after a median follow up of 6 years showed 5 years LR rate of 5.6% for preoperative RT versus 10.9% for TME alone (Peeters et al., 2007). A recent update of the trial with a median follow-up of 11 years showed patients receiving preoperative RT and TME had a statistically significant lower 10 year LR rate at 5% compared to TME only at 11% (van Gijn et al., 2011). However, the 10 year OS was similar in both groups. Another landmark study on short course preoperative RT initiated by the Medical Research Council UK and National Cancer Institute of Canada reported a 3 year LR rate of 4.4% for preoperative RT versus 10.6% for selective postoperative chemoradiotherapy (CRT). In addition there was an absolute difference of 6% in disease free survival at 3 years (77.5% vs 71.5%) in favour of preoperative RT (Sebag-Montefiore et al., 2009). However, overall survival did not differ between the 2 groups.

Historically, postoperative CRT has been shown to reduce LR and improve survival for locally advanced rectal cancer (Krook et al., 1991; Gastrointestinal Tumour Study Group, 1992). In recent times, preoperative CRT has become the standard treatment for cT3 and/or N+ rectal tumour (Minsky et al., 2010). The incorporation of chemotherapy into the neo-adjuvant combined-modality approach was established by two large European randomized trials. The addition of 5-fluorouracil (5-FU) to preoperative long course RT (45Gy/25 fractions) has been shown in two European randomized trials to improve LC in resectable rectal cancer (5 year LR 8.1% vs 16.5%, $p<0.05$; 5 year LR 8.7% vs 17.1%, p-value=0.002) (Bosset et al., 2006; Gerard et al., 2006). In addition, preoperative CRT has been shown in a German trial to be more effective than postoperative CRT in terms of LC (5 year LR 6% vs 13%, p-value=0.006), sphincter preservation, as well as lower rates of acute and chronic toxicity (Sauer et al., 2004). The latest update of this trial reported the 10 year LR rate of 7.1% versus 10.1% in favour of preoperative CRT (Sauer et al., 2012). Based on the available clinical data largely derived from studies conducted mostly in developed countries in the past 20 years, concurrent CRT prior to surgery has been shown to reduce the risk of LR in patients with operable, stage II-III rectal cancer to less than 10%. Preoperative long course CRT is the commonest approach adopted for the treatment of rectal cancer in Malaysia. However, there has been no published data from Malaysia with regards to treatment outcome using this approach.

Materials and Methods

This study retrospectively analyzed all newly diagnosed patients with rectal adenocarcinoma who underwent long course preoperative RT at the Department of Radiotherapy and Oncology, HKL between 1st January 2004 and 31st December 2010. The aim of the study was to determine the radiological response post RT, pathological response including Circumferential Resection Margin (CRM) status, 3 year OS, 3 years disease free survival (DFS) and 3 years LC rate. Patients lost to follow-up were contacted via phone to determine their current status and if any of these patients were not contactable, their current survival status was determined by contacting the National Registration Department. Statistical analysis was performed using the SPSS software. Kaplan-Meier and log rank analysis were used to determine survival outcomes. Positive CRM was defined as presence of microscopic tumour at ≤2mm from the inked circumferential resection margin. Threatened CRM was defined radiologically as presence of tumour within 2mm of mesorectal fascia.

The standard treatment in HKL for patients with non-metastatic rectal carcinoma with threatened CRM is to undergo neo-adjuvant long course RT with concurrent chemotherapy to be followed by definitive surgery with TME within 6-8 weeks of completion of neo-adjuvant treatment. The radiation dose prescribed is 45Gy in 25 fractions given daily over 5 weeks. The chemotherapy regime given concurrently with RT for all patients consists of intravenous (IV) bolus 5-Flourouracil (5FU) and folinic acid (Mayo's regime). The dose for 5-FU is between 300-325mg/m^2 with folinic acid 20mg/m^2 with both drugs administered daily for five days on week 1 and week 5 of pelvic RT. Post-operatively, patients will receive another 4 cycles of adjuvant chemotherapy with Mayo's regime at the standard 5-FU dose of 375-425mg/m^2 with folinic acid

Results

Between 1st January 2004 and 31st December 2010, a total of 507 patients with rectal cancer underwent radiotherapy at HKL. There were 67 patients who underwent long course pre-operative RT who were eligible for this study. Thirty four patients who had pre-operative RT followed by surgery at other hospitals were excluded due to non- standardized histopathology reports. Two hundred patients received pelvic RT postoperatively, 87 had metastatic disease at presentation, 20 received RT for recurrent disease, 3 had other malignancies and the records of 96 patients were missing.

The clinico-pathological characteristics of the 67 eligible patients are summarized in Table 1. Median age at diagnosis was 60 years old (range 26-78 years). The median tumour location was at 6 cm from the anal verge with the majority located at the lower and middle rectum (89.6%). Most patients had suspicion of mesorectum involvement (95.5%) and 28.4% of patients had enlarged pelvic lymph nodes on staging computed tomography (CT) scan. All patients had neo-adjuvant CRT except for five patients who had neo-adjuvant long course RT alone.

Sixty one patients had post-RT abdominopelvic CT reassessment for radiological response. There were 2 complete response (CR), 30 partial response (PR), 26 stable disease (SD) and 3 progressive disease (PD). Post RT and radiological investigation, patients were evaluated for definitive surgery. Out of a total of 67 patients, only 38

Table 1. Clinico-Pathological and Treatment Characteristics

Characteristics		n=67	%
Age	≤50	13	19.3
	51-69	46	68.8
	≥70	8	11.9
Gender	Male	48	71.6
	Female	19	28.4
Ethnic group	Malay	38	56.7
	Chinese	16	23.9
	Indian	13	19.4
Tumour distance from anal verge (cm)			
	0-5	29	43.3
	6-10	31	46.3
	11-15	5	7.5
	Unknown	2	3.0
Baseline CT findings			
Mesorectum involvement	Yes	64	95.5
	No	3	4.5
Lymph node involvement	Yes	19	28.4
	No	48	71.6
Post RT CT scan	Yes	61	91.0
	No	6	9.0
Radiological response (n=61)	Complete response	2	3.3
	Partial response	30	49.2
	Stable disease	26	42.6
	Progressive disease	3	4.9
Surgery	Yes	38	56.7
	Defaulted	21	31.3
	Inoperable	8	11.9
Pathological response (n=38)			
ypT-stage	T0	4	10.5
	T1	5	13.2
	T2	5	13.2
	T3	16	42.1
	T4	8	21.1
ypN-stage	N0	30	78.9
	N1	5	13.2
	N2	3	7.9
Differentiation	Well	3	7.9
	Moderate	30	78.9
	Poor	5	13.2
Lymphovascular invasion	Yes	4	10.5
	No	34	89.5
Circumferential resection margin	≤2 mm	7	18.4
	>2 mm	27	71.1
	CR	4	10.5

patients underwent definitive surgery. Five patients were deemed to be inoperable radiologically. Another 3 patients were found to have unresectable disease intraoperatively. The remaining 21 patients (31.3%) defaulted the post RT surgical review and the reasons were unknown. The median time from completion of RT to surgery was 8 weeks (range 5.6 to 29.4 weeks). Fifteen patients (39.5%) underwent surgery more than 8 weeks after completion of RT. The pathological features of the 38 patients who underwent surgery are presented in Table 1. Complete pathological response was noted in 4 patients (10.5%). The pathological CRM positive rate after RT was 18.4%.

With regards to the treatment outcome, at a median follow-up time of 38.8 months, there are 25 patients who are alive without recurrence, 3 alive with recurrence, 6 alive with unknown status and 33 have died. Distant metastasis (DM) occurred in more than one third of the patients (38%) and approximately 84.2% of recurrences occur within the first 2 years. The 3 year OS rate for the 67 patients was 57.3%. The 3 year OS according to ypT stage for T0, T1, T2, T3 and T4 were 100%, 66.7%, 75.0%, 61.6% and 85.7% respectively (p=0.141). All patients who achieved pCR were still alive at the time of analysis. All patients with pathological positive CRM status were dead by 4 years whereas the survival for CRM negative patients appeared to be plateauing at 60%. The 3 years DFS rate for the whole group was 44.8%. The 3 years DFS for T0, T1, T2, T3 and T4 were 66.7%, 80.0%, 60.0%, 40.2% and 85.7% (p=0.386). The 3 years LC rate was 67%. The 3 years LC rate for CRM positive (≤2 mm) group, CRM clear (>2 mm) group and pCR group were 0%, 88.1% and 100% respectively (p-value of 0.007).

Discussion

The main result of this study is the 3 year LR rate of 33% which is much higher compared to the current accepted rate of below 10% with the usage of neo-adjuvant RT/CRT followed by TME surgery. The rates were achievable by only the patients who obtained a clear CRM and those with pathological complete response and CRM>2 mm with LR of 0% and 11.9% respectively. However, all patients had LR when the CRM<2 mm. Time to surgery post completion of neo-adjuvant RT was also important in determining the rate of local control. When the time exceeded 8 weeks the LR rate was 33.3% whereas in those who had surgery in less than 8 weeks, the LR rate was 13.6%. In this study, 39.5% of patients had surgery more than 8 weeks post completion of neo-adjuvant RT. The reason for the delay was not clearly documented. Moreover, 21 patients (31.3%) defaulted from the surgical review session post neo-adjuvant RT. Patients' compliance with surgery post neo-adjuvant RT is a major problem in this country. Possible reasons for the high default rate could be fear of surgery, widespread usage of alternative or traditional medicine, financial constraints and miscommunication between medical personnel and patients. This is a major consideration before embarking on this approach and should only be offered to patients who are fully cognizant of the need for definitive surgery post RT.

The 3 year OS rate was 57.3%. This rate is low compared to those reported in the literature for patients with rectal cancer who had undergone long course neo-adjuvant RT which ranged from 65.2% to 72% for 5 year OS (Sauer et al., 2004; Bosset et al., 2006; Gerard et al., 2006). The high rate of LR in this study definitely contributed to the low survival rate. Furthermore, with a significant number of patients defaulting post neo-adjuvant RT (31.3%), these patients would also have missed out on the possible survival benefit of adjuvant chemotherapy especially in stage III rectal cancer. A study based in University Malaya Medical Centre, Malaysia on patients with locally advanced breast cancer showed a default rate of 14.5% post neo-adjuvant chemotherapy (Chong et al., 2010). Another Malaysian study on neo-adjuvant chemotherapy for locally advanced breast

cancer also showed a high rate of default (17.8%) post neo-adjuvant treatment (Azrif et al., 2011). This is a common problem amongst patients seeking treatment in Malaysian hospitals. It is not possible to improve the LC or OS rates if the issue of patient defaulting is not addressed. In two studies on defaulting from tuberculosis treatment, poor doctor-patient rapport and communication, patients' socio-economic constraints, poor understanding of the disease and treatment and additional inconveniences to the patient in the form of referrals and consultations within a large busy public hospital have been cited as predisposing factors for defaulting (Buu et al., 2003; Hill et al., 2005). Firstly, we need to acknowledge the existence of this problem and identify the exact causes of patient defaulting post neo-adjuvant treatment in our local setting. All efforts must be made to ensure that patients embarking on neo-adjuvant RT or CRT understand that this treatment needs to be followed by definitive surgery. Coordination between the oncology and surgical team is of utmost importance especially in a large public hospital such as HKL where the operating list is perennially booked. Booking for surgery cannot be done only after reassessment CT scan post neo-adjuvant RT or CRT. This will inadvertently lead to delayed surgery due to the long waiting list. Patients embarking on this approach need to be assured of a surgical date 6-8 weeks post neo-adjuvant RT or CRT. Our study clearly shows increased rate of LR when surgery was done after 8 weeks (33.3% vs 13.6%). An alarmingly high number of patients in our study (39.5%) had surgery after 8 weeks post RT. The most efficient method of avoiding this problem will be booking of a surgical date when the patient is first seen in the multidisciplinary clinic when the dates for CRT are determined. We take into account of the possibility that some cancellations will occur due to inoperability post neo-adjuvant CRT but this should only occur in a small number of cases. In this study only 11.9% of patients were not able to proceed to definitive surgery due to inoperability.

In conclusion, the approach of neo-adjuvant CRT for rectal cancer needs to be re-examined in our local setting. The high rate of LR is worrying and is mainly due to patient defaulting post neo-adjuvant treatment and delayed definitive surgery.

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