TREATMENT OF COLORECTAL CANCER A MALAYSIAN EXPERIENCE

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ABSTRACT

Three hundred and twenty patients with colorectal cancer who had undergone treatment in the Institute of Radiotherapy and Oncology, Hospital Kuala Lumpur between 1986 and 1994 were analysed. Patients with tumours of the rectum or rectosigmoid colon made up the largest group (62.5%). Dukes' A disease (1.9%) appeared to be underrepresented while the proportion of patients (11.6%) under the age of 40 years was higher than other studies. The largest racial group in this series was Chinese (61.9%).

Treatment with surgery, radiotherapy and chemotherapy together with the difficulties involved was discussed. The highlights were the lack of serious toxicity of chemotherapy even when used in combination with radiotherapy. The patterns of treatment have been influenced largely by the late stage at presentation, the practical considerations in the population as well as the available resources.

Keywords: colorectal cancer, epidemiology, radiotherapy, chemotherapy, recurrence, crude survival

INTRODUCTION

Rectal cancer was among the four most frequently reported cancers in Penang among Malays, Chinese males and Indian males.[1] Colorectal cancer comprised 7% of the diagnoses of new patients seen in the Institute of Radiotherapy and Oncology, Hospital Kuala Lumpur[2] which is the national referral centre for cancer in Malaysia.

Modest improvements in overall survival and disease-free survival have been demonstrated in trials on adjuvant chemotherapy and adjuvant radiotherapy.[3,4,5,6,7,8,9] On the other hand, the role of palliative radiotherapy and palliative chemotherapy have been established in other studies.[10]

The objectives of this study are to review treatment of colorectal cancer in this centre, the morbidity associated with chemotherapy and radiotherapy, the problems encountered, and the patterns of recurrence and survival of these patients.

MATERIALS AND METHODS

A retrospective study of patients with colorectal cancer treated at the Institute of Radiotherapy and Oncology, Hospital Kuala Lumpur was conducted. The study population were patients presenting as new cases of colorectal cancer and who had undergone treatment in this Institute between 1986 and 1994.

The sample included all patients who met the following inclusion criteria: any primary malignant tumour arising for the colon or rectum (between the ileo-caecal junction and the anorectal junction), and histologically verified by a pathologist. The exclusion criteria applied in this study were: patients with primary anal cancers, metastatic cancers with unknown primary sites of disease, no histological verification, and patients whose records could not be traced.

Data was collected using a check-list ques-

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tionnaire. Case notes, referral letters, histopathology reports, laboratory tests, operation findings, radiotherapy records, simulator films and other relevant investigations were reviewed. The records were retrieved manually. Information on chemotherapy, radiotherapy treatment and complications of treatment was retrieved from the case notes. Staging of colorectal cancer was based on the Dukes' Classification.[11] Chemotherapy toxicities were graded according to recommendations by the World Health Organization.[12] Marrow suppression that was recorded in this study reflected the most severe of the various haematological toxicities. Performance status of patients on presentation to the Radiotherapy Clinic was based on Zubrod Scale.[13]

Crude survival time was calculated from the date of primary surgery to the date of last follow-up or to the date of death due to any cause. Relapse-free interval was calculated from the date of Primary Surgery to the date of first relapse. Patients who had macroscopic residual disease post-operatively were considered to have no disease-free interval. The dates of notification of death of patients who were lost to follow-up were provided by the Malaysian National Registration Department. The status of 16 patients are still unknown as their identification card numbers were not traceable from our records or they were from areas other than Peninsular Malaysia. Data was entered into a database management programme (DBASE IV) and analysed using EPID INFO Version 5.

RESULTS

Data from a total of 320 patients' records were analysed. The median age of the study population was 56 years with the age distribution ranging from 13 years to 87 years. The male:female ratio was 1.3: 1. The majority of the patients were Chinese. Patients with tumours involving the rectum or rectosigmoid regions made up the largest group (62.5%). Only a fifth of the tumours were well-differentiated in grade. Patients who had tumours that were limited to the bowel wall formed a distinct minority. At least half of the patients had metastatic disease at presentation [Table 1]. The commonest presenting symptoms in this study were alteration in bowel habits (53.8%), rectal bleeding (44.1%) and abdominal pain (37.2%).

Concurrent diseases were: villous adenoma (2 cases), ulcerative colitis/inflammatory bowel disease (1 case), Familial Polyposis Coli (2 cases). The majority of the patients had a Zubrod status of 0 to 2 (83.8%). Performance status was poor in 15.6% while it was unknown in 0.6%.

Forty per cent of patients are known to have died [Table 2]. Recurrences occurred in nearly 60% of patients. Sole recurrences at the local site was the commonest form of relapse [Table 3]. Dukes' C patients had the highest local relapse rate (29.2%) compared to Dukes' A and B (16.5%).

Some sites of disease spread were: forehead (1 patient), parametrium (1 patient), vagina (2 patients), Fallopian tube (1 patient) and anterior abdominal wall (2 patients) and one patient experienced recurrence in the bladder eight years later. Other sites of spread included the anus, scrotum, para-aortic and inguinal lymph nodes. Spread to the supraclavicular fossa lymph nodes was not a prominent feature.

Three hundred and eight patients (96.2%) had records of having surgery, 222 patients (69.4%) had chemotherapy while 168 patients (52.5%) had radiotherapy. Treatment was multimodal in most of the patients.

Abdomino-perineal resections, anterior resections and Hartman's procedures together accounted for 53.7% of the operations. Palliative surgery such as defunctioning colostomy was possible in 9.4% while no surgery was performed in 3.7%. Bulky disease was a feature in at least a third of patients presenting to our department.

Chemotherapy was given in 222 patients (69.4% of the study population). Palliative chemotherapy was given in 123 while adjuvant chemotherapy was used in 98. The intent of chemotherapy for one patient was not ascertainable as it was received at another hospital.

A regime containing 5-fluorouracil was used in all chemotherapy patients except in one patient. 5-Fluorouracil alone was the most frequently used regime (64%). Levamisole was used together with 5-fluorouracil in both adjuvant and palliative settings

in 16%. Leucovorin factor plus 5-fluorouracil was given palliatively in only 2% of patients. Fluorouracil was most frequently prescribed via the oral route (48%); a continuous infusion over 5 days once every three weeks was employed in 23%.

The chemotherapy used was generally well tolerated. This was reflected in the toxicity profile of the patients [Table 4]; the majority of the patients experienced minimal diarrhoea, nausea and vomitting, mucositis, alopecia and marrow suppression. The single patient who had grade 3 marrow toxicity had advanced liver metastases. One patient with thalasaemic trait developed grade 2 anaemia. The other side effects encountered were thrombophlebitis due to a direct irritant effect of the drug on the vein used in chemotherapy, hyperpigmentation of the skin and nails and a generalised pruritic skin rash. Toxicity was an uncommon reason for stopping chemotherapy (2.7%). The most frequent reasons for stopping chemotherapy were progressive disease (29.7%) and defaulting of treatment (18.0%) [Table 5] .

In the 8 patients who had palliative chemotherapy without preceding definitive surgery, the overall crude survival ranged from 1 to 52 months.

Radiotherapy was prescribed in 168 patients. Palliative radiotherapy was given in 103 while adjuvant pelvic radiotherapy was given in 64 patients. The intent of treatment was not known in one patient as it was given at another centre.

In the group of patients who received palliative radiotherapy, 8 patients did not undergo prior definitive surgery. The patient and treatment characteristics of these eight patients and a further 13 patients with only colostomy as the sole surgical procedure are summarized in Table 6. The total dose delivered in a palliative setting varied between 2 Gy and 60 Gy, with a median of 45 Gy. The most commonly used number of fractions were 20 to 25 fractions (50%). The *two* field technique was the most frequently used (76%).

Adjuvant pelvic radiotherapy was given to 64 patients. The delay after primary definitive surgery ranged from less than one month to nine months, with a median of two months. The total dose delivered in the adjuvant setting ranged between 10 Gy and 60 Gy, the most frequently used doses being 50 Gy (54.7%) and 45 Gy (31.3%). The number of fractions used most frequently were 20 to 25 fractions (78.1%). The most frequently used radiotherapy technique was again the *two* field technique (84.4%), followed by the *three*-field technique (9.4%) and the *four*-field technique (6.3%). The perineal boost was used in 14.1% of the patients. The upper border of the radiotherapy field was at the junction between the fifth lumbar and first sacral vertebrae (L5/S1 junction) in 78.1%. Preoperative radiotherapy was given in the adjuvant setting in only two patients.

DISCUSSION

Our patients appear to present at an earlier age in contrast with other series in which the proportion of patients less than 40 years old was only 4.5%.[14] Sex distribution for rectal cancer was less extreme than in published literature[15] where the male to female ratio is reported to be approximately 2:1. The distribution by site is similar to published data[16] in which three quarters of all tumours within the large bowel are found in the rectum, rectosigmoid and sigmoid colon. Although the proportion of patients with Dukes' A disease may be lower than in other series,[17,18] it has to be noted that one fifth of our data on stage could not be determined. Moreover, many patients who were in Dukes' Stage A may not be referred to our Institute. The proportion of the tumours that were recorded as adenocarcinoma is similar to published figures of 90% to 95%.[19] While the proportion of our tumours that are poorly differentiated or undifferentiated is compatible with the data from Singapore,[18] it is lower when compared to other published series from the West where the figures are around 20% of the cases.[17]

Only a minority of patients in this series were found to have a predisposing factor to colorectal cancer. This finding contrasts with Western populations in which approximately a third of cancer cases have associated polyps.

Although adjuvant therapy has been shown to have the greatest impact on patients with Dukes'C disease,[9] the practice of this institute has been the use of adjuvant treatment for Dukes' B as well as Dukes' C colorectal cancer. This is partly due to the

fact that the incidence of morbidity in our centre appears to be lower than that reported in other centres. Although serious toxicity was seen in 35% of patients in the combined chemo/radiotherapy arm of the Gastrointestinal Tumor Study Group (GITSG) trial,[3] the addition of 5-fluorouracil to radiotherapy did not add significantly to morbidity in our experience. This could be related to the route and method of administration of 5-fluorouracil which was often given orally or via a continuous intravenous infusion. Moreover, the upper border of the pelvic radiotherapy field was not extended higher than the junction between the fifth lumbar and first sacral vertebrae in the majority of patients, thus further minimising morbidity.

Fluorouracil has remained the mainstay of palliative chemotherapy despite a general response rate of approximately 20% and a median duration of response of 5 months in patients with advanced colorectal cancer.[16] The toxicity of a combination of folinic acid with 5-fluorouracil is greater than with 5-fluorouracil alone and thus only a minority of our patients were given this combination.

The survival in the eight patients with rectal cancers in this study who received only radiotherapy and the thirteen patients who had only defunctioning colostomy and radiotherapy highlights the role of primary radiotherapy and palliative surgery in such cases. Although the quality of life could not be clearly demonstrated in this retrospective study, the crude survival of patients receiving radiotherapy as the primary modality of treatment has been demonstrated to be at least 3 years in half of these patients.

In conclusion, the epidemiological characteristics of the patients with colorectal cancer were similar to other published series except for a younger age at presentation and an underrepresentation of localized (Dukes' A) disease. The patterns of treatment have been influenced by the late stage at presentation, the practical considerations in the population as well as the resources that were available. As the toxicities of therapy experienced by our patients appeared to be less than in other centres, the use of adjuvant treatment in Dukes' B patients was not unjustified. A limitation in this study was the lack of details on the quality of life, especially in the group of patients who had been given palliative treatment.

TABLE 1 Patient characteristics

Total number of patients	320
Age	
Mean	55.4 years
s.d.	12.7 years
Less than 40 years	11.6 %
Sex	
Male	183 (57.2%)
Female	137 (42.8%)
Race	
Malay	94 (29.4%)
Chinese	198 (61.9%)
Indian	23 (7.2%)
Other	5 (1.5%)
Site of Primary tumour	
Rectum	163 (50.9%)
Recto-sigmoid colon	37 (11.6%)
Sigmoid colon	48 (15.0%)
Ascending colon	21 (6.6%)
Transverse colon	16 (5.0%)
Descending colon	17 (5.3%)
Caecum	14 (4.4%)
Unrecorded	4 (1.2%)
Dukes' Stage	
A	6 (1.9%)
B	85 (26.6%)
C	106 (33.1%)
Disseminated	57 (17.8%)
Unrecorded	66 (20.6%)
Histological Type	
Adenocarcinoma	286 (89.4%)
Unrecorded	34 (10.6%)
Grade	
Well differentiated	62 (19.4%)
Moderately well differentiated	157 (49.1%)
Poorly or Undifferentiated	30 (9.4%)
Unrecorded	71 (22.2%)

TABLE 2 SURVIVAL STATUS

	Alive	169 (52.8%)
	Dead	134 (41.9%)
	Unknown	17 (5.3%)
	Total	320 (100%)
Crude survival		
	Mean	27.2 mths
	(s.d.)	(24.4 mths)
	Median	19.0 mths
	Range	1 - 112 mths
Disease free survival		
	Mean	12.4 mths
	(s.d.)	(17.2 mths)
	Median	7.0 mths
	Range	0 - 125 mths

TABLE 3 Recurrence Pattern

ALL PATIENTS (n=320)		
No recurrence	133	41.6%
Local recurrence only	82	25.6%
Local recurrence + Distant recurrence	30	9.4%
Distant recurrence only	73	22.8%
Unrecorded	2	0.6%
Total	320	100.0%

N.B. The liver was involved in 61 patients (18.9%).

TABLE 4 Toxicity of chemotherapy

	Grade 0 No. (%)	Grade 1 No. (%)	Grade 2 No. (%)	Grade 3 No. (%)	Grade Unrecorded No. (%)
Diarrhoea	159 (71.6)	9 (4.1)	9 (4.1)	1 (0.4)	44 (19.8)
Nausea / vomitting	167 (15.3)	6 (2.7)	4 (1.8)	1 (0.4)	44 (19.8)
Mucositis	172 (77.5)	3 (1.3)	2 (0.9)	0 (0)	45 (20.3)
Marrow suppression	158 (71.1)	11 (5.0)	9 (4.1)	1 (0.4)	43 (19.4)
Alopecia	168 (75.7)	4 (1.8)	4 (1.8)	0 (0)	46 (20.7)

TABLE 5 Reasons for stopping chemotherapy

REASONS FOR STOPPING CHEMOTHERAPY	Number	Percentage
PROGRESSIVE DISEASE	66	29.7
DEFAULTED TREATMENT	40	18.0
COMPLETED TREATMENT	38	17.1
TOXICITY	6	2.7
PATIENT'S CHOICE	2	0.9
UNKNOWN	18	8.1
TOTAL	**170 #**	**76.6**

 # Fifty two patients (23.4%) were still undergoing chemotherapy.

TABLE 6. Patients receiving palliative radiotherapy without preceding surgery or with only colostomy

Patients who had undergone only radiotherapy without any preceding surgery

age (yrs)	Duke	zubro status	status	survive (mths)	dose (Gy)	no. frac.	no. fields
49	unk.	2	alive	73	50	25	2
59	unk.	3	alive	47	30	15	2
45	unk.	2	alive	36	50	25	2
65	unk.	1	alive	36	50	25	2
87	unk.	1	alive	21	59	20	4
67	unk.	1	dead	11	30	10	1
62	unk.	1	dead	7	60	20	2
61	D	5	dead	5	30	10	1

Patients who had undergone only colostomy and palliative radiotherapy

age (yrs)	Duke	zubro status	status	survive(mths)	dose (Gy)	no. frac.	no. fields
32	C	2	dead	4	10	4	2
38	unk.	3	alive	15	30	10	2
41	unk.	2	alive	48	60	30	2
43	C	2	dead	4	30	10	2
43	unk.	3	alive	1	30	10	2
54	unk.	3	dead	13	50	20	2
58	unk.	3	dead	12	45	20	2
60	C	1	dead	7	50	25	2
63	D	2	dead	10	45	20	2
65	unk.	2	dead	3	30	10	2
67	D	4	dead	3	40	18	2
67	unk.	2	alive	24	50	25	2
70	D	2	dead	18	45	15	2

unk = unknown

Those patients being treated with only one field were treated with a single perineal field.

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