EUROPEAN JOURNAL OF CANCER 44 (2008) 2340–2343

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Short Communication

Treatment of primary rectal squamous cell carcinoma by primary chemoradiotherapy: Should surgery still be considered a standard of care?

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ARTICLE INFO

Article history:
Received 16 May 2008
Received in revised form
23 June 2008
Accepted 1 July 2008
Available online 15 August 2008

Keywords:
Rectal squamous cell carcinoma (SCC)
Rectal cancer
Primary chemoradiotherapy
Stoma avoidance

ABSTRACT

Rectal squamous cell carcinoma is a rare tumour accounting for only 0.25% of all rectal carcinomas, yet it carries a significant mortality and morbidity. Radical surgery has been advocated as the primary treatment modality with or without adjunctive therapies despite the proven benefits of primary chemoradiotherapy for squamous cell carcinoma (SCC) of the anus.

This report describes 7 cases of rectal squamous cell carcinoma from a single institution over a four-year period, treated with primary chemoradiotherapy. All patients demonstrated significant tumour regression, and surgery to the primary tumour was avoided in all but one of these cases.

Primary chemoradiotherapy can achieve excellent local control for rectal squamous cell carcinoma with surgery employed only for unresponsive or recurrent tumours.

1. Introduction

Colorectal carcinoma remains a leading cause of cancer in the United Kingdom with 36,000 cases diagnosed per year.[1] Approximately, one-third of these are rectal in origin and over 97% of these are adenocarcinomas.[2] Primary rectal squamous cell carcinoma (SCC) is a rare tumour accounting for only 0.25% of all rectal cancers.[2,3] Previously reported treatment strategies vary considerably as there is a lack of scientific data due to this tumour's rarity; however, there is a common perception that treatment should involve primary resection of the tumour.

Following the ACT 1 trial, a UK multicentre trial that showed that radiation in combination with 5-Fluorouracil and Mitomycin C chemotherapy was superior to radiation alone for SCC anus, primary chemoradiotherapy has become the treatment of choice for tumours not suitable for local excision, so avoiding the high morbidity and particularly permanent colostomy associated with abdominoperineal resection (APR).[4,5] APR is now reserved for treatment failures.

This report reviews the management of seven cases of primary rectal SCC undertaken at a single specialist centre, who were treated with primary chemoradiotherapy, and discusses

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0959-8049/$ - see front matter
doi:10.1016/j.ejca.2008.07.004

whether surgical intervention continues to be the treatment of choice for rectal SCC.

2. Methods

Cases of rectal SCC were identified from our prospective, lower gastrointestinal cancer database between January 2004 and December 2007. The diagnosis in each case was clinically found to be rectal in origin and was confirmed histologically by a single pathologist. Staging was completed with a total body computer tomography (CT) scan and rectal magnetic resonance imaging (MRI) in all cases. Demographics, pathology, treatment and outcome data were obtained from the database and were confirmed by a review of the patients' medical records. All tumours were radiologically staged according to the tumour, node, metastasis (TNM) classification for rectal adenocarcinomas.[6] Descriptive statistics were performed based on the available data.

3. Patient and tumour characteristics

Patient demographics, stage and treatment of each case are summarised in Table 1. Staging investigations in one patient showed two metastatic lesions in the left lobe of the liver which was confirmed to be the only site of secondary disease on positron emission tomography (PET). In another patient high pelvic lymphadenopathy was described. No metastatic deposits were elicited in the remaining cases.

4. Treatment

All cases were treated with a similar chemoradiation protocol. Radiation doses and chemotherapy regimens were based on those used in the on-going ACTII anal SCC phase III study.[7] Phase 1 radiotherapy was administered as a planned 3 or 4 field volume to the pelvis except for those cases in which the inguinal areas were treated, in which case parallel opposed fields were employed. The phase 1 volume was treated to a dose of 30.6 Gy in 17 daily fractions, which is the standard 'microscopic' phase 1 dose employed in the UK and has been chosen as the control arm of the ACT II study. The phase 2 volume consisted the primary tumour with a margin of 2 cm and was treated to a dose of 19.8 Gy in 11 fractions. Treatment was administered without breaks, Monday to Friday. Radiation fields were planned according to the position of the primary tumour. The Phase I fields resembled those routinely used for adenocarcinoma of the rectum, and included the primary tumour, pre-sacral space, obturator nodes, internal iliac nodes and lower common iliac nodes. Inguinal nodes were not routinely included except for very low rectal cancers, in contrast to the routine irradiation of this site for the treatment of all but very early anal SCC. In

Table 1 – The patient and tumour characteristics with the treatment regimens employed

Patient reference	Age	Sex	Clinical stage (as for rectal adenocarcinoma)	Grade	Distance from anal verge (cm)	Radiotherapy	Chemotherapy
1	75	M	T3N1M0	Poor	4–6	50.4 Gy in 2 phases 28#	5-FU/Cisplatin
2	71	F	T4N1M0	Poor	6–13	50.4 Gy in 2 phases 28#	5-FU/Mit. C
3	42	F	T4N1M1	Poor	8–10	50.4 Gy in 2 phases 28#	5-FU/Mit. C + further 4 cycles of Cisplatin and 5FU
4	70	M	T4N2M1[b]	Poor	4–10	50.4 Gy in 2 phases 28#	5-FU/Mit. C
5	55	F	T4N2M0[a]	Poor	5–10	54 Gy in 2 phases 30#	5-FU/Cisplatin
6	45	F	T4N1M0	Poor	5–8	50.4 Gy in 2 phases 28#	Capecitabine/Cisplatin
7	71	F	T3N0M0	Moderate	5–7	50.4 Gy in 2 phases 28#	5-FU/Cisplatin

Abbreviations: Mit C, Mitomycin C, #, fractions.
a Break in radiotherapy regimen for 1 week due to anal soreness.
b M1 staging as tumour has extended to para-aortic lymph nodes.

Table 2 – Patient outcomes

Patient reference	Follow-up (months) to June 2008	Surgical resection (Yes-type/NO)	Recurrence (Yes-site/NO)
1	20	No	No
2	31	No	No
3	13	No[a]	No
4	14	No	No
5	19	Anterior resection[b]	No
6	23	No	No
7	5	No	No

Follow-up as determined from end of treatment to current date.
a No resection was undertaken for the primary tumour but a hepatic lobectomy for liver metastasis was performed.
b Anterior resection performed at 6 months post completion of chemoradiotherapy.

case 2, the lower part of the para-aortic chain was judged to be involved and was included in the phase 1 volume. Concurrent chemotherapy was administered in the form of 5-Fluorouracil (5-FU) (days 1–4, week 1 and week 5 of radiation) in combination with either Mitomycin C (day 1, week 1) or Cisplatin (day 1, weeks 1 and 5). In one case the 5-FU was substituted for Capecitabine. One patient with liver metastases was given a further 4 cycles of chemotherapy consisting of Cisplatin with continuous 5-FU infusion commencing immediately after the chemoradiotherapy regimen was finished. This patient subsequently underwent a left hepatectomy. The patient completed 2 cycles of adjuvant 5-FU and Cisplatin post liver resection.

One patient had a 7-day break in the radiotherapy treatment towards the end of the 5th week regimen due to intense anal soreness. Treatment was concluded after symptom resolution. In two patients a diverting sigmoid loop colostomy was fashioned laparoscopically to relieve symptoms of severe tenesmus, urgency and incontinence prior to commencing chemoradiation. Both have been reversed successfully with a good bowel function.

Follow-up was with clinical review at 6 weeks by the Oncologist, then clinical and radiological restaging with whole body CT and MRI pelvis which was undertaken at 18 weeks post completion of treatment. Examination with proctosigmoidoscopy was performed at this time with biopsies taken from the relevant sites. If complete response was observed (clinically and radiologically) the patients were followed up clinically 2 monthly for the first year, 3 monthly for the second and 6 monthly thereafter until year five with CT surveillance at 6, 12, 18 and 24 months post completion of treatment.

5. Results

On initial repeat staging, all patients showed a good radiological response to the chemoradiotherapy which was confirmed clinically. At a median follow-up of 18 months (range 5–31) post treatment, there have been no local or distant recurrences in this group of patients. Table 2 summarises the outcomes.

In case 5, the primary tumour showed a limited reduction in size radiologically at 18 weeks post chemoradiotherapy when images were compared to baseline. Examination under anaesthesia and biopsies of the lesions revealed no evidence of residual disease, and PET scan was negative. At the patient's request, anterior resection (AR) with total mesorectal excision was undertaken without any postoperative complications. Histology of the specimen confirmed only hyalinised fibrosis with no viable tumour being identified.

In case 3, the specimen from the left hepatectomy, undertaken due to the liver metastasis, demonstrated a complete pathological response following chemotherapy. The primary tumour in this case also demonstrated a complete clinical

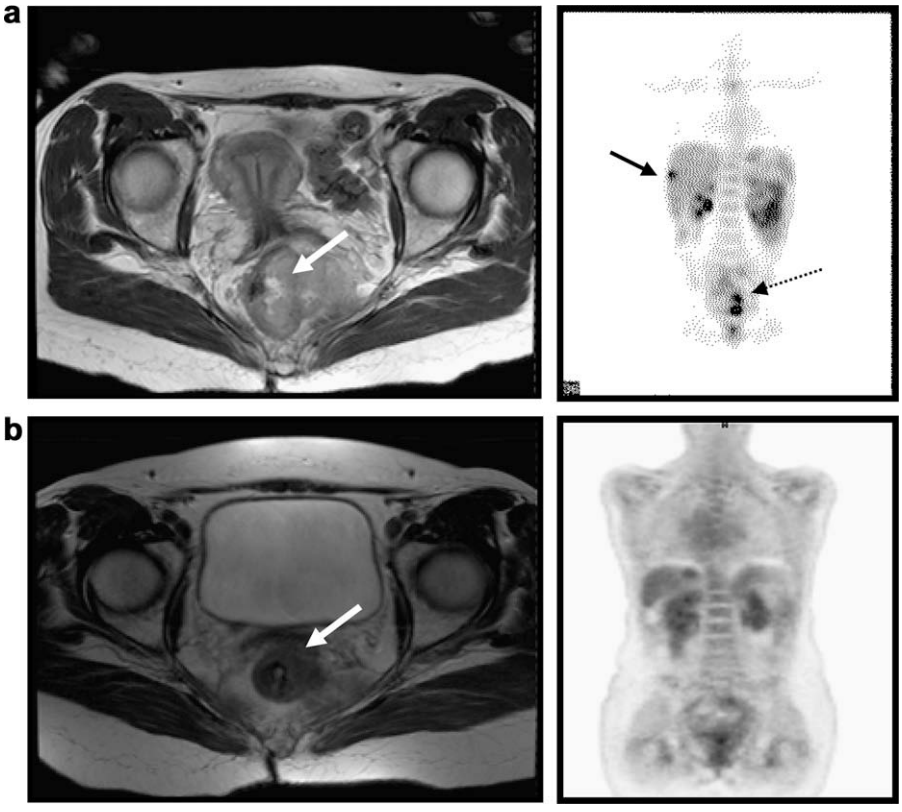

Fig. 1 – Staging MR and PET images (a) and follow-up MRI and PET (b) 12 months later shows good reduction in the size of the rectal primary (white arrow). Although there is still some residual thickening, PET scan shows that pre-treatment rectal activity (dashed black arrow) has resolved confirming complete response. Also of note, FDG uptake in the liver (solid black arrow) has also disappeared after liver resection.

response which was confirmed by PET (Fig. 1). At the time of hepatectomy, examination of the pelvic contents by the surgeon revealed no abnormal clinical features.

6. Discussion

Previous case reports describe surgery as the primary treatment, with AR or APR of the rectum being employed and with generally poor outcomes. These operations carry a significant mortality (1–7%)[8] and morbidity (13–46%).[8,9] Therefore, avoidance of any surgical intervention of this nature would be beneficial to the patient.

The initial introduction of chemoradiotherapy to the treatment plan was found to offer only moderate improvements to the outcome.[10] In this series, we have shown that primary chemoradiotherapy, similar to that used in the management of squamous cell carcinoma of the anus, results in good local control of the primary tumour. Follow-up for this patient cohort is limited, but for primary SCC anus it has been shown that following a complete radiological and clinical response to chemoradiation, 60% of local and systemic recurrences occur within 1.2 years from completing treatment,[11] and it is assumed that SCC rectum has a similar tendency to relapse at a relatively early time point.

Two reports have described results with neoadjuvant chemotherapy followed by resection,[12,13] but chemotherapy regimens varied and would now be considered outdated. The most recent series reports on 12 cases of primary rectal SCC.[14] All the patients survived and were disease free at follow-up. Two underwent primary surgery with adjuvant radiotherapy whilst another received only primary chemotherapy. Nine patients received chemoradiotherapy as per standard anal SCC protocols as in this series, following which two showed a complete radiological and clinical response and did not receive surgery. The other seven underwent surgery, of which two required an abdominoperineal excision. In six of these seven patients, a complete pathological response was found, the remaining case demonstrating a 95% tumour regression. These results would suggest that the use of chemoradiotherapy for rectal SCC may offer definitive therapy, with surgery reserved for non-responders or recurrent disease as with anal SCC. The authors justified surgery as they found it difficult to assess tumour response clinically, but surgery was timed as early as 10 weeks post treatment. Tumour response in anal SCC can continue for up to 6 months after completion of chemoradiotherapy. Therefore, a more prolonged assessment may have allowed for a clearer evaluation of tumour response and averted the need for surgery. PET imaging may also aid in the assessment of tumour response.

When considering the patient with metastatic liver disease, treatment by chemoradiotherapy to the primary followed by 4 cycles of chemotherapy was shown to produce complete pathological regression of the metastatic liver disease. Similar results have been reported previously in the literature.[15]

7. Conclusion

This is a rare cancer so large comparative series or randomised trials are unlikely to be possible to help determine the optimal treatment. However, the outcomes from these cases demonstrate that good results can be obtained from using chemoradiotherapy as the primary treatment. Close clinical and radiological follow-up should be maintained with subsequent surgery being employed only for non-responders or tumour recurrence.

Conflict of interest statement

None declared.

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