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ORIGINAL ARTICLE

Could a wait and see policy be justified in T3/4 rectal cancers after chemo-radiotherapy?

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Abstract

Chemoradiotherapy (CRT) followed by total mesorectal excision is the standard when MRI staging demonstrates threatened surgical margins in locally advanced rectal cancer (LARC). Interest in non-surgical management of LARC as an alternative to a resection has been provoked by published excellent long-term outcomes of patients who achieve clinical complete responses (cCR) after CRT. The present retrospective study aimed to determine whether similar rates of local disease control are seen in a UK cancer centre in patients with T3-4 tumours, who obtained a cCR after preoperative CRT, but did not undergo surgery. *Method.* The outcome and treatment details of 266 patients who underwent CRT for clinically staged T3-4 rectal adenocarcinomas between 1993 and 2005 were reviewed. *Results.* Fifty-eight patients did not proceed to surgery, 10 of whom were identified as having a cCR. Six of these 10 patients subsequently developed intrapelvic recurrent disease with a median time to local progression of 20 months. Local relapse preceded the development of metastatic disease or occurred simultaneously. No patients underwent salvage resection. *Conclusion.* CRT alone in cT3/T4 rectal cancers has a high rate of local relapse even after cCR. Delaying or avoiding surgery might be appropriate for cT1 or cT2 tumours, or elderly and frail patients with co-morbidity, but these results do not support the current uncritical move to extrapolate this approach to all surgically fit patients with rectal cancer.

Preoperative chemoradiation (CRT) followed by total mesorectal excision (TME) is currently the standard of care in patients with locally advanced rectal cancer. Pathological complete response (pCR) rates of 13–30% have been reported in phase II and phase III trials following 5FU based preoperative CRT [1,2]. A recent review identified 3 157 patients from 77 phase II and phase III trials. The overall pCR rate in these studies was 13.5% [3]. Thus a small proportion of patients, if predicted prior to surgery, might be permanently controlled by non-surgical treatment.

Surgical resection is associated with significant morbidity especially in the elderly, and often entails the need for a permanent stoma. Patients, who obtain symptomatic benefit during CRT may often question the need to proceed with surgical resection. Surgeons who review a pCR in an abdomino-perineal resection (APR) specimen resection specimen sometimes think likewise.

As approximately 50% of patients presenting with locally advanced rectal cancer (LARC) will subsequently develop metastatic disease. Then, additional local treatment with surgery, when a clinical complete response (cCR) is observed, may be unnecessary, as overall survival would be determined by the development of metastatic disease.

For these reasons, support is growing in the UK for the concept of "wait and see" and not proceeding to surgery when a cCR is observed following neoadjuvant chemoradiation. A prospective observational study is underway [4].

The interest in a "wait and see" approach has been fuelled by the excellent long-term outcomes reported by Habr Gama [5]. In this series 265 patients were clinically staged as localised disease within 7 cm of the anal verge (20% clinically T2), and all considered appropriate for an APR. After completing preoperative CRT, they were assessed eight weeks after the end of treatment. Of these, 71 patients (26.8%), who appeared to have had a cCR (defined by clinical examination, and CT scan), were closely followed up rather than undergoing immediate surgery. Any suspicion of persistent disease was

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subjected to excisional biopsy. With a follow-up of 57 months only five (5%) patients experienced a local recurrence, all of which were considered salvageable by surgery. The data was further updated in 2005 and 2006 [6,7]. Overall survival and local disease control rates were reported to be higher than published surgical series in rectal cancer [8,9], with the majority of relapses being metastatic. The authors comment that local recurrences in this series were always endoluminal and hence easily amenable to surgical salvage.

The aim of the present study was to assess the long-term outcome of patients in our unit, who had a cCR at 6–8 weeks after the completion of preoperative CRT and did not proceed to surgery, from a prospectively maintained database of 266 patients.

Methods

The characteristics, treatment details and outcome of 266 patients undergoing preoperative CRT for T3-4 rectal carcinomas between November 1993 and December 2005 at Mount Vernon Hospital were reviewed. From this prospectively maintained database, we aimed to identify patients who achieved a cCR and had not proceeded to surgery, and examine their long-term outcomes with regard to local control, surgical salvage and the development of metastases.

Clinical examination, ultrasound and CT scanning determined pre-treatment tumour stage. Since 1997, 147 patients (55%) in addition had preoperative pelvic MRI scans.

Treatment planning was delivered using a 3 or 4 field box technique using mega voltage radiotherapy to a dose of 45 Gy in 25 fractions of 1.8 Gy per day prescribed to the International Commission on Radiation Units (ICRU) intersection point. In addition, six patients received a brachytherapy boost after the completion of external beam treatment of 10–12 Gy in 2 fractions.

Concurrent chemotherapy was given according to either to a 5 Fluorouracil /folinic acid (Bosset) regime with 350 mg/m^2 and 20 mg/m^2 days 1–5 and 29–34 (196 patients, 74%), with continual infused 5-Fluorouracil at 200 mg/m^2/day (22 patients, 8%) or with capecitabine 850 mg/m^2 bid Monday-Friday during radiotherapy (20 patients, 8%). In addition, 23 patients (9%) received combination chemotherapy with either irinotecan or oxaliplatin as part of phase I/II studies.

Patients were reassessed both clinically and with repeat imaging 6–8 weeks after completing CRT. Surgical resection was planned for between 6 to 12 weeks after treatment.

Results

Of the 266 patients within our database, 58 patients did not proceed to surgery either due to metastatic disease (10), insufficient downstaging (9), co-morbid factors (12) or patient choice (5). Two patients died prior to surgery. In 20 patients the reason for not proceeding was either a combination of the above (15) or unclear (5).

Ten of these 58 patients were identified as having had a cCR at clinical reassessment 6 to 8 weeks after CRT, – defined as complete resolution of tumour on digital rectal examination, and after 1997 on MRI criteria as well. These 10 patients form the basis of our study. Patients achieving cCR were not subjected to excisional biopsy.

Patients within the study group had a median age 14 years older compared to those who underwent surgical resection (78.5 years vs. 64 years). All patients had locally advanced clinically staged T3 or T4 tumours prior to treatment with a mean tumour length of 3.5 cm (range 2–8.8 cm).

The reasons for not proceeding with surgery in these 10 patients were patient choice in three patients, and comorbidity in seven patients (old age and frailty in three patients, ischaemic heart or peripheral vascular disease in two patients, multiple sclerosis in one patient, second malignancy in one patient).

Eight of the10 patients have died, six from recurrent disease and two from concurrent medical problems (both of whom were considered disease-free at the time of death at 4.4 and 51 months after treatment respectively). Both of the surviving patients remain disease free at 22 and 71 months. Median overall survival was 34.6 months (range 4.4–85.8 months). All six patients who developed recurrent disease developed metastases.

Local recurrence within the pelvis occurred prior to systemic progression in five of the six patients, and simultaneously in the remaining patient. Only one patient was considered for salvage surgery but did not proceed to resection. The median time to metastatic disease was 30 months (range 10–81 months) whereas the median time to local disease progression was 20 months (range 10–80 months). The median interval between developing local recurrence and metastatic disease was 9.6 months.

Discussion

For low rectal tumours, surgeons and oncologists have collaborated to produce less mutilating approaches. Thus strategies such as preoperative chemoradiation followed by sphincter sparing surgery or local excision have been explored [10,11]. Our present series prospectively collected data for

patients undergoing CRT for cT3 and T4 tumours over a period of 12 years. Despite the long period of data collection and 266 patients treated, only 10 patients were identified who fulfilled the criteria for observation as described by Habr Gama [5]. The much lower rate of cCR following CRT may reflect the more advanced pre-treatment stage of the patients in our series, 96% of whom had clearly defined T3 and T4 disease, often with potentially threatened surgical resection margins on MRI.

In our series, a high rate of local relapse was observed with six of 10 patients showing local disease progression. Recurrence was not confined to the endoluminal surface in these patients, and only one patient was considered potentially suitable for salvage resection, but did not proceed because of comorbidity. Pelvic relapse was a precursor to systemic disease and death.

There is also concern that clinical examination is unreliable in assessing tumour response post CRT. Up to 75% of patients who appear to have obtained a cCR still have microscopic disease at the time of full thickness biopsy [12,13]. Similarly in a small series 76% of patients who were subsequently demonstrated have had a pCR had palpable abnormalities with the rectum consistent with residual tumour [14]. The difficulties of accurate prediction of complete pathological response limit the use of clinical response alone as an end point for determining future management.

An excisional tumour biopsy was not performed to confirm cCR in any of the patients in our study. The original tumour site was not tattooed for later identification and localisation. Many small observational studies show that pCR (ypT0) in the primary tumour, only partially correlates with sterilisation of microscopic disease within the pelvic lymph nodes [15–19] therefore 15–25% of patients may still have positive lymph nodes leading to the potential of local disease relapse.

The schedule of chemoradiotherapy used by Habr Gama differs to that used in our centre. Habr Gama gave 5FU 425 mg/m^2 days 1–3 and for the final three days of treatment. The radiotherapy protocol also differed with a higher prescribed dose of 50.4 Gy in 28 fractions. Neither the different radiotherapy nor chemotherapy schedules would be predicted to significantly affect the observed treatment outcomes.

Excellent local disease control and overall long term survival have been demonstrated for patients with early stage T1 and T2 tumours, treated with contact or brachytherapy, yet high rates of local failure is seen in series where there are significant numbers of patients with T3 disease [20]. In a recent Australian series 18/48 patients with locally advanced disease who either declined or were medically unfit for surgery eventually relapsed despite periods of local disease control and palliation [21]. The degree of tumour fixation and local tumour extent appear to predict for particularly poor outcomes [21].

Habr-Gama's updated experience with longer follow-up, relates to 71 selected patients who continued to maintain a complete clinical response after 14 months [5]. With a median follow-up of almost five years, there are no deaths due to rectal cancer and only three patients have relapsed locally. This suggests that a plateau is reached after 14 months after which there is an extremely low rate of local disease relapse. Our series, although small, demonstrated no plateau phase with a steady development of local relapses. The longest relapse developed 80 months after CRT.

Several studies have examined local excision alone for T1/T2 rectal cancers. These demonstrate a small proportion of patients (between 10 and 30%) are disadvantaged by this approach [22,23]. It could be suggested that a similar percentage of patients might be disadvantaged by deciding not to proceed with surgery, both in terms of an unacceptable local recurrence rate and a poor salvage rate. In studies of local excision, many of those who subsequently relapse are unsuitable for surgical salvage, since recurrent rectal cancer is often a diffuse pelvic process following radiotherapy. The results of salvage surgery are not as good as initial radical treatment [24].

In our series 6/10 patients suffered local recurrence. Clearly there are many limitations to this study, which represents a very small and uncontrolled subset analysis examined retrospectively with relatively short follow-up. Our patients were older and some had tumours higher in the rectum than in the Habr-Gama series. Excisional biopsy was not used as routine for predicting pathological response. Also we were not proactive in attempting to detect local recurrence at a stage when surgical salvage could have been an option. In contrast, Habr-Gama used a meticulous monthly programme of follow-up for the first year. However, the risk of local recurrence might be predicted to be higher in a group of younger fitter patients because of longer predicted survivals. Hence, the decision not to proceed with definitive surgical treatment needs to be taken with care and thoroughly explored with the patient [25].

Conclusion

Delaying radical surgery and adopting a 'wait and see' strategy might be appropriate for selected cT1 or cT2 tumours who achieve a cCR, where the patient is unfit because of comorbidty, or is unwilling to undergo radical surgery. However our long-term

results do not support the current uncritical move to extrapolate this approach to all surgically fit patients with clinically staged T3 and T4 rectal cancers. We will need clinical trials with careful methodology and patience to determine suitable patients.

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