Improving outcomes in rectal cancer

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Concerted efforts are being made to improve the poor surgical outcomes in rectal carcinomas and this includes the use of total mesorectal excision by specially trained colorectal surgeons, in addition to the use of pre- or postoperative radiotherapy and chemotherapy. The role of each modality should be carefully evaluated, and benefits weighed against toxicity and added costs.

In the UK over 10 000 cases of rectal carcinomas are reported each year. The mortality is also as high as in colon carcinoma with only 37% of the patients surviving 5 years.

Up to half of the patients undergoing curative resection for rectal cancer will develop recurrent disease within 2 years. The local extent of the tumour, nodal involvement and the involvement of the circumferential resection margin are the factors mainly responsible for the local recurrence (Quirke et al, 1986). Patients with local recurrence may experience intractable pelvic pain, bleeding or rectal discharge which may be troublesome and could result in poor quality of life for the duration of their survival. Many of these patients could also have metastatic disease in the liver, lungs or bones and their survival is usually limited to less than 1 year.

Recently, radiotherapy has been offered widely to improve local control and two main schedules are used, either short course preoperative radiotherapy or long course postoperative radiotherapy (Krook et al, 1991). Although early studies using low dose radiation were disappointing, more recent studies have shown encouraging results in terms of reducing local recurrences. However, only a few trials have shown clear benefit on survival. The role of systemic adjuvant chemotherapy is still under investigation.

SURGERY

Surgery has been the mainstay in the management of rectal carcinomas in the past and this is likely to continue for the foreseeable future.

The majority of rectal carcinomas are operable at presentation and although curative resection can be offered, only less than half of these patients will survive 5 years. Of patients who are offered curative surgical resection, 20–50% will develop incurable recurrences within 2 years of surgery and the majority of these patients will die (McCall et al, 1995). Concerted efforts are being made to improve surgical outcomes. One approach is to use total mesorectal excision of the rectum, a technique that has been popularized by Professor Bill Heald (McFarland et al, 1993). The other is to restrict these operations to surgeons who are specially trained and to manage these patients together with the multidisciplinary team. This is the basis of the Calman–Hine reforms and it remains to be seen whether these changes will actually improve the surgical results.

RADIOTHERAPY

In the past, radiotherapy has only been reserved for symptomatic local recurrences after surgery. Although more than 80% of symptoms can be improved by radiation, local cures are rarely achieved. Duration of symptom relief is variable and may require additional forms of palliative treatment such as chemotherapy. Therefore, it is best to use radiotherapy to prevent such recurrences. Both preoperative and postoperative radiotherapy could be used to improve local control.

There are at least twenty randomized trials comparing surgery alone with surgery plus either pre- or postoperative radiotherapy. Earlier trials using low dose preoperative radiotherapy showed no significant effects on local control or survival. However, at least four more recent randomized trials using preoperative radiotherapy have shown significant reduction in local recurrences and a trend towards survival benefit.

PREOPERATIVE RADIOTHERAPY

The Swedish rectal cancer trial randomized 1168 patients with operable rectal cancer tumours to either surgery alone or a short course preoperative

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radiotherapy (25 Gy in 5 fractions over 5 days) followed by definitive surgery within a week. After a median follow-up period of 5 years, the local recurrence rate was reduced from 27% to 11% when radiotherapy was given before surgery. This reduction in local recurrence was seen in all stages of rectal cancer including patients with Dukes' A carcinomas. Moreover, this was the first trial to show an improvement in both overall and cancer-specific survival without the use of adjuvant chemotherapy. The overall 5-year survival rate for radiotherapy plus surgery was 58% compared to 48% for surgery alone ($P \leq 0.004$)(Swedish Rectal Cancer Trial, 1997). The previously reported increase in mortality has been overcome by using the carefully planned three fields technique (*Figure 1*) rather than large parallel opposing fields (Frykholm et al, 1996). However, there was considerable morbidity associated with this type of treatment and it should only be offered to those patients who would benefit.

The difficulty is in selecting patients who may benefit and this type of treatment approach is now being evaluated in the UK Coordinating Committee on Cancer Research (UKCCCR) CRO7 trial. Moreover, this approach does not address the important question of sphincter preservation (Minsky et al, 1991). Patients with fixed inoperable tumours are offered long course preoperative radiotherapy, with or without chemotherapy, to downstage tumours in order to render them operable. The Medical Research Council (MRC) has evaluated the role of long course preoperative radiotherapy in patients with clinically fixed rectal tumours and this has shown a significant reduction in local recurrences and an improvement in the chance of operability (MRC Rectal Cancer Working Party trial, 1996a).

POSTOPERATIVE RADIOTHERAPY

There is a considerable debate on whether preoperative radiotherapy offers any benefit over postoperative radiotherapy, which is the standard treatment in the USA and to a lesser extent in the UK. There is some evidence that postoperative radiotherapy is much more toxic and it has been shown in the largest UKCCR colorectal trial (Adjuvant X-ray and 5FU Infusion Study; AXIS) that less than 60% of the patients completed the full course of treatment.

The MRC CRO3 trial randomized 469 patients with Dukes' B and C rectal carcinomas after curative resection into two groups receiving no further treatment or 4 weeks of postoperative radiotherapy. There was a significant reduction in local recurrences in the treatment arm, 21% *vs* 34%. However, the trial did not demonstrate a clear survival benefit (MRC Rectal Cancer Working Party trial, 1996b).

PALLIATIVE RADIOTHERAPY FOR RECTAL CARCINOMAS

Radiotherapy is very effective in controlling symptoms from recurrent disease after surgery (*Figure 2*) or in those patients presenting with locally advanced tumours who are not fit for surgery. External beam radiation alone or in

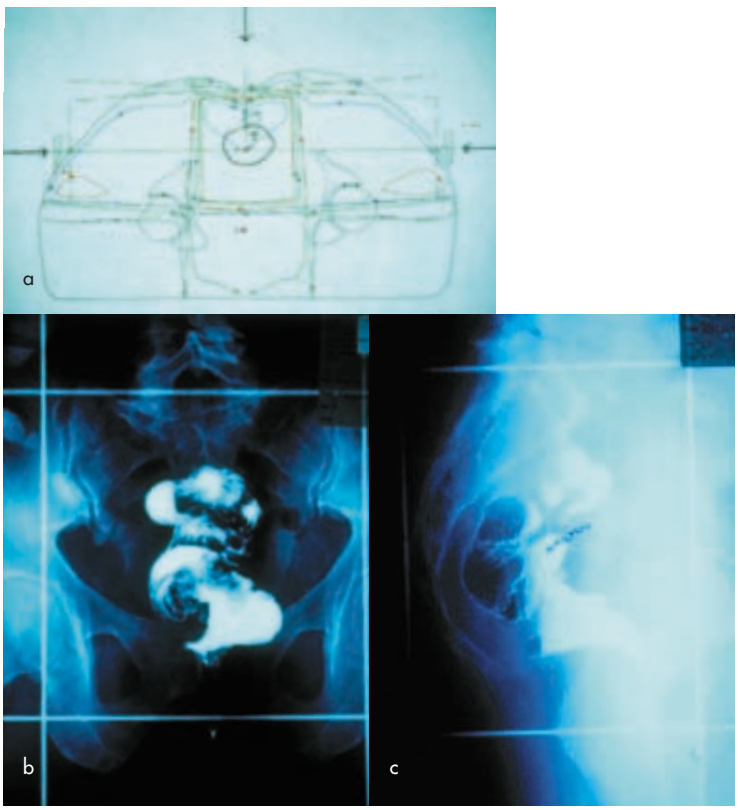

Figure 1. Careful radiotherapy planning using three fields is essential to reduce radiation-related side-effects. a. Isodose plan for rectal tumour using three fields set up. b. Posterior radiation field. c. Lateral radiation field.

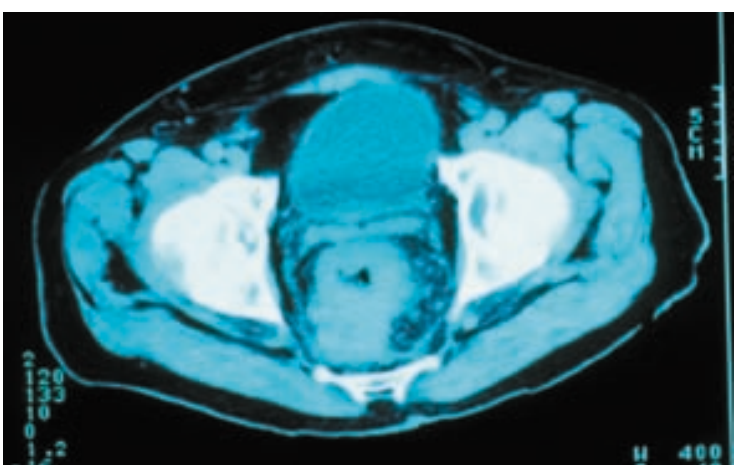

Figure 2. Computed tomography scan showing local recurrence of rectal tumour following surgery.

combination with chemotherapy could be offered. This treatment could be supplemented by using intraluminal brachytherapy to boost the radiation dose (Myint, 2000).

LOCAL TREATMENT OF SMALL RECTAL CARCINOMAS

In cases with low rectal carcinomas, the conventional treatment is to offer abdomino-perineal excision of rectum (APER) with permanent colostomy. However, patients with small rectal carcinomas (T1) which are <3 cm in size with well-differentiated histology could be offered conservative treatment either using manual transanal resection of tumours (TART) or transanal endoscopic microsurgery (TEM) (Hershman et al, 1999).

One of the advantages of TEM over TART is that full thickness resection could be carried out using this technique to resect tumours which are located high up in the rectum (*Figure 3*). It is important to stage the tumour carefully using intra-anal ultrasound (*Figure 4*) or intra-anal magnetic resonance imaging (*Figure 5,6*) to assess the local extent of the tumour and to exclude metastatic lymphadenopathy. In patients who are not fit for surgery, radical contact radiotherapy could be offered (*Figure 7*). Professor Papillon from Lyon has shown in his personal series of 280 patients treated over a 40-year period that local control of 90% of patients can be achieved in elderly and infirm patients (Papillon, 1990).

For mobile tumours greater than 3 cm or T2 tumours, external beam long course preoperative radiotherapy could be offered, with or without chemotherapy, to downstage the tumour in order to reduce the tumour size. This could then be

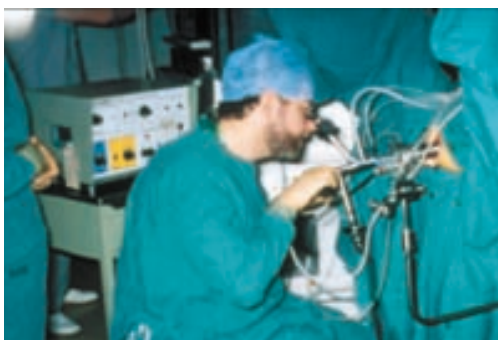

Figure 3. Local resection of tumour using transanal endoscopic microsurgical (TEM) technique.

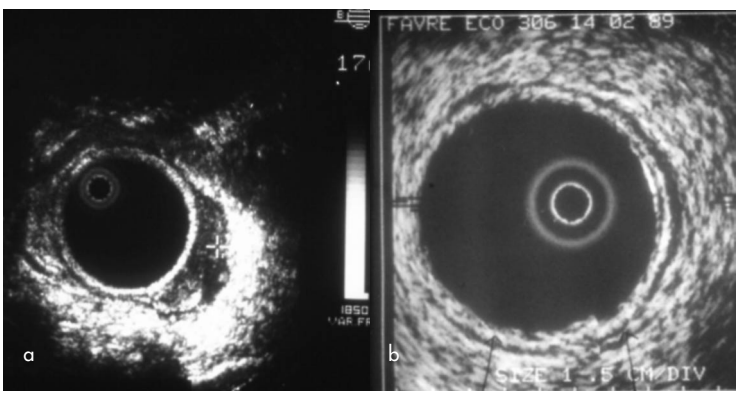

Figure 4. a. Intra-anal ultrasound scan showing T2 tumour. b. Intra-anal ultrasound scan showing complete response 3 months following contact local radiotherapy.

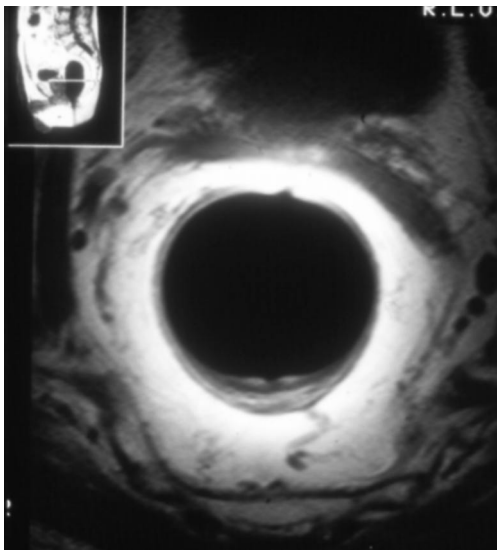

Figure 5. Intra-anal magnetic resonance imaging showing T1 rectal tumour that is suitable for local contact radiotherapy or transanal endoscopic microsurgery.

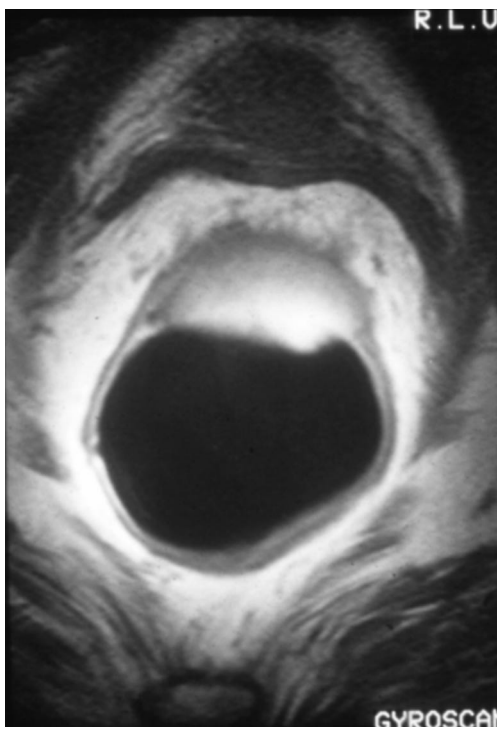

Figure 6. Intra-anal magnetic resonance imaging scan showing T3 tumour, which is not suitable for local treatment.

followed by transanal resection, using either TART or TEM. Again, in patients who are not suitable or fit for surgery, a radical contact radiotherapy boost either using Papillon technique or high dose rate brachytherapy intraluminal boost could be offered. This could avoid APER with permanent colostomy in elderly patients with low-lying T1 or T2 rectal carcinomas. The efficacy of this approach should be evaluated in a randomized trial, but as the number of patients accrued will be very small in each country, a multicentre international trial may be necessary.

CHEMOTHERAPY

Postoperative chemoradiotherapy

Although postoperative radiotherapy trials have not shown any survival benefit, there is a suggestion that the addition of chemotherapy to postoperative radiotherapy may not only improve local control but also survival. The consensus statement for the postoperative trials (GTSG-7175 and NCCTGT 79-47-51) analysed by the Nationa Cancer Institute has shown survival benefit for postoperative chemoradiotherapy compared to postoperative radiotherapy or surgery alone (Woolley et al, 1992).

The NCCTG 86-47-51 trial compared the enhancement of postoperative radiotherapy by concurrent administration of bolus injection or continuous infusion. Both groups received adjuvant chemotherapy. After a median follow-up of 46 months, patients who received continuous infusion had significantly improved survival and disease-free interval ($P \leq 0.001$). However, there was a significant increase in toxicity with 24% of patients experiencing grade 3 or 4 diarrhoea. This highlights the importance of being aware of the price these patients have to pay to achieve better local control and survival (O'Connell et al, 1994). European Society for Therapeutic Radiology and Oncology (EORTC) is currently evaluating the role of chemotherapy given preoperatively (neoadjuvant) or postoperatively (adjuvant) with or without long course preoperative radiotherapy. The results are awaited with interest.

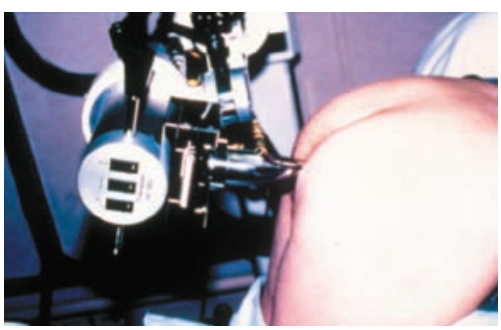

Figure 7. Local contact radiotherapy for small rectal tumour.

Adjuvant chemotherapy

Most trials published so far include both rectal and colon cancers with very few trials addressing the role of systemic chemotherapy in rectal cancers only. Moreover, the increasing use of chemoradiotherapy in rectal cancer will make the contribution of adjuvant chemotherapy alone very difficult to evaluate. Therefore, the role of adjuvant chemotherapy in rectal carcinoma is still not clear and is currently being investigated in a number of randomized clinical trials.

Chemotherapy for metastatic disease

5-fluorouracil (5-FU) has been the only drug available for the past 40 years. However, in the past 5 years there has been an explosion of new drugs that are now available for patients with metastatic carcinomas. The two main new agents are irinotecan (Cunningham et al, 1998) and oxaliplatin. The preliminary result of CR06 trial has confirmed the efficacy of the De Gramont's regimen, which is most widely used outside trials in the UK. The ongoing CRO8 (FOCUS) trial randomizes between 5 different drug regimens and the sequence of second-line chemotherapy. Recently, there is much interest in oral chemotherapeutic agents and there are several that will be available for use.

Capcetabine is one of the oral preparations and has interesting pharmacological properties in that when taken orally it is an inactive prodrug which rapidly converts into active 5-FU by thymidine phosphorylase, which is present in higher concentration inside the tumour cells compared to normal. The oral preparations may in the future replace infusion chemotherapy and their role is currently being assessed in a number of randomized trials.

MANAGEMENT OF HEPATIC METASTASIS

Twenty per cent of patients have liver metastases at presentation and about 50% of treated patients will develop hepatic metastases from which they will eventually die. Careful assessment is essential to determine whether the liver metastases are resectable. Approximately 10% of patients with liver metastases have a solitary lesion, confined to a single lobe. Resection can still be possible for multiple metastases; however, results are poor if more than four metastases are present. Patients with borderline operable disease could be offered neoadjuvant chemotherapy and in selected patients resection may be feasible after chemotherapy (Bismuth et al, 1996).

Several centres in the UK are participating in the current EORTC neoadjuvant trial using oxaliplatin and a modified De Gramont regimen.

In patients who have had curative resection, a 40% 5-year survival can be expected. Adjuvant chemotherapy has been used following hepatic resection to improve the results and both systemic chemotherapy or intrahepatic infusion chemotherapy have been used (Kemeny et al, 1999). For those patients who are not suitable for resection, other modalities such as cryotherapy, interstitial laser photocoagulation and radiofrequency ablation could be considered. Palliative radiotherapy could also be offered in suitable patients with symptomatic inoperable liver metastases (Myint, 1999).

CONCLUSION

The management of rectal carcinomas has become quite complex and demanding. These patients, especially those with fixed tumours and those with small low lying mobile tumours ,should be treated only by surgeons who are specially trained and working closely with a multidisciplinary team of oncologists, radiologists, pathologists, nurse specialists and a palliative care team. Early detection through screening programmes is being evaluated in the UK at present and could be offered to a target population if they are found to be beneficial. These measures will certainly help to improve the surgical outcomes, which are very poor at present in the UK with only 37% of patients surviving 5 years.

A meta-analysis of the results of randomized trials of radiotherapy *vs* no radiotherapy shows a significant reduction in local recurrences and in deaths from rectal carcinoma in patients who have had curative resection. So far, these trials have not shown statistically significant improvement in overall survival. Whether preoperative radiotherapy is better than postoperative radiotherapy and also whether chemoradiotherapy is better than radiotherapy alone in the management of rectal carcinoma is still controversial (Palhlman et al, 1990). Clinical practice in the UK and Europe differs quite substantially from that in the USA. Therefore, it is important to continue evaluating the role of radiotherapy in properly conducted randomized trials such as CR07, so that patients who could benefit may be identified and offered treatment while avoiding toxicity for those who do not need it. **HM**

KEY POINTS

- Although surgical resection is possible in the majority of patients, over half will develop local recurrence or metastatic disease within 2 years.
- Surgical results for rectal carcinomas are poor with only 37% of the patients surviving 5 years.
- Specially trained colorectal surgeon working together with multidisciplinary team is necessary to improve surgical results.
- Either pre- or postoperative radiotherapy can reduce local recurrences and may improve survival.
- Radiotherapy technique is important to reduce side-effects.
- The role of adjuvant chemotherapy is still not clear in rectal carcinomas.
- Local treatment of small rectal tumours can be offered to avoid abdominoperineal excision of rectum with permanent colostomy.

Conflict of interest: none.

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