Original article

Radiochemotherapy in rectal cancer: the role of oxaliplatin

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Abstract

Radiation therapy is well established in the treatment of early and locally advanced rectal cancer, where it has been used in both the pre-operative and postoperative settings. Pre-operatively, radiation therapy has been shown in a series of studies culminating in the Dutch total mesorectal excision (TME) study to significantly reduce the rate of local recurrence at 2 years. However, the overall rate of survival was not improved in this study because radiotherapy failed to reduce the incidence of distant metastases. Chemotherapy, however, may reduce distant metastatic spread, as well as increasing the rate of R0 resectability and sphincter-saving surgery when used in combination with radiotherapy in the neoadjuvant setting. Oxaliplatin is a prime candidate for radiochemotherapy in rectal cancer because it frequently has large and rapid cytoreductive effects in colorectal malignancies and has been shown *in vitro* and preclinical models to be radiosensitizing. In an Italian phase I/II study, weekly oxaliplatin combined with standard infusional 5-FU and pre-operative radiotherapy has shown low toxicity and promising antitumour activity. These encouraging results are now being followed up in a more extensive trials programme. A randomized trial comparing this regimen with standard infusional FUra and radiotherapy (STAR, Studio nazonaleTerapia neoAdiuvante Retto [National Study on Neoadjuvant Treatment of Rectal cancer]) is being launched in Italy. A new phase II study, CORE (Capecitabine, Oxaliplatin, Radiotherapy and Excision), is now in development in Europe and will use a similar weekly treatment regimen with an oral fluropyrimidine in place of infusional FUra, and a number of further oxaliplatin-based radiochemotherapy studies in rectal cancer are planned or in progress. In summary, radiochemotherapy appears to have the potential to significantly improve clinical outcomes in rectal cancer, and oxaliplatin-based treatment is proving central to its ongoing development.

Keywords Radiochemotherapy, rectal cancer, TME, oxaliplatin, radiotherapy, chemoradiation, CORE study

Introduction

As with other forms of colorectal cancer, surgery is the basis of treatment for rectal cancer and offers the only prospect of cure for most patients [1,2]. However, rectal carcinoma is distinctive in that it is also treatable with localized and accurately directed radiotherapy, which has now become established as an important adjunct to surgery [2,3]. Radiotherapy has a variety of uses in rectal cancer, including reducing local recurrence, downsizing initially unresectable tumours and downsizing tumours to allow sphincter-preserving surgery [3]. In cases where cancer is diagnosed at a very early stage it may be possible to achieve cure using radiotherapy without recourse to surgery [3].

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By contrast, the role of chemotherapy in combination with radiotherapy in rectal cancer is less well defined, although there is an increasing enthusiasm for radiochemotherapy in the management of rectal cancer. Postoperative chemotherapy undoubtedly has a role in reducing the risk of distant metastases and in treating metastatic disease much as it is used in colon cancer [4,5]. It also, however, has a potential role in further reducing local recurrence rates and downsizing tumours when administered in combination with radiotherapy. However, the clinical role of radiochemotherapy has yet to be adequately delineated, and the optimal means of combining these modalities to maximize response and minimize toxicity remain under investigation.

Chemotherapy for colorectal cancer has been significantly advanced by the introduction of oxaliplatin. In advanced colorectal cancer, oxaliplatin improves response rates and extends the duration of disease-free and overall survival compared with 5-FU/leucovrin-based therapy [6–8]. In cases involving limited metastatic spread,

oxaliplatin-based treatment permits curative intervention in a subset of patients by downsizing initially unresectable liver metastases [R. Adam, personal communication]. The use of oxaliplatin to reduce recurrence rates after resection of nonmetastatic disease is also being investigated in clinical trials. Oxaliplatin is therefore a lead candidate for the investigation of radiochemotherapy in rectal cancer.

Current status of surgery and radiotherapy

The emergence of chemoradiation as an important strategy in rectal cancer comes against a background of significant progress in both surgery and radiotherapy in recent years. Surgical resection in particular has achieved increasing success rates as operative techniques have improved and new quality assurance standards have been developed. Historically, local recurrence rates after resection were high with studies reporting rates from 15% to as high as 50%, but the introduction of total mesorectal excision (TME) has significantly reduced recurrence rates [9,10]. Parallel advances have been made in radiotherapy, with a number of studies showing that high-dose, low volume radiation alone can be a successful treatment for early stage rectal cancer. For instance, in two French studies of T1 N0 rectal cancer involving 312 and 116 patients, respectively, local control was achieved in 98–90% of cases, with a 5-year survival of 75–83% [11]. In stage T2-3 cancer, a local control rate of 71% was achieved by radiotherapy alone, while 5-year survival was 64% [11]. These data indicate that in early stage cancer, high-dose, low volume radiation can be effective in the absence of surgery; but for the large majority of presenting cases, surgery supported by radiotherapy remains the foundation of management.

Radiotherapy plus surgery

Combining radiotherapy and surgery is an evolving art, with a variety of different strategies under investigation [2]. Historically, radiation has largely been given pre-operatively in Europe, but postoperatively in the United States, and the relative merits of the two approaches have still not been decisively clarified. In the United States, a number of studies have investigated postoperative treatment with both radiotherapy and supplementary chemotherapy in T3 or N1 rectal cancer. Studies with 45–50 Gy radiotherapy plus 5-FU/leucovorin with or without adjuvant chemotherapy reported improved local control, increased survival with an infusional 5-FU regimen [12–14]. In European studies of pre-operative radiotherapy, no benefit was found for doses of below 40 Gy although doses of 45 Gy or greater were associated with improved local control and an acceptable toxicity level [15,16].

Significant progress in improving the ratio between efficacy and toxicity has been made by studies in which 5 fractions of 25 Gy were given pre-operatively on consecutive days to patients with early and locally advanced rectal carcinoma. In a study at Uppsala, Sweden involving 347 patients, this regimen was found to be superior to 60 Gy postoperatively, with a local control rate of 86% compared with 74% for the postoperative regimen [17]. Grade 3 toxicities were also reduced at 5% compared with 11% for postoperative radiotherapy. In a larger Swedish trial involving 1168 patients using the same 25 Gy/5 day regimen, local control was further increased and 5-year survival increased from 48% in the group receiving surgery alone to 58% in the group receiving pre-operative radiotherapy [18]. The dose, timing and volume of radiotherapy are also under ongoing investigation, although small volume, high dose radiation appears to be the most effective approach.

The strongest vindication of combined pre-operative radiotherapy and surgery to have emerged to date is the Dutch TME study [19]. In this study, surgery by TME was assessed with or without radiotherapy, with radiotherapy once again administered at 25 Gy/day in 5 consecutive daily fractions. The trial was distinguished by its use of high standards and quality assurance for surgery, pathology and radiotherapy that help to define a benchmark for good practice in this field. Patients in the trial had rectal carcinoma of up to T3/N1 severity, with presentations in the upper rectum, and in both the lower and middle rectum. In total, local failure occurred within 2 years in 8.2% of patients who received surgery alone, and in only 2.4% of patients who received pre-operative radiotherapy ($P = 0.001$; Fig. 1). These findings give strong support both to the value of TME as a surgical technique, and to the additional benefits of pre-operative radiotherapy. Even in patients with stage T3 tumours, local failure was only 15% in patients who received surgery only, and as low as 4.3% in patients who received pre-operative radiotherapy. It should be borne in mind, however, that in previous studies of rectal carcinoma surgery [12], more than half of the local recurrences were observed after 2 years, so higher rates of local recurrence may ultimately be recorded in this study.

A further important finding of the Dutch TME study was its confirmation of the importance of a negative resection margin to long-term outcome. The low 2-year local failure rates described above, of 8.2% for surgery alone and 2.4% for surgery preceded by radiotherapy, were achieved in patients with an R0 resection, but in an additional 238 patients who had an R1 resection, local

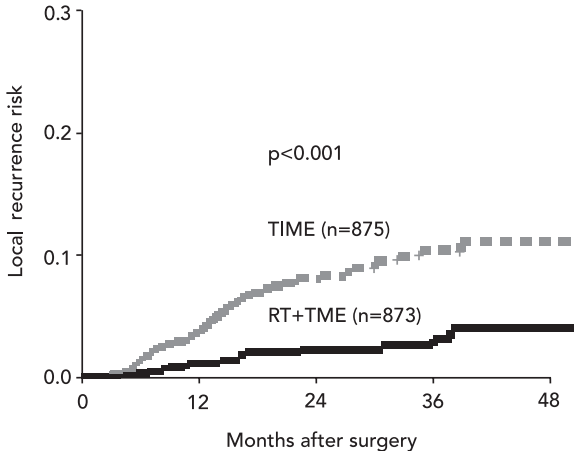

Figure 1 Dutch TME study: impact of pre-operative radiotherapy on local recurrence at 2 years.

failure at 2 years was 20% with surgery only and 16% with radiotherapy plus surgery.

There is therefore no evidence from this study that pre-operative radiotherapy compensates for a positive resection margin. It should be noted, however, that the 122 patients with a positive margin who did not receive pre-operative radiotherapy were given postoperative radiotherapy at 50 Gy. It is therefore not possible to evaluate the value of pre-operative radiotherapy *vs.* no radiotherapy in this group of patients. Interestingly, in 99 patients with a close margin (1.1–2 mm), 17% had local failure in the surgery only group, but no patients who received pre-operative radiation had local failure at 2 years.

Furthermore, although radiation reduced the rate of local recurrence, it had no effect on overall survival. This was due to a similar incidence of distant metastases in both groups, with 16.8% of patients in the surgery-only group and 14.8% in the surgery plus radiotherapy group having distant metastases at 2 years.

In summary, the Dutch TME study indicates that even with good TME surgery, pre-operative radiotherapy improves local control in tumours of up to T3/N1 severity in both the lower and middle rectum. The lateral resection margin is a strong predictor of local control, with pre-operative radiotherapy proving beneficial with close margins. The value of pre-operative radiotherapy in R1 resections is not clear given the confounding effect of postoperative radiotherapy, but is unlikely to be high. Overall survival is not, however, improved significantly by radiation because it fails to prevent metastatic disease.

Locally advanced disease

Although the Dutch TME and other studies demonstrated the advantages of radiotherapy in operable rectal cancer, the picture is less clear with regard to locally advanced and unresectable disease. As yet, there is not even a standardized definition for either of these conditions and achieving this will be an important step to assessing the benefits of radiotherapy. Fortunately, advances in magnetic resonance imaging (MRI) are now helping to clarify this problem [20,21]. MRI undertaken in advance of surgery helps identify a potentially positive circumferential margin, the depth of invasion, the involvement of other organs such as the prostate, the involvement of peritoneal reflection and the degree of lymph node spread. Recently a concordance rate of 83% between MRI and the surgical specimen was recorded [21]. Using effective imaging techniques in future pre-operative radiotherapy studies will help to clarify the value of this modality in locally advanced disease.

Sphincter-saving surgery

A further outstanding issue in combined radiotherapy and surgery concerns sphincter saving surgery. Despite the increased use of radiotherapy in rectal cancer over the last two decades, there has probably not been a marked increase in the number of patients whose sphincters are preserved. Sphincter preservation can clearly be achieved more frequently with pre-operative as opposed to postoperative radiotherapy, and increased use of pre-operative radiotherapy to achieve more effective tumour downsizing may help to address this problem. In a study in Lyon comparing immediate and delayed surgery after pre-operative radiotherapy [22], sphincter preservation was achieved in 79% of patients with a long interval before surgery, compared with 69% of patients where the interval was only short. Neither local relapse nor overall survival within 5 years differed between the two groups. No differences were found in the degree of local control, overall survival or surgical complications between the two groups. This indicates that a delay between pre-operative radiotherapy and surgery is necessary to optimize response rates and sphincter preservation.

Chemoradiation

Introducing chemotherapy into rectal cancer as a third modality in combination with surgery and radiotherapy involves several different applications. Postoperative chemotherapy can be used to reduce the local recurrence rate and the incidence of metastatic disease much as it does in colon cancer. As discussed above, a major finding of the Dutch TME study was that although radiation reduced the rate of local recurrence, it had no effect on overall survival. This finding strongly supports the use of

postoperative chemotherapy in rectal cancer to reduce the rate of metastases. Undoubtedly, resections of the primary tumour that leaves a positive margin also need chemoradiation.

Neoadjuvant chemotherapy in combination with radiotherapy to downsize tumours prior to surgery is becoming an important approach in rectal cancer. Indications for neoadjuvant chemotherapy include tumours that are fixed or tethered on the digital rectal examination, lower rectal tumours, circumferentially bulky tumours, cases where the MRI suggests an R1 resection is likely, and tumours in patients with a narrow pelvis, particularly when these have an anterior location at the level of the prostate.

Historically, the concomitant use of chemotherapy and radiotherapy has been compromised by the issue of toxicity. There have been concerns that the dose and intensity of systemic chemotherapy could be limited by acute toxicity when given with radiation, reducing the likelihood of a beneficial effect on the frequency of distant metastases. These concerns have in more recent years been allayed with the development of appropriate regimens but remain important [23]. In cervical cancer, a highly significant reduction in the rate of distant metastases was recently demonstrated in an extensive meta-analysis of chemoradiation [24] and this has acted as a spur to further develop the use of chemoradiation in other malignancies including rectal cancer.

Various chemotherapeutic agents are under investigation for combined use with radiotherapy in rectal cancer. Fluoropyrimidine therapy may be based on 5-FU/leucovorin or on oral agents such as capecitabine. An EORTC study is currently comparing 45 Gy with or without 5-FU/leucovorin, with or without adjuvant in a 2×2 factorial design of neoadjuvant chemoradiation for rectal cancer. Fluoropyrimidines can be combined with oxaliplatin or irinotecan to achieve synergistic effects, with oxaliplatin likely to prove particularly promising in the neoadjuvant setting following its effective introduction as a neoadjuvant treatment for hepatic metastases of colorectal cancer.

As these and other agents are investigated, the problem of how to drive trials more quickly is likely to grow in importance. Although local recurrence is a useful endpoint, overall survival requires a long duration of follow-up and can be influenced by many confounding factors arising after the trial procedures have been completed. Histologically confirmed R0 resection in particular is perhaps the most practical, useful, quick and discriminatory endpoint in the setting of rectal cancer, and can produce informative data within 6 weeks of completing treatment. Other useful surrogate endpoints are pathological complete response and pathological degree of downsizing other than R0 resectability. Downsizing should also be considered as potential short-term endpoints in neoadjuvant trials, while other endpoints such as organ sparing and the degree of surgical complications may also prove useful, particularly in composite evaluations of treatment response. Rectal cancer in fact represents an excellent model for the development and validation of novel and composite endpoints.

Oxaliplatin

Oxaliplatin is being investigated as a suitable agent for combined use with radiation on the basis of its successful use in colorectal cancer, coupled with preclinical data demonstrating that the effects of oxaliplatin and radiation are synergistic. Oxaliplatin has been shown to have radiosensitizing effects in both cell cultures and mouse xenografts. In preclinical models of combined radiation and oxaliplatin, 8-h oxaliplatin exposure was associated with a dose-related cell kill rate (Fig. 2) [25]. Synergistic effects with radiation were observed when oxaliplatin was given both before and after radiation. In mouse xenograft models of colorectal cancer, tumour growth has been shown to be inhibited by combined oxaliplatin and radiation [26]. Assays are still needed to quantify precisely the level of DNA damage associated with radiation and oxaliplatin used separately and in combination, but the preclinical studies to date strongly confirm that oxaliplatin is a potent radiosensitiser.

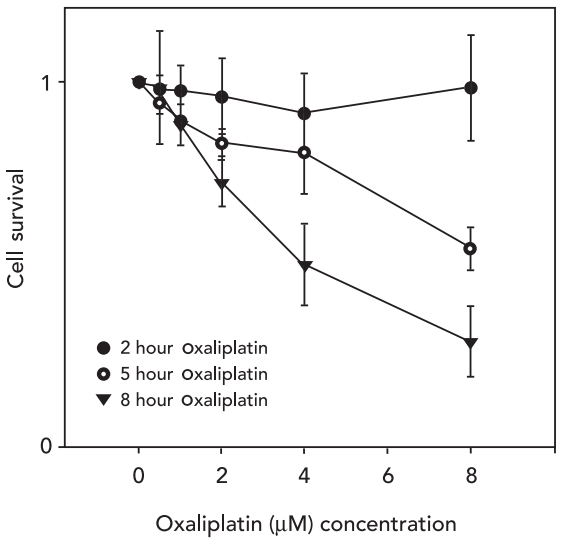

Figure 2 Radiosensitizing effects of oxaliplatin: concentration-dependence of *in vitro* kill rates depending on oxaliplatin exposure time.

A phase I-II study of oxaliplatin and 5-FU in the pre-operative treatment of locally advanced rectal cancer has recently been conducted in Italy [27]. A weekly treatment schedule was developed for the study, with the objective of reducing acute toxicity through dose fractionation, and achieving greater overall dose intensity. The first, phase I stage of the study was designed to define the maximum tolerated dose and dose limiting toxicities. Radiotherapy was given at a standard 50.4 Gy in 28 daily fractions of 1.8 Gy given in 5 fractions per week. Chemotherapy was with 5-FU 200 mg/m^2/day escalated to 225 mg/m^2/day, with oxaliplatin increasing in steps through 25, 35, 45 and finally 60 mg/m^2 given as a 2-h infusion once weekly for 6 weeks. In the second, phase II stage of the study, an initial assessment was made of the clinical activity of combined oxaliplatin and radiotherapy. The trial was open to adult patients aged 18 years old or older.

Interim results were reported in May 2002, at which point 39 patients, including 23 males and 16 females had entered the trial, with a median age of 60 years [28]. All the patients had locally advanced rectal cancer and 30 patients had nodal involvement.

The weekly oxaliplatin-based treatment schedule proved well tolerated. The maximum planned dose intensity of 225 mg/m^2 5-FU plus 60 mg/m^2 oxaliplatin was achieved readily without reaching the maximum tolerated dose. At the time of this interim report, all patients completed radiotherapy as planned and only two patients failed to receive all the planned chemotherapy due to grade III or IV toxicity. Of a planned total of 234 courses of chemotherapy, only 15 were delayed or modified and only five were omitted, indicating a high level of compliance consistent with good tolerability.

In total, 38 of these 39 patients had progressed to surgery by May 2002. A preliminary analysis of efficacy suggested that the combined use of radiation and oxaliplatin-based chemotherapy was highly active (Fig. 3). Tumour downsizing was observed in 26 of the 38 patients treated, a response rate of 68%. Pathologically complete responses were observed in 11 patients (29%). The study therefore indicated that combined oxaliplatin-based chemotherapy and radiation is not only feasible with good tolerability, but has highly promising clinical efficacy. The recommended dose of chemotherapy for future studies was set at 60 mg/m^2 oxaliplatin/225 mg/m^2 5-FU in a weekly regimen. Final results from this phase I/II study are anticipated shortly.

Other studies of oxaliplatin in radiochemotherapy are now in progress. In the United States, two clinical trials are now investigating the combined use of weekly oxaliplatin and radiotherapy in rectal cancer. In Italy, a randomized trial is being launched that will compare this regimen with standard infusional FUra and radiotherapy (STAR). In Europe, a new phase II study, CORE (Capecitabine, Oxaliplatin, Radiotherapy and Excision) is now in development. Capecitabine 825 mg/m^2 bd will be given for 5 consecutive days each week, with oxaliplatin 60 mg/m^2 once weekly. Radiotherapy will be given in 25 fractions.

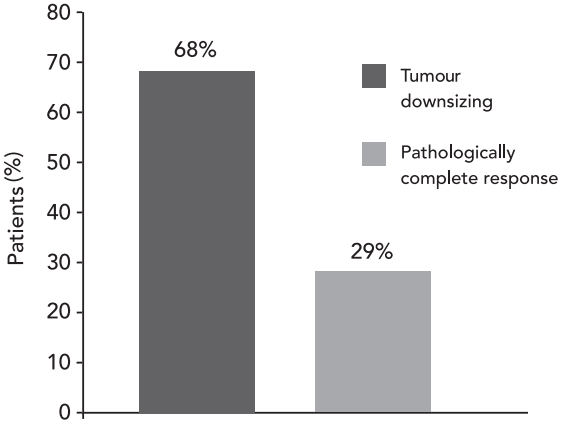

Figure 3 Oxaliplatin, 5FU and radiotherapy in locally advanced rectal cancer: response rates in a phase I/II study [28].

The CORE study will be open to patients with MRI-defined unresectable rectal cancer. The primary endpoint in the CORE study will be the frequency of pathologically complete response. Secondary endpoints will include pathological downsizing, the pathological R0 resection rate, the proportion of sphincter-saving procedures, the incidence of surgical complications and tolerance and safety. It is hoped that the results of this and other ongoing studies will further clarify the role of oxaliplatin-based radiochemotherapy in the pre-operative setting.

Conclusions

Radiotherapy plays a key role in the treatment of early stage and locally advanced rectal cancer in the wake of a series of clinical trials culminating in the Dutch TME study, but its overall value is limited. Although neoadjuvant radiotherapy can downsize tumours, increase the rate of sphincter saving surgery and reduce the rate of local recurrence, its role in advanced disease is usually only palliative and even in early and locally advanced disease it does not increase overall survival because the incidence of distant metastases is unchanged. The case for introducing chemotherapy in combination with radiotherapy is therefore compelling, both to achieve more effective local downsizing, R0 resectability and sphincter preservation, and to reduce metastatic spread.

The wider adoption of radiochemotherapy in rectal cancer will, however, depend on more randomized studies, with high standards and quality assurance for surgery, pathology and radiotherapy as set out in the Dutch TME study. Early studies with oxaliplatin have shown it to be an effective radiosensitizer and initial clinical studies using weekly treatment with oxaliplatin, fluoropyrimidine therapy and 5 daily fractions of high dose, low volume radiotherapy have proved highly promising in terms of both efficacy and tolerability. The CORE study will further clarify the potential of this approach in locally advanced rectal cancer. While further studies with both oxaliplatin and other agents, as well as the introduction and validation of novel endpoints, are urgently required, the findings to have emerged to date suggest that radiochemotherapy has the potential to significantly improve long-term outcomes in rectal cancer, both in terms of quality of life and overall survival.

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