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CONSERVATIVE TREATMENT OF RECTAL ADENO-CARCINOMA AFTER NEOADJUVANT CHEMORADIO-THERAPY, IS IT ACCEPTABLE?

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Abstract

The traditional treatment of patients with adenocarcinoma of the rectum involved some form of radical surgery in fit patients followed by radiotherapy, or chemotherapy, or both depending on the stage of the disease and the general condition of the patient. More recently the emergence of neoadjuvant chemoradiotherapy (CRT) has fundamentally changed the management of these patients. Although initially it was recommended for locally advanced disease in an attempt of downstaging the tumour to make it resectable, the indication in using this modality had been widened.

In clinical trials, up to 30% complete pathological response (pCR) of tumours have raised the question as to whether surgery, especially radical could be avoided in certain group of patients. A trial of omission of surgery in this group of patients has shown favourable long-term results.

This article is an outline of the emerging factors for achieving complete pathological response; the non-operative or the minimal surgery strategies, methods of predicting response to chemo-radiotherapy, and means of judging the complete pathological response.

Introduction

Colorectal cancer is the fourth most common non-cutaneous malignancy in the United States and the second most frequent cause of cancer-related deaths. In 2008 an estimated 148,810 new cases will be diagnosed and will account for 49,960 deaths[1]. Of these cancers, 70% will arise in the colon, while 30% will occur in the rectum[2]. More than 13,000 people are diagnosed with rectal cancer in the UK each year[3]. Colorectal cancer is very common in New Zealand with approximately 2500 new cases being diagnosed annually, and approximately 1000 patients die from this disease each year[4]. At diagnosis, approximately 25% of colon cancers are noted to have local extension through the muscularis of the bowel wall. In contrast, 50% of cancers in the rectum exhibit this progression. Lymph node metastases seen in approximately two thirds of the cases[3,5], and in three-quarters of the cases, the disease will be localised to the primary site[3]. For purposes of treatment regimens variability exists in defining the junction between the colon and rectum. The colon is defined as greater than 12 cm and the rectum as 12 cm or less from the anal verge using rigid sigmoidoscopy[6]. There are several anatomic variations exists between colon and rectal cancers. The extraperitoneal part of the rectum lies within the narrow and bony part of the pelvis, making the surgical resection approach different from that of the colon. Additionally the absence of serosa below the peritoneal reflection facilitates deeper tumour growth in the perirectal fat and may contribute to a higher rate of locoregional failure[7].

The mainstay treatment for patients who have rectal cancer has been curative surgical resection, with emphasis on mini-

mizing morbidity and mortality. Significant improvements in local control and overall survival have been seen in patients who have resectable rectal cancer[8]. However, a greater understanding of the natural history of the disease, patterns of recurrence and more precise histopathologic reporting have helped define patients who have a high risk for local recurrence and disease progression after curative resection. Besides the surgical approach, the integration of expertise from different disciplines, such as pathology, medical and radiation oncology, gastroenterology and radiology created ground for multidisciplinary approach to treatment[9].

Nowadays, the routine means for staging rectal cancer involves all or most of the following depending on their availability; colonoscopy, CT scan of the chest, abdomen and pelvis, endorectal ultrasound scan, and MRI (Magnetic Resonance Image) usually of the pelvis but might include the abdomen. Surgical resection will constitute the cornerstone of treatment however many patients with T3, T4, and node-positive rectal cancers will be referred for preoperative (neoadjuvant) chemoradiotherapy (CRT) to reduce the risk of local failure and to ensure negative margins at surgery[3].

Preoperative versus postoperative CRT

Postoperative radiotherapy or CRT has been the standard care for many years for stage II and III rectal cancers[10,11]. As a result pathological complete responses (pCR) cannot be considered a relevant endpoint in assessing the effect of this approach. Postoperative radiotherapy has several disadvantages. Residual neoplastic cells within a hypoxic postoperative tumour are poorly oxygenated and, therefore their sensitivity to radiotherapy is decreased. When surgery precedes radiotherapy there is a risk of tumour spillage into the operative field, which can be reduced by preoperative treatment. Additionally, loops of small bowel, frequently settle in the pelvis and becomes fixed by adhesions, thus increase the volume of the bowel exposed to radiation and thus increase the side effects[3].

The seminal German CAO/ARO/AIO-94 trial[12] successfully randomized 823 patients with T3, T4 or node-positive rectal cancer to preoperative or postoperative treatment. Five-year cumulative local relapses was 6% in the preoperative group versus 13% in the postoperative group (p=0.006). Grade III and IV acute toxic effects were (27% versus 40%) in the preoperative and postoperative groups, respectively (p=0.001) and chronic toxic effects (14% versus 24%; p=0.001) were more frequent in the postoperative group). Overall survival was equivalent (76% versus 74%; p=0.80).

These results contributed to the significant shift that preoperative treatment has been accepted as the standard of care and postoperative radiotherapy in this setting has become almost redundant. Furthermore the preoperative trials have the ability to record surgical and histopathological outcome, including the pCR, which became an endpoint for measuring the effectiveness of preoperative treatment.

Factors affecting pathological complete response

Downstaging of the tumour in response to preoperative CRT depends on several factors:

Tumour stage and size: Tumour Regression Grading (TRG) is a pathological grading system based on histological degree of tumour regression and fibrosis present in a rectal cancer specimen after preoperative treatment[13]. TRG has proven to be of prognostic significance when assessed in 385 patients receiving preoperative CRT within CAO/ARO/AIO-94 trial[14]. Tumour size is also important in predicting tumour response,

and indeed the size of the tumour measured on preoperative CT scan correlate with pCR after CRT in some studies[15].

Radiotherapy: Adenocarcinoma of the rectum is radiosensitive tumour, and radiotherapy has the potential to eradicate the disease even when used as the sole modality of treatment. However, it cannot be treated using the curative dose of greater than 70 Gy using the standard external-beam radiotherapy because of the side effects to the rectum and the small bowel. To overcome this problem endocavitary irradiation[16] was used in conjunction with either interstitial brachytherapy[17] or external-beam radiotherapy[18] or both, with acceptable toxic-effects[18]. Anorectal function was excellent or good in two thirds of the patients[3].

Concomitant chemotherapy with a fluoropyrimidine is the most common approach in order to augment the local response. In addition, impressive rates of downstaging and pCR can result from the addition of induction chemotherapy using new agents, like oxalipatin[19].

*Interval to surgery***:** The effect of radiotherapy on tumour, and consequent tumour response, is variable both in extent and duration[3]. Because response to chemoradiotherapy is a continuous process, then the optimum interval between completion of radiotherapy and surgery is not clear[3]. However, some findings suggest that response to radiotherapy continues for 6-8 weeks[20], and there is no reliable data to indicate that response continues after that period[3].

Prediction of response to preoperative treatment

At present there is no reliable technique or investigation for predicting complete clinical or/and pathological tumour response after CRT. Few promising modalities could be presented.

Radiologic imaging including *Transrectal Ultrasound*, *MRI,* and *PET* have not been reliable to predict response[21,22]**.** The ability of MRI to predict pCR after CRT has not been established, and follow up MRI are rarely normal even in patients who show pCR at surgery[3]. Further work is needed before the effect of PET is known, although inclusion of PET in non-operative protocols might be desirable[23].

Digital Rectal Examination (DRE) /Assessment seems to have a low positive predictive value in assessing complete response[3]. Guillem and colleagues[24] reported that DRE underestimated response in 78% of patients undergoing neoadjuvant therapy

*Molecular prediction***:** Despite the attempt of several dedicated studies the prospect of combining clinical, radiological and molecular information to adjust and monitor preoperative treatment for locally advanced rectal cancers is attractive. However, reliance can't yet be placed on molecular data, but as the weight of evidence increases for markers that predict radiosensitivity, the confidence with which surgery might be omitted for complete responders will increase[3].

Conservative management of T2/T3 tumours after neoadjuvant therapy

Local excision is generally accepted as an option for the treatment of T1 adenocarcinoma of the rectum with favourable outcomes and is associated with low postoperative morbidity and low recurrence rate[9,25]. Local excision for more advanced tumours (T2 and T3) has been reported to have unacceptably high recurrence rates (17%-62%), even with the use of adjuvant chemoradiation therapy[9,26]. Therefore this line of surgical treatment for these types of tumours has waned significantly.

With the increasing use of neoadjuvant chemoradiotherapy a pCR may be achieved in approximately 30% of the patients[3,9,27]. Radical surgery is still considered the standard care for these pa-

tients but may be associated with significant morbidity especially in certain group of patients. Consequently the question has been raised as to whether radical surgery can be avoided in patients who achieved pCR. Habr-Gama and colleagues[28] presented long-term results of 256 with low rectal cancer deemed resectable and underwent neoadjuvant CRT from 1991 to 2000. Those who had incomplete response received radical surgery, while those who had radiological and clinical evidence of complete response after neoadjuvant CRT were observed. Rates of 5-year overall and disease free survival were 88% and 83% respectively, in the resection group and 100% and 92% respectively, in the observed group. This series was updated in 2005 and again in 2006[23,29], now extending to 360 patients treated up to 2005. Local recurrence developed in five (in total) patients, all amenable to salvage surgery, and none of whom have developed further recurrence. These results are impressive, and seem to confirm that a non-operative approach might be safe for complete responders to neoadjuvant therapy.

Others have explored the option of local excision for patients who had T2 / T3 tumours exhibiting substantial response to neoadjuvant treatment. These studies, which contain heterogeneous groups of T2, T3, and T4 tumours have reported a local and distant recurrence rates of 0% to 12.5% and 0% to 20% respectively[30]. Recently, Nair and colleagues[31] reported outcomes for patients who had T2/T3 tumours undergoing local excision after neoadjuvant treatment. They showed a 9% local recurrence and 5-year survival rates of 84% for T2/T3 N0 and 81% for T2/T3 N1 tumours.

Conclusions

The need to believe in non-operative strategies for rectal cancer is significant, although not unprecedented in gastrointestinal oncology. Surgery remains the standard of care after neoadjuvant CRT irrespective of the extent of response, but results from rigorous controlled trial using modern imaging techniques will be essential to guide oncologists in the selection of appropriate patients for non-operative management of rectal cancer patients after CRT[3].

Despite the results of local excision approach after CRT, in the absence of randomized studies, local excision for T2/T3 tumours should remain reserved for patients who are unable to tolerate or refuse radical surgery, or in the setting of clinical trials[9]. There is an ongoing trial (ACOSOG Z6041), which in due time will shed additional light on the role of local excision of T2 rectal cancer after preoperative combined modality therapy[9].

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