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MRI and its importance in rectal cancer

R J Heald

North Hampshire Hospital, Basingstoke, UK

Principles from the world of surgery

Cancer medicine is slowly embracing the uncomfortable reality that adjuvant modalities are often best administered *before* operative surgery rather than after. Cedermark points out that there are 20 published series which show a clear survival advantage for pre-operative radiotherapy in rectal cancer and only one showing such advantage for post-operative radiotherapy. Similarly direct comparison of pre- and post-operative short course radiotherapy in the Swedish Rectal cancer trial showed a clear advantage for the pre-operative option. Pahlman and Glimelius state that 'surgery fails at the margins, radiotherapy in the centre' (of solid tumours).

One of the principal risks of surgical failure is an exposed circumferential margin (CMI): what therefore could be more logical than to minimize by pre-operative radiotherapy the risk that such exposure will prove lethal? Cells spilled from an irrradiated cancer must be intrinsically less likely to be viable and thus able to implant whilst an operation field widely contaminated with viable cells is unlikely to be treated cytostatically by post-operative radiotherapy. Furthermore the modern J Colon Pouch with an ultralow anastromosis is far better unirradiated in terms of lavatory function. Similar advantages may also apply to the use of pre-operative chemotherapy as benefit is known to be greatest with small deposits of malignant cells — probably micrometastases, circulating cells and perhaps cells spilled during surgery. Surely therefore the future will bring a pressing need to decide who needs radiotherapy and who needs chemotherapy at an initial assessment which culminates in a treatment plan where the final and hopefully victorious surgical assault is upon a suitably subdued enemy?

The age of imaging is dawning!

Surgical audit — rectal cancer is the paradigm

During a recent 'masterclass' at the Royal College of Surgeons, Paul Sugarbaker of the Washington Cancer Institute described total mesorectal excision (TME) as the 'paradigm for the surgery of solid tumours'. All cancer surgery should be an exercise in morbid anatomy — the excision of a block of tissue which is definable by and teachable to surgeons. This block of tissue should encompass the whole of the field of spread of the cancer. If such a surgically definable block does encompass the common field of spread then a cancer is surgically curable, if it does not do so it is not.

For the future I would suggest as a personal view, based upon long experience and common sense, that radiotherapy is necessary for those patients whose predicted surgical margins include an area where CMI is a particular danger. Similarly, the likelihood of surgical breaching of a tumour margin may be much reduced if the surgeon is warned about the precise anatomy of the cancer in relation to the margin. This may also predict the need for the highly specialized surgery necessary for the excision of adjuvant structures such as vesicles, hypogastric plexuses (with their implied danger to sexual function), internal iliac vessels, bladder, etc. The interface with the prostate and the indication for pelvic exenteration are also crucially dependent upon refinement of the imaging.

Histopathological audit in rectal cancer

The work of Professor Phil Quirke on the outcomes of rectal cancer surgery in Leeds a decade ago established important fundamental principles. He was dealing with what we may call 'conventional' surgery which was delivering a local recurrence rate of 36% for all cases and 26% for those considered 'curative' by the surgeon. For these cases Quirke demonstrated by detailed histopathological audit of the margins of the specimen that CMI had had a high positive predictive value for both local recurrence and death.

During the last decade Quirke and Heald have worked together on a series of rectal cancer 'workshops'. Together they have evaluated and modified the routine of what we may call 'specimen management' to take account of modern imaging techniques. Instead of the surgeon cutting open the specimen in a random fashion

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which disorientates the histopathologist, the specimen is left untouched and placed in Formalin intact. Only the colonic (top) end of the specimen is cut open to allow the Formalin to seep in for fixation purposes. The orientated specimen can then be examined in an objective way, particularly by the naked eye, to see whether the mesorectal surround is intact. There is little doubt that tearing of the tissues by the surgeon is one of the key causes of margin involvement, either by the primary or by nodal secondary deposits. This can be objectively assessed on the fixed specimen which is then close sliced and photographed to provide an audit series of transverse sections directly comparable with the fine slice pre-operative MRI. Seminal work on the correlation of those fine slice MRIs and whole mount post-operative audit section has been undertaken by Dr Gina Brown and Professor Geraint Williams. Dr Brown's notes will illustrate some of the patients we have shared in whom this correlation has been uniquely valuable. We believe that the routine inclusion of such histopathology audit information in the patients' notes can provide a major spur to the improvement of cancer surgery.

For the pelvis — who needs an MRI? Who needs endorectal ultrasound?

In Basingstoke one of our principal areas of development is the avoidance of unnecessary sacrifice of the anal sphincters. The use of 3D ultrasound in the assessment of cancers of the anal canal and the lowest 2–3 cm of rectum is under assessment by Darren Gold. The technique at present is highly operator–dependent but we believe that it can, in the right hands, show excellent definition of the muscle layers and perimuscular spread of a few millimetres. We are setting up a prospective comparison between this and MRI, but it is clear that the value of ultrasound in defining the mesorectal/parietal interface in the mid and upper rectum is in no way comparable with what can be achieved by the best MRI.

As the situation in the liver and para-aortic regions is so important it is likely that standard future imaging workup will comprise:

Spiral CT
Enhanced T2 fine slice MRI
? 3D ultrasound for lesions
Below 4 cm above the anal verge

What imaging issues govern the decision to sacrifice the anal sphincters?

Two key histopathological realities govern this decision:

(1) The extreme rarity of intramural downward spread of adenocarcinoma occurring in the rectum. We now have on our own database more than 200 operation patients with less than 1 cm distal bowel wall clearance beyond the visible and palpable lower edge. To this must be added a further few millimetres of 'stapled doughnut'. The latter is invariably checked for carcinoma cells and has been found only twice in over 500 patients to contain tumour.
(2) The tapering visceral–parietal interface as the rectal wall, enveloped in tapering and rapidly thinning mesorectum, is inserted into the funnel-shaped skeletal muscle of the pelvic floor, pubo-rectal sling and external (voluntary) sphincter. The arrangement is somewhat like a flowerpot inserted into another which fans out around its circumference to a diaphragm.

Surgical anatomy

The Surgeon follows the plane around the mesorectum down into the intersphincteric plane. What is not realized by many is that this extends right down to the intersphincteric groove which is palpable from below. It is crossed only occasionally by a significant middle rectal artery and vein (20%), by a few vessels in the anorectal junction area and by a few slips of sphincter muscle.

It is thus a completely enveloping visceral–parietal interface which extends distally from the retroperitoneum in front of the aortic bifurcation with its pre-aortic autonomic nerves around the extraperitoneal hind gut structures of rectum and mesorectum right down to the anal verge.

What I call 'holy plane navigation' is the pursuit of this recognizable areolar separation zone into the surgically inaccessible depths of the pelvis. What governs most the feasibility of excising a cancer successfully without sacrificing the anal sphincter mechanism is whether the tumour transgresses the plane low down. Higher up, such transgression is an indication for excising an adherent structure such as vesicle, autonomic plexus or vaginal wall. Low down it indicates that an attempt to perform an anterior resection will carry a high risk of an involved margin (CMI) and consequent local recurrence.

It is enigmatic that surgical experience tends to suggest that overstaging is more of a problem than understaging, both for the surgeon and for the intensely interested and co-operating radiologist. Even before radiology was taking its now indispensable place in the assessment schedule it became apparent that careful surgery produced a far greater improvement in local recurrence than was expected. There appeared to be two reasons for this: first apparent tumour adherence was often inflammatory; second the cancer that transgressed the mesorectal envelope has usually metastasized already even if these metastases are not apparent.

A similar consideration applies to extensive nodal involvement. Table 1 shows the local recurrence figures according to the number of involved nodes in my own personal series which certainly contains the most 'determined' TME operations so far published. These data

Table 1 Recurrence anywhere compared with local recurrence in 'curative' anterior resections with TME

Number of nodes	Local recurrence	Recurrence of any kind
0 (n=258)	3%	14%
1–4 (n=114)	4%	30%
5–7 (n=12)	0%	37%
8–10 (n=8)	14% (n=1)	72%
>10 (n=6)	0%	100%

Kaplan–Meier curves.

show that the much repeated concept that nodal involvement is a predictor of local recurrence is no longer correct if great care is exercised in the removal of the integral visceral hindgut mesentery — the mesorectum.

From these data we believe that nodal involvement is not an indication for radiotherapy though the involvement of many nodes may indicate chemotherapy against metastases. We also believe that chemoradiotherapy may make most cancers without metastases operable. What is an inoperable cancer? . . . We simply do not know.

By applying this essentially simple principle we have been able to reduce abdominoperineal resection to a rare operation; well below 10% of all rectal cancer operations in our series. This has been done without any increase in the local recurrence rate which remains well below 10% if all operations are included and below 5% if only cases classified as 'curative' are considered. Radiotherapy has been used pre-operatively only on a selective basis in around 20% of cases and we urgently seek to define precisely what the indications should be. The crude clinical scheme of giving 'fixed' tumours long course radiotherapy and 'low' tumours (below 4 cm) short course radiotherapy to make the 'close shave' safer is simplistic and inaccurate. Some fixed tumours are large tumours in narrow pelves with inflammatory margins and so not perhaps really needing radiotherapy. Low anterior tumours may appear fixed or mobile and involve a vesicle or a nerve plexus and might benefit from radiotherapy. Perhaps the radiotherapy should be specifically planned to neutralize the threatened margin.

The future

The improvements in imaging of rectal cancer in the last decade provide the key to cancer treatment planning in the future. If chemo and radiotherapy are to be given before surgery the indications for all these therapies need redefinition. Furthermore, surgery can be planned with a clear knowledge of where the dangers of failure lie.

The likelihood of surgical breaching of a tumour margin will be much reduced if the surgeon is warned about the precise anatomy of the cancer in relation to the margin. This may also predict the need for the highly specialized surgery necessary for the excision of adjacent structures such as vesicles, hypogastric plexuses (with their implied danger to sexual function), internal iliac vessels, bladder, etc., etc. The interface with the prostate and the indications for pelvic exenteration are also crucially dependent upon refinement of the imaging.

The combined efforts of radiologist, oncologist, and surgeon can revolutionize the management of rectal cancer so that both local recurrence and permanent colostomy may become extremely rare in the future. Similarly refined imaging techniques may prove to be the key to improving outcomes in the other common pelvic malignancies — uterine body and cervix, bladder, ovary and prostate. Revolutions in each of these important cancers will surely be led by the rapid growth of imaging technology which will have a major impact on the quality of surgery and the selective pre-operative use of better adjuvant modalities.

The role of MRI in the local staging of rectal cancer

Gina Brown

Department of Diagnostic Imaging, The Royal Marsden Hospital, Sutton, UK

MR imaging is particularly suited to examination of the pelvis because of the high intrinsic contrast of normal pelvic structures and the high contrast between malignant and normal tissue on T2-weighted images. Recent advances in MRI have permitted increased spatial resolution images to be obtained in acceptable scanning times without compromising the T2-weighted tissue contrast. This has been achieved through the development of fast spin-echo imaging (FSE) and pelvic phased array coils.

Colorectal cancer is the second most common cause of cancer death in the UK[1]. Rectal cancers pose a particular problem as the location of these tumours within the bony pelvis limits the ability to obtain wide radial

resection margins, increasing the risk of local recurrence. Incomplete removal of the tumour has been implicated as a major cause of local treatment failure following surgery for rectal cancer[2]. Not only is local recurrence painful and difficult to palliate, but it has also been shown that the results of surgical resection for local recurrence are disappointing[3,4]. Thus, one major aim in managing patients with rectal cancer is to select the primary treatment that is most likely to reduce the risk of residual disease within the pelvis. There is good evidence to suggest that involvement of the circumferential resection margin (CRM) is associated with local recurrence. In a large study assessing the prognostic value of CRM involvement, the risk of local recurrence in CRM-positive patients was significantly higher than in CRM-negative patients and the risk of death was three times higher than in CRM-negative patients. Furthermore, CRM-positive patients have only a 15% 5-year survival rate[5]. CRM involvement has therefore emerged as a powerful predictor of local recurrence and has become an important new addition to the pathological staging of rectal cancer. With the availability of preoperative neoadjuvant therapy, a good preoperative staging technique should predict the likelihood of CRM involvement and thus identify those patients at risk of local recurrence.

The multimodality approach to treating rectal cancer

New treatment strategies are emerging which are aimed at improving survival through reducing the risk of local recurrence. Specific therapeutic advances are beginning to have a significant impact on reducing the frequency of local recurrence and improving survival, namely, total mesorectal excision (TME) surgery[6–9] and preoperative radiotherapy and chemotherapy[10,11].

The rationale behind TME surgery is that all perirectal deposits are removed — particularly foci of discontinuous tumour deposits within the mesorectum. The technique involves sharp and meticulous dissection along the plane that separates the visceral from the parietal layers of the perirectal pelvic fascia, thus allowing radical removal of the rectum and its surrounding mesorectum[12]. This, in contrast with conventional blunt dissection, avoids inadvertent tumour perforation due to disruption of the mesorectum. With regard to surgical planning in TME, there are a number of important staging questions that can only be answered by precise delineation of the tumour and its local spread. One important staging issue is prediction of CRM involvement by defining the relationship of tumour to the mesorectal fascia. In particular, it is important to determine accurately anterior spread of the tumour where the TME margins are minimal. In patients with low rectal tumours the distance to the sphincter and the extent of extramural spread at this level are of importance in determining whether a patient is suitable for sphincter-sparing surgery.

With precise anatomical localization of the tumour, the surgical margins required for adequate tumour clearance can therefore be assessed with respect to nerve-sparing, sphincter-sparing, and circumferential TME margins.

Treatments options available to reduce local recurrence and improve survival include total mesorectal excision (TME), radical TME, transanal endoscopic microsurgery (TEM), preoperative short course radiotherapy (25 Gy in 5 fractions), preoperative radical (long course) radiotherapy and neoadjuvant systemic chemotherapy. It is recognized that certain patients in poor prognostic groups can benefit from preoperative neoadjuvant therapy[13]. Such prognostic factors include depth of extramural spread[14], lymph node involvement and involvement of the mesorectal fascia[15]. Currently these can only be identified in the pathological specimen. Thus, any potentially useful staging technique will not only identify the local tumour characteristics and anatomical factors that may influence surgical approach, but will also identify poor pathological prognostic factors. This will improve patient selection so treatment can be maximized where appropriate, whilst avoiding potentially harmful overtreatment in those patients with low-risk tumours[16].

Existing staging methods

At present, local staging of rectal cancers is often limited to assessing the mobility of the tumour[17]. This determines which patients will undergo preoperative radiotherapy. However, digital rectal examination is subjective and depends on the clinical experience of the observer. It is also limited by its inability to stage high rectal tumours and painful tumours. It is recognized that in patients undergoing optimized surgery, preoperative radiotherapy is superfluous for early tumours. If a rectal tumour is assessed as fixed or tethered the patient is recommended to receive prolonged radiotherapy. Such treatment based on clinical judgement will overstage a number of patients with apparent tethering or fixity due to peritumoural benign fibrosis and inflammation. In addition, a bulky intraluminal tumour with little extramural spread confined within the pelvis may feel fixed on clinical examination. Such factors can potentially lead to overtreatment with preoperative radiotherapy. Conversely, the inability to detect extramural spread of disease may lead to clinical understaging[18].

Endoscopic ultrasonography is considered to be a highly accurate method for determining tumour extent within and through the wall of the rectum[19]. Although studies evaluating endoluminal ultrasound have shown high staging accuracies in selected patients, the technique is limited by the inability to examine large bulky, stricturing or high rectal tumours (approximately 20% of cases)[20]. Moreover, in some cases only the lower portion of the tumour may be imaged, which can lead to understaging.

MR techniques

The results of studies evaluating the accuracy of body coil MRI in the local staging of rectal cancer have been disappointing[21–25]. A recent report using the phased array pelvic coil has also shown inaccuracies[26]. In all of these studies, this can be attributed to the use of thick slices and large fields of view resulting in low spatial resolution images that fail to resolve the layers of the rectal wall. These studies also reported overstaging of tumours as a major problem. This is likely to be due to acquiring axial images of the pelvis rather than true axial scans of the tumour itself. Oblique scans through the tumour will result in overestimation of extramural spread.

In a prospective study[27,28], a high resolution thin slice MR technique (in-plane resolution of 0.6×0.6 mm), employed revised image interpretation criteria derived from meticulous correlation with wholemount pathology sections to assess the local staging of rectal cancers[29]. The diagnostic accuracy of this form of MR imaging in determining the extent of local tumour infiltration was assessed by comparing preoperative MR findings with matched histological sections of surgical resection specimens as the gold standard. Preliminary results indicate that excellent preoperative prediction of the T stage of rectal cancer can be achieved. The technique also provided a reliable measurement of the extent of extramural tumour penetration which showed direct agreement with histopathology measurements. This has major potential implications for improving the management of the disease by virtue of accurate preoperative spatial depiction of the tumour and identification of patients with poor prognosis. This improvement in accuracy with a surface coil was achieved through thin slice acquisitions with high spatial resolution parameters and by obtaining images as true axial scans of the tumour itself, rather than of the pelvis as a whole. This reduced overestimation of the depth of extramural spread from oblique imaging.

Noninvasive high resolution MR imaging has a number of potential advantages over endoluminal ultrasound or endorectal MRI. First, it can be used in all patients, irrespective of the size or location of the tumour. Second, it can depict the precise spatial relationship of the tumour to the mesorectum and adjacent pelvic structures because of its relatively large field of view compared with the inherently small field of view associated with EUS (or endorectal MR). A noninvasive technique also overcomes the major limitation of EUS in the evaluation of polypoid, bulky or fungating tumours as the probe must be placed tangential rather than perpendicular to these tumours resulting in difficulties in interpretation of the depth of tumour invasion[30]. EUS overstaging due to inability to distinguish peritumoural fibrosis from tumour infiltration[31] is also overcome by MRI through accurate depiction of extramural spread[28].

Basic thin slice scanning technique in rectal cancers

The sagittal plane is initially used to localize the rectal tumour and is helpful in determining its relationship to the anal sphincter and the peritoneal reflection. The superior rectal vessel and higher lymph nodes of the mesorectum may also be demonstrated. These sagittal scans are then used to plan high resolution axial oblique scans so that images are obtained axial to the tumour itself. Thus, overstaging due to imaging the tumour obliquely with resulting overestimation of its true depth is avoided. The scans are routinely obtained using a 4-coil phased array flexible coil and a 16-cm field of view for the high spatial resolution images. The resulting image resolution is similar to that achieved with endorectal coils but with the advantage of being noninvasive and thus suitable for evaluation of all rectal tumours. In the author's experience, T1-weighted images are unhelpful because of a lack of contrast between the tumour and the bowel wall, and the layers of the bowel wall are also not well demonstrated. Fast spin-echo T2-weighted images will clearly show the intermediate signal intensity tumour contrasted with low signal longitudinal and circular muscle layers and high signal intensity submucosal layer and high signal intensity fat[28]. Axial scans also depict the mesorectal fascia and thus the plane of surgical excision in TME surgery[28].

Summary

The potential value of thin slice, high resolution MRI of the pelvis is in assessing the important surgical prognostic risk factors. In the local staging of rectal cancer high resolution MRI should not only be used to predict the T stage but assessment should also include the depth of extramural spread of tumour, the relationship of the tumour to the peritoneal reflection and to the anal sphincter complex, the relationship between the outermost extension of the tumour and the mesorectal fascia, the presence and location of mesorectal deposits and identification of other prognostic factors such as extramural venous invasion and peritoneal invasion. Preoperative identification of patients with adverse prognostic features may allow targeting of such patients for the most appropriate preoperative adjuvant therapy, assist in surgical planning and serve as an accurate baseline study from which to assess the success of different treatment strategies.

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The role of chemo-radiation in colorectal cancer

Diana Tait

Department of Clinical Oncology, Royal Marsden Hospital, Sutton, UK

Introduction

Colorectal cancer is the fourth most common malignancy, world-wide, with more than 130 000 new cases per year in Europe and 150 000 in the USA and therefore poses a significant health care issue. Taking all stages of the disease together, about 50% of patients will develop recurrent disease, either locally or at distant sites, and will ultimately die from their colorectal cancer. However, the outcome is highly linked to stage at presentation, with T1 tumours carrying a greater than 90% chance of survival in contrast to T4 tumours where survival is more in the region of 20%.

Table 1 TNM definition, 1997

Primary tumour (T)	
TX:	Primary tumour cannot be assessed
T0:	No evidence of primary tumour
Tis:	Carcinoma in situ
T1:	Tumour invades submucosa
T2:	Tumour invades muscularis propria
T3:	Tumour invades through the muscularis propria into the subserosa, or into nonperitonealized pericolic or perirectal tissues
T4:	Tumour directly invades other organs or structures, and/or perforates visceral peritoneum
Regional lymph nodes (N)	
NX:	Regional nodes cannot be assessed
N0:	No regional lymph node metastasis
N1:	Metastasis in 1 to 3 regional lymph nodes
N2:	Metastasis in 4 or more regional lymph nodes
Distant metastasis (M)	
MX:	Distant metastasis cannot be assessed
M0:	No distant metastasis
M1:	Distant metastasis

Previously considered a primarily surgical management problem, the contribution of chemotherapy, radiotherapy and the combination of chemo-radiation, to the management of colorectal cancer has now been demonstrated. A multidisciplinary approach is therefore appropriate, with every case being discussed by the multidisciplinary team prior to the institution of any intervention.

Staging

Traditionally, the Dukes staging system has been used to indicate the two most prognostically relevant histopathological findings; the degree of penetration of tumour through the bowel wall and the involvement of local regional lymph nodes. However, the Dukes system has undergone modification with resultant confusion in the precise definition of disease. The UICC TNM system avoids this and gives precise information regarding depth of bowel wall invasion, invasion into adjacent structures, the involvement regional lymph nodes and the presence of distant metastasis. These definitions are identical for both colon and rectal cancer (Table 1).

TNM staging has generally been applied as a post-operative, histopathological grading, but the introduction of imaging techniques, particularly MRI and endoscopic ultrasound, at least in the case of rectal cancer, allows some categorization of stage pre-operatively.

Whether staged pre- or post-operatively, T3 are a heterogeneous group of tumours with a wide variation in outcome, depending on the extent of invasion. Local failure rates of 7%, 25% and 51% have been recorded for invasion depths of <2 mm, 2–8 mm and >8 mm, respectively[1]. An analysis of tumours with <2 mm invasion into pericolic fat and with other good prognostic factors yielded a recurrence-free survival of 87%, compared with 55% for patients with moderate to deep perirectal fat invasion and other poor prognostic features[1].

Pre-operative staging will obviously include clinical examination; colonoscopy and biopsy are generally required to establish the diagnosis. Imaging techniques which contribute to diagnosis and staging include barium enema, CT, MRI and endoscopic ultrasound. CT allows identification of metastatic disease whereas the other techniques concentrate on defining local tumour. Although employment of detailed local imaging is becoming routine in rectal cancer, colon cancer, the more common of the partnership, does not generally receive pre-operative CT. The exceptions to this are caecal tumours and fixed sigmoid tumours where the surgeon may feel that further information is required prior to operation. In reality, these tumours often present, at an advanced stage, with obstruction and proceed to urgent laparotomy. Endoscopic ultrasound (EUS) is reported to predict tumour stage with up to 95% accuracy and nodal stage with up to 74% accuracy[2].

Pre-operative staging aims to divide rectal, and selected colonic, cancers into four treatment groups:

- Operable cancers with low risk of residual disease and no adverse factors
- Operable cancers with low risk of residual disease but adverse factors
- Borderline operable tumours with high risk or subsequent residual disease
- Inoperable tumours

Neo-adjuvant treatment should be considered for the latter two groups.

Adjuvant and neo-adjuvant treatments

Chemotherapy and radiotherapy, used in conjunction with surgery, can be applied either pre- (neo-adjuvantly) or post- (adjuvantly) operatively. Generally, those tumours deemed operable will receive primary surgery and be considered for adjuvant treatment on the basis of the histopathological details. An exception to this is the use of short course pre-operative radiotherapy which is currently widely used in the UK and is advocated in the COG guidelines, unless centres can demonstrate that their local recurrence rates are <10% with surgery alone. For inoperable or borderline inoperable tumours, pre operative chemotherapy and radiotherapy perform three functions:

- The possibility of down-staging the tumour and converting it to an operable tumour.
- Associated with down-staging, the possibility of sphincter preservation.
- The opportunity to deliver systemic treatment early in a group of patients with a high risk of distant metastasis.

The optimum scheduling of surgery, chemotherapy and radiotherapy is not established for every clinical situation and, in addition to employing the most active

Table 2 Reduction in frequency of disease recurrence and death following systemic adjuvant chemotherapy

Trial	Stage	Reference	Reduction in recurrence rate (%)	*p*	Reduction in recurrence rate (%)	*p*
Intergroup	C	Moertel 1990, 1995[7,18]	40	<0.0001	33	0.0007
NSABP C-01	B+C	Wolmark 1998[19]	29	0.02	28	0.05
NCCTG	B+C	O'Connell 1997[20]		0.002		0.02
IMPACT	B+C	Int' Multicentre 1995[21]	35	<0.0001	22	+0.029
NASBP C-03	B+C	Wolmark 1993[22]		0.0004	32	0.003

All these trials used chemotherapy schedules based on 5-fluorouracil.

means of combating disease the question of overlapping toxicities needs to be considered. For example pre-operative radiotherapy seems to carry less morbidity than post-operative treatment[3].

Short course pre-operative radiotherapy for rectal cancer

This approach was pioneered in Sweden and has been the subject of a number of large, randomized trials. However, there is debate over the role of pre-operative neo-adjuvant radiotherapy for operable rectal cancer because although local control and subsequent survival can be improved[3,4], it exposes low-risk patients to unnecessary treatment and potential toxicity. In cases where surgery alone carries a high rate of local control, adjuvant radiotherapy will have less absolute impact. There does appear to be a trend for control rates by surgery alone to be improving, which may reduce the proportion of patients who would potentially benefit from pre-operative radiotherapy[5,6]. However, in addition to supplementing surgery in terms of local control, this type of pre-operative radiotherapy has shown a significant improvement in overall survival from 48%–58%, an absolute benefit of 10% ($p=0.004$) and odds improvement of 20.8%. Current trials are exploring the role of this neo-adjuvant short course style radiotherapy for operable rectal cancer but in the setting of surgery, which would now be considered total mesorectal excision.

Post-operative chemotherapy

Prior to the publication in 1990 of a large randomized trial of post-operative chemotherapy[7], there was no accepted role for adjuvant chemotherapy in colorectal cancer. However, there are now a number of large randomized trials which have demonstrated a survival benefit following complete surgical excision (Table 2).

These trials have established the role of systemic chemotherapy for Dukes C colorectal cancer. The value of this approach for Dukes B tumours remains controversial despite the large trial sizes, and this is because less events occur in this group of patients compared with Dukes C and, therefore, a survival benefit is more difficult to detect, with the same number of patients. Having said this, the data from the above trials suggest an improvement in event-free survival for B2 and B3 tumours (T3 and T4). The risk–benefit ratio of adjuvant treatment is such that it is prudent to select younger patients (<70 years). The risk–benefit ratio in older patients may shift in favour of treatment in the presence of poor prognostic factors such as vascular or neural invasion, perforated or obstructing tumour.

Post-operative radiotherapy

Randomized trials have demonstrated that both pre and post-operative radiotherapy can reduce local recurrence rates and that this occurs without chemotherapy, but is enhanced by combining the two adjuvant treatments. The scheduling of radiotherapy, with respect to surgery, remains controversial and there are advantages and disadvantages to both approaches (Table 3).

The most compelling argument for post-operative radiotherapy is the ability to select patients on the basis of their risk of local recurrence. However, a randomized trial comparing pre- with post-operative radiotherapy demonstrated less late toxicity in the pre-operative radiotherapy arm[3]. This trial also demonstrated a superior local control rate in the pre-operative group (12%) compared with 21% ($p<0.02$) in the post-operative group.

That radiotherapy given post-operatively can improve the rate of local recurrence in resected higher risk rectal cancer, stage T3–4 node positive or grade 3, has been demonstrated (Gastrointestinal Tumour Study Group, 1992). Two post-operative chemo-radiotherapy trials have also demonstrated an overall survival advantage [8–10].

To include the surgical tumour bed and local regional lymph nodes, a relatively large pelvic volume is treated with consequent risk to critical normal tissues. In this setting, small bowel obstruction has been demonstrated to be as high as 30–40%, depending on the superior extent of the treatment volume[11,12]. To reduce the risk of this late complication, a number of measures have

Table 3 Pre vs post-operative radiotherapy for rectal cancer; advantages and disadvantages

Pre-operative	Post-operative
Advantages	
Better tissue oxygenation→improved cell kill	Patient selection by histopathological staging
Sterilization cells subsequently disseminated	Marking of at-risk sites by clips
Decreased small bowel in pelvis	Surgical procedure to reduce pelvic small bowel
No fixed loops small bowel	
Possible avoidance of abdominoperineal resection	
No gap between RT and surgery	
Disadvantages	
Overtreatment of early disease	Vascular compromise of tumour bed
	Fixed loops of small bowel
	Required 4–6 week gap between surgery and RT

been employed but those that seem most successful, and least prone to their own complications, are the positioning of the patient in the prone position and treating with a full bladder.

Locally advanced colorectal cancer

Large tumours invading adjacent normal tissue structures are difficult to excise surgically, carry a high rate of local recurrence and are associated with poor survival. For these reasons, pre-operative treatment with chemotherapy, radiotherapy or chemo-radiation is being investigated with the aim of achieving a degree of down-staging which will allow better surgery and, by its impact on micro-metastatic disease and local regional nodal disease, improve survival[13–15,23,16].

Although not tested in a randomized trial, it appears that chemo-radiation produces the best chance of useful down-staging and its main role is in rectal cancers. Colon cancers of this advanced type usually present with obstruction and require early operative intervention. However, increased use of pre-operative staging will probably identify more patients, particularly those with caecal tumours, which may benefit from this approach. As far as radiotherapy is concerned, delivering treatment to colon cancers is technically challenging because of the close proximity of a number of critical structures. In addition to small bowel, kidney, liver and spinal cord may encroach on the treatment volume.

Series documenting the impact of chemo-radiation on locally advanced tumours demonstrate down-staging of tumours in around 60% of cases, complete histopathological response rates of up to 30%, with <5% occurrence of progression on treatment.

Pre-operative down-staging may convert an irresectable tumour into a resectable one, a tumour likely to have positive resection margins to one with negative resection margins or permit a sphincter-sparing procedure. The NSABP R-03 trial of pre-operative against post-operative chemo-radiotherapy has shown down-staging, and demonstrated an improvement in the rate of sphincter-preserving operations from 31% to 50% in the pre-operative arm. Survival data and late toxicity are not yet available[17].

Future developments in colorectal cancer

This is an active area of research and there are currently a number of important trials in progress. These will continue to look at the most appropriate chemotherapy agents and their scheduling, the role of improved surgical technique and the input of radiotherapy in the setting of the new technologies available. As each of the multidisciplinary components is refined the challenge is to identify the optimum inclusion and scheduling such that best tumour outcome is combined with lowest treatment toxicity.

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CT patterns of recurrent disease in colorectal cancer

Gina Brown

Academic Department of Radiology, The Royal Marsden Hospital, Sutton, UK

Introduction

There is wide variation in the methods selected to follow-up patients following surgery for colorectal cancer. For most patients follow-up is in the form of regular clinical assessment, carcinoembryonic antigen (CEA) level monitoring and colonoscopy supported by regular CT follow-up as a means of detecting lung and liver metastases as well as local regional recurrence. It has been shown that a rising CEA should prompt a search for recurrence and that liver metastases are known to cause the highest rise in CEA levels[1]. The development of symptoms such as pelvic pain will also instigate a search for recurrent disease. However, clinical assessment and CEA measurement alone are insufficient, as identification of recurrence before the onset of symptoms may allow earlier and more effective treatment, it is also well recognized that recurrence may occur in the absence of rising CEA. The frequency of CT examinations and clinical assessment is also subject to variation. It is currently recommended that CT be performed as a postoperative baseline study at 3 months after surgery with 6 monthly follow-up for 3 years and annual follow-up thereafter[2]. The majority of patients

relapse within the first 2 years following surgery and over 75% within 5 years[3]. Clearly, the frequency and timing of scans will be influenced by the stage, histology and site of the primary tumour as well as factors that predict for relapse such as positive circumferential resection margins[2].

The baseline CT

A clear understanding of the anatomical changes following both abdominoperineal resection (APR) and anterior resection is essential in the follow-up of such patients to prevent misdiagnosis of recurrence or missing subtle small volume recurrence. Following APR, CT monitoring is the only means of assessing the primary surgery site and the characteristic findings following surgery should be understood. Husband *et al.*[4] were the first to describe the role of CT in the detection of recurrent disease by defining post-APR appearances and demonstrating that a mass in the presacral hollow predicted for local recurrence. They observed that care should be taken not to confuse this with post-surgical findings. Thus, comparison should always be made with the baseline postoperative CT examination: an enlarging mass is good evidence for local recurrence, and biopsy may not always be necessary[5]. Increasingly, PET is proving to be of immense value as a complementary test to CT in solving such problem cases.

The site and stage of tumour predicts for pattern of relapse

In colorectal cancer, the stage at diagnosis is an important factor in predicting recurrence. Once tumour has penetrated the bowel wall the chance of local failure with or without distant metastases increases with the degree of spread beyond the bowel wall. It is also known that local recurrence is a manifestation of the lateral spread of the tumour rather than distal clearance[6]. In a series of 818 patients with colorectal cancer, local recurrent disease was present in 43%. Other studies have shown similar frequencies of local recurrence[7,8]. When compared with Dukes' C disease, stage B rectal cancer is associated with more local and regional recurrences and fewer retroperitoneal nodes. Stage C disease is more often associated with nodal or hepatic recurrence[6].

Mechanisms for dissemination and recurrence

Lymphatic permeation — lymph node spread

Lymph node metastasis is a progressive process with carcinoma spreading along lymphatic channels along anatomical pathways from node to node. In rectal cancers it occurs as lateral spread to lymph nodes within the mesorectum, then laterally to locoregional nodes in the obturator fossa as well as upward spread along superior, middle and inferior rectal vessels and internal iliac chain nodes. With left- and right-sided colonic primaries, nodal spread is along their draining vessels namely left colic artery and ileocolic vessels, respectively. When spread to the regional lymph nodes occurs, lymph flow can be blocked and so-called retrograde (downward) lymphatic metastasis may then occur[9]. This is a rare occurrence in patients undergoing resection with curative intent; it is usually only apparent in advanced cancer and is associated with a poor prognosis.

Spread to inguinal lymph nodes occurs rarely (approximately 2% of rectal cancers) and is usually associated with low rectal primaries growing into the anal canal.

Venous embolization and haematogenous spread

Talbot *et al.*[10] demonstrated that tumours within 'thick-walled' extramural veins have a significantly lower survival rate and a significantly higher incidence of blood-borne metastatic disease. It is thought that the primary tumour, by growing into the relatively low resistance venous system, thus has a direct mechanism by which to produce blood-borne metastases. This is a poor prognostic factor that is independent of Dukes stage and results in a reduction in 5-year survival from 55% to about 30%. Blood-borne spread is, however, determined by factors other than the ability to invade veins. For example, it is not known to what extent blood-borne metastases have a single clonal origin from a few cells shed into the circulation rather than arise in larger tumour emboli from tongues of tumour contained within extramural veins. The liver is the most commonly involved organ (77%), followed by lungs (15%), bones (5%)[11] and brain[12,13]. There is no evidence that the distribution of liver metastases is determined by the location of the primary growth within the large bowel[14]. Ovarian tumours occur in 6–8% of patients and may be easily mistaken for primary mucinous adenocarcinoma of the ovary. The gross macroscopic and imaging findings may be identical and are only distinguished with difficulty microscopically by the presence of necrosis which suggests a colorectal origin. The spleen[15], kidneys, pancreas, adrenals, breast, thyroid and skin[16] are rarely involved.

Transperitoneal seeding — peritoneal deposits

The upper rectum and colon is invested by a sheet of connective tissue containing blood vessels and lymphatics which together with an elastic lamina and a layer of

flattened mesenchymal cells comprises the peritoneum. The peritoneum is a relatively resistant barrier to spread but once a tumour has ulcerated through this layer transcoelomic spread and intraperitoneal deposits will ensue. Local peritoneal involvement is a common event in colorectal cancer and is an independent predictor of subsequent intraperitoneal recurrence. It is known that such deposits have a predilection for specific sites[17–20]:

superior and inferior ileocolic recesses;
rectovesical pouch (Pouch of Douglas);
undersurface of the diaphragm;
transverse mesocolon.

Poorly differentiated tumours are likely to produce diffuse seeding whereas well-differentiated tumours may produce solitary deposits. The ureter is at particular risk from such lesions and associated hydronephrosis is not uncommon.

Local spread due to tumour regrowth at the primary surgical bed

The incidence of regrowth of carcinoma in the pelvis after excision of the rectum is up to 57%[21]. This occurs most frequently with carcinomas of the lower rectum, because of its relative inaccessibility within the narrowing pelvic funnel. This makes adequate surgical removal of the primary tumour a technically difficult procedure. Pelvic recurrence is most common in rectal cancers which have extensive local spread in continuity. In assessing outcomes and after surgery it is essential to have detailed knowledge of the clinicopathological tumour status so that surgery can be defined as curative or non-curative. This has implications for both postoperative follow-up and treatment. Noncurative surgery is defined as microscopic or macroscopic residual tumour due to either incomplete removal of tumour or evidence of distant spread. There is also a subgroup of patients with occult residual disease who are at high risk of local recurrence. These include patients with tumour at the circumferential resection margins and those in whom bowel perforation and tumour spillage has occurred. Thus, positive CRM is emerging as a powerful predictor for local recurrence with a 12-fold increase in the risk of local recurrence after a 'curative' operation[22].

Another important mechanism for local recurrence is implantation. This can occur both intraluminally or extramurally. Implantation metastasis from carcinoma of the colon and rectum has been described in anal fistulae and wounds particularly relating to abdominoperineal excisions. Most recurrences in abdominal incisions, around colostomies and in the perineum after excision of the rectum for cancer are likely to be the result of implantation from either the peritoneal surface of the growth or as a result of tumour spillage during surgery. Suture line recurrences may also occur due to inadequate resection of the primary growth. There is clinical and experimental evidence that tumour growth can occur preferentially at an anastomotic site and this suggests that the anastomosis in some way acts as a tumour promoting factor.

Outcome following recurrence[7,8]

Ninety-nine per cent of patients relapsing will do so within 5 years. Only 8% of patients will have resectable recurrent disease. The outlook for patients with recurrent disease is poor with a mean survival of 1 year after detection of recurrence. Attempts at curative resection are often disappointing with only a few patients having truly resectable disease. Thus treatment is aimed at local control and palliation, both of which are more successful if local recurrence is detected earlier. In one series only 6% of patients survived for 5 years following recurrence.

Key points

Post-therapy fibrosis:
need a baseline scan — enlarging mass more likely to represent disease. Biopsy may not always be helpful due to sampling error. Role for PET.
Detection of microscopic disease or deposits within normal lymph nodes — concomitant use of PET and CT or MRI for anatomical localization and characterization.
Anastomotic recurrence — though rare is readily detected by sigmoidoscopy or colonoscopy.
Understanding of anatomical appearances following APR and anterior resection.
High index of suspicion for CRM-positive patients.
Hydronephrosis can be an early sign of recurrent disease.
Rising CEA with normal CT survey — PET scan very useful.
Patterns of local recurrence in patients with anterior resection.
Peritoneal recurrence is often associated with hydronephrosis.
Krukenberg type ovarian metastases rare but can be distinguished from peritoneal recurrence by analysis of anatomic plane.
CT detectable lymph node recurrence relatively rare — patterns of LN dissemination dependent on primary site.

Future issues

The consequence of detecting local recurrence — can additional nonsurgical treatment prolong survival?

Curative resection in patients with recurrent disease can potentially give a survival benefit for the individual patient but there is a need to:

(1) eliminate local recurrence through (a) improved surgery, and (b) improved targeting of patients for preoperative therapy;
(2) detect recurrent disease earlier — possible role of PET in conjunction with CT or MR.

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