

RECTAL CANCER TREATMENT: A MULTIDISCIPLINARY APPROACH

Rectal cancer claimed the lives of over 4,500 people in the UK in 2006. We are developing a multidisciplinary team approach to improve treatment options and outcomes for patients.



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Introduction

Patients with operable rectal cancer are optimally managed by a multidisciplinary team (MDT). Indeed, rectal cancer presents a variety of challenges so that a successful treatment outcome very much depends on the expertise contributed by the various specialists who constitute the MDT. In contrast to colon cancer, there is a higher risk of rectal cancer coming back (called recurrence) after surgery because of the proximity of the rectum and other organs within the pelvis, as well as the relative closeness of the rectum to the routes by which cancer can spread (or metastasise) to other locations in the body. It is for the latter reason that rectal cancer is associated with a higher risk of distant metastasis.

Magnetic resonance imaging (MRI) is able to predict accurately the likelihood of microscopic tumour involvement at the circumferential resection margin (the area surrounding where the tumour was removed). The technique is also being used at the start of treatment to assess the extent (stage) of the tumour and to look for features which suggest a high risk of unsuccessful surgery or cancer recurrence, either within the pelvis or at a distant site (metastasis)(see article by Dr Gina Brown, p.42-45). MRI has become a useful tool for separating patients into different risk groups so that treatment can be tailored to address their individual needs.

Surgical techniques

Surgical treatment for rectal cancer varies according to the extent of tumour involvement and the location of the cancer. For example, some rectal cancers are very small and limited to the surface of the rectal lining while others have grown through the entire rectal wall and are attached to nearby structures and organs. The extent of surgery that will be needed to remove these two tumour types is very different.

The least invasive approach for early rectal cancer is without an abdominal incision by inserting instruments through the anal opening. This method, termed local

transanal excision or Transanal Endoscopic Microsurgery (TEMS), can be used for removing large polyps and early tumours that are small, superficial and located relatively close to the anus. To treat cancers located well above the anus, Low Anterior Resection (LAR) is commonly used. During an LAR, the entire rectal cancer, adjacent normal rectal tissue and surrounding lymph nodes are removed through an incision made in the lower abdomen. This is done using an innovative surgical technique, called Total Mesorectal Excision (TME), which is designed to remove all cancerous rectal tissue carefully without severing the nerves involved in sexual or urinary function. After the cancer is removed, the cut ends of the rectum are sewn or stapled back together. LAR is used whenever possible in order to maintain rectal function as the passage of stool from the large intestine through the anus is preserved. If the cancer is lower in the rectum, the cut end of the large bowel may be attached directly to the anus, a procedure known as colo-anal anastomosis. In cases where the tumour is very close to the anus, the entire rectal cancer, adjacent normal rectum (rectal sphincter or anus) and surrounding lymph nodes are removed. This method, termed abdominoperineal resection (APR), requires an abdominal incision and an incision to remove the anus; this results in the need for a permanent colostomy.

Minimally invasive (laparoscopic) surgery of the rectum requires advanced surgical skills as it relies on use of a laparoscope - a pencil-thin instrument with its own lighting system and miniature video camera. Only small incisions are needed to insert the miniature camera and instruments to perform the surgery. Both LAR and APR are feasible using a minimally invasive approach, but laparoscopic surgery has not become absorbed into the everyday practice of colorectal surgery mainly because of the complexity of the procedure and early concerns about its efficacy and oncological safety. However, modern results indicate at least equivalence for the oncological safety of laparoscopic surgery for cancer, although long-term data from the major randomised trials are not yet available. Traditional surgical treatment for many rectal



disorders has required a long midline abdominal incision and a lengthy recovery period of 4-8 weeks. The minimally invasive approach is perhaps THE leading advance in colorectal surgery in the last decade.

▣ The excellent outcomes from laparoscopic surgery, particularly an early return to work, better cosmesis and the reduced need for pain medication, ensure a prominent role for this approach in the future. ▣

Improving results from surgery

Preoperative treatment is used to try and improve on the results obtained from surgery for rectal cancer. Either preoperative radiotherapy given over five days or chemoradiotherapy given over 5-6 weeks is preferred in different treatment centres. There is currently no clear evidence to suggest that one treatment strategy is better than the other as they have not been compared directly in a prospective randomised trial. Whilst both are beneficial in terms of reducing local recurrence rates, neither has managed to improve the overall survival of patients undergoing optimal surgery. This is due, at least in part, to the inability of these localised therapies to achieve adequate systemic control of disease. In addition, there are subgroups of patients in whom other treatment outcomes may also be important, such as the ability to perform complete resections in patients with locally advanced disease, or sphincter preserving surgery (LAR instead of APR) in patients with tumours close to the anus.

Postoperative examination of the surgical specimen by the histopathologists should provide information confirming the completeness of resection and the preoperative radiological findings, as well as feedback on the quality of the surgery performed.

Rectal cancer research at The Royal Marsden

Significant advances have been made in the management of patients with metastatic colorectal cancer, namely the advent of combination chemotherapy and the use of novel targeted agents. For example, combining the chemotherapy agents oxaliplatin or irinotecan with 5-fluorouracil (5FU) has been shown to improve survival and response rates in advanced disease compared to 5FU alone. Cetuximab, an anti-epidermal growth factor receptor (EGFR) antibody, has also been shown to improve

response rate and reverse chemoresistance in irinotecan refractory patients (BOND trial; Chief Investigator: Professor David Cunningham). In addition, a particularly high response rate was observed in a single-arm trial of untreated patients when cetuximab was used in combination with an oxaliplatin-based chemotherapy regimen.

■ The avenues for research in rectal cancer being explored by the Gastrointestinal Unit of The Royal Marsden include neoadjuvant chemotherapy, and use of multiple radiosensitisers in combination with preoperative radiotherapy. ■

Neoadjuvant chemotherapy

Neoadjuvant chemotherapy involves initial delivery of systemic therapy in order to control or eliminate distal micrometastases, and also induce a response in the known



tumour prior to preoperative chemoradiotherapy. As part of the systemic therapy, which might otherwise be delivered after surgery, is given at the start of treatment, the overall duration of treatment is not prolonged.

Neoadjuvant chemotherapy was initially shown to be feasible in an earlier clinical trial and has since been followed by The Royal Marsden EXPERT trial which was designed to take advantage of the increased anticancer activity that might be expected from an oxaliplatin-based combination. MRI was used to identify patients with rectal tumours considered at high risk of recurrence who were treated with 12 weeks of neoadjuvant chemotherapy followed by six weeks of chemoradiotherapy with concurrent capecitabine, and then total mesorectal excision (TME) surgery and postoperative chemotherapy for 12 weeks. Preliminary results for the first 77 patients showed encouraging MRI-assessed response to neoadjuvant chemotherapy and rapid improvement of tumour-related symptoms.

■ Sixteen patients did not have any residual tumour when the surgical specimens were examined histopathologically (pathological complete responses). Results for the complete cohort of 109 patients are expected during 2007. ■

The treatment concept of neoadjuvant chemotherapy is being developed further in the ongoing EXPERT-C study, a randomised trial comparing the use of this treatment strategy with or without cetuximab. In addition, the synergy between cetuximab and radiotherapy (shown by the results from a randomised trial in head and neck cancer) is also being tested in rectal cancer in this study as patients in the cetuximab arm will also receive cetuximab during chemoradiotherapy. Initiated and led by the Gastrointestinal Trials Unit at The Royal Marsden, EXPERT-C opened to accrual in late 2005, with the participation of 17 centres in the UK, Spain and Sweden. As there is potential for increased side effects from treatment, this intensive therapy may not be appropriate for all patients. Hence, MRI has an important role again in selecting patients with high-risk tumours who are most likely to benefit from treatment. The successful conduct of the trial will depend on high quality oncological care, radiotherapy, surgery, radiology and histopathological evaluation.

Intensive observation programme

Another study being conducted by the Unit is evaluating the use of an intensive observation programme, including MRI, as an alternative to surgery in patients with rectal cancer who have shown a good response to preoperative treatment. If found to be feasible, this may be a useful option for certain patients such as those with low rectal tumours in whom surgery may result in the need for a permanent colostomy or those who are not medically fit for surgery.

The future of surgery

Research in surgical technology and emerging minimally invasive techniques has a well-established track record at Imperial College, and spans across a number of departments of the Engineering and Medical Faculties. This includes pioneering work in the field of minimal invasive surgery and allied technologies, such as robotics and image guided surgery. The group has also implemented the first robotic surgical programme in the UK.

The future of surgery undoubtedly will continue to be focused on the principle and goal of minimally invasive access. Current research, being conducted by the Department of Surgical Oncology and Technology at Imperial College in conjunction with The Royal Marsden, also focuses on the emerging field described as Natural Orifice Translumenal Endoscopic Surgery (NOTES) which brings together laparoscopic surgery and flexible endoscopy (see Figure 1). The natural orifices such as the stomach or the rectum seem to provide a feasible entry point for surgical interventions in the peritoneal cavity, thereby avoiding abdominal wall incisions. It seems possible that major intraperitoneal surgery may soon be performed without skin incisions. The potential use of natural orifices and lumens to accomplish therapeutic goals is a logical extension of the less invasive mind-set, which has stimulated a genuine paradigm shift in surgical therapy over the past 15 years. NOTES is a burgeoning field that is still in its infancy and the Department of Surgery is currently one of the centres where this innovation develops as a safe clinical practice.

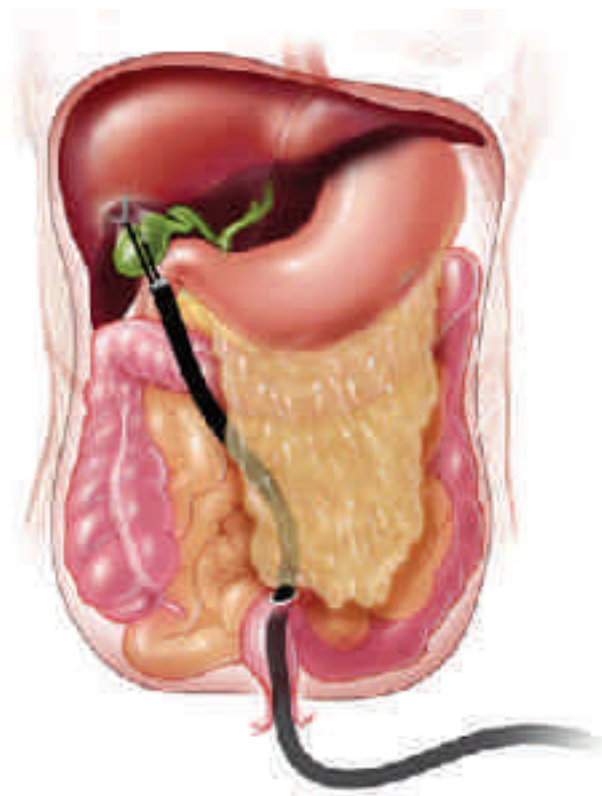


Figure 1: Natural Orifice Translumenal Endoscopic Surgery (NOTES).