

Section II

Advanced Colorectal Cancer

CHAPTER 19 RECURRENT AND ADVANCED COLORECTAL CANCER: GENERAL APPROACH AND LOCAL MANAGEMENT

19.1 General approach

Advanced rectal cancer incorporates a wide spectrum of conditions including:

- locally advanced potentially operable
- locally advanced inoperable
- synchronous local and distant disease
- isolated local recurrence
- local and distant recurrence

Decisions regarding management in these groups of patients can be very complex and frequently needs to be individualised according to the extent of disease, the type and severity of symptoms and the health and wishes of the patient. The coordinated efforts of a team of professionals are likely to be helpful in managing such patients. Surgeons, medical and radiation oncologists, palliative care physicians and nurses (oncology, palliative care, stomal therapy and domiciliary) may all play a critical role in patient management. Of particular importance is the role of the general practitioner in the management of both the patient and family. Unfortunately there is a lack of good quality clinical trials in which various treatment alternatives have been compared, often making the decision about the appropriate option complex and difficult.

Patients with advanced cancer suffer from a variety of symptoms and disturbances that are common to all cancers, and not specific to Colorectal Cancer. The management of these symptoms, such as pain (particularly nerve root pain),¹ anorexia, cachexia and psychological problems, among others, requires therapeutic measures that are part of the general care of patients with advanced cancer. These matters will not be described further in this chapter. This exclusion in no way underestimates the crucial significance of the control of these symptoms to the wellbeing of the patient. Management of these matters is the first priority of any clinician caring for a patient with advanced Colorectal Cancer.

There are some specific principles that can be applied in the management of people with Colorectal Cancer when the disease is advanced. The following chapters discuss some of the various and often complex therapeutic options available to such a patient with advanced Colorectal Cancer.

19.2 Locally advanced rectal cancer deemed potentially operable

Such advanced cancers (T4) are often initially inoperable due to local extension and fixity. Preoperative radiotherapy or chemoradiation may shrink bulky tumours and mobilise those tethered within the pelvis, enabling successful resection in such cases previously deemed inoperable. This will improve local control, quality of life and may well confer a survival benefit.

In patients with severe obstructive symptoms, it may be appropriate to recommend a defunctioning colostomy before commencing radiotherapy to avoid complete obstruction during therapy and the requirement of an emergency laparotomy.

Two randomised trials^{2,3} and an uncontrolled study have shown the benefit of pre-operative radiotherapy in such cases. Recent studies also suggest that combining radiation and chemotherapy preoperatively can enhance the effect of treatment without increasing surgical morbidity, and should

be considered in locally advanced cases.⁴⁻¹¹ Such chemotherapy should consist of a 5-FU-based regimen.

For patients who have had a complete resection, postoperative 5-FU chemotherapy is recommended as per the adjuvant therapy guidelines for high-risk rectal cancer.

For locally advanced or recurrent rectal cancer, the technique of intra-operative radiotherapy may be of benefit.^{12,13} This allows the delivery of a single high dose of radiation to the tumour bed or region of post-surgical residual disease. Critical structures such as small bowel can be moved out of the treatment field. Its role, however, is controversial and needs to be evaluated in further clinical trials.^{14,15}

What are the recommendations for recurrent and advanced rectal cancer?

Guideline — Preoperative radiotherapy	Level of evidence	Practice recommendation	Refs
Radiotherapy, generally combined with chemotherapy, is recommended in rectal cancers fixed or tethered within the pelvis.	II	Recommend	2,3

19.3 Locally advanced rectal cancer deemed inoperable

In patients with regionally advanced cancers deemed inoperable, radiotherapy may offer excellent palliation with a small group (less than 10%) showing long-term control.¹⁶ The combination of chemotherapy with radiotherapy appears to improve response rates and local control, though its impact on survival is unclear.⁶⁻⁹

It is important to deliver relatively high doses of radiotherapy to provide the best opportunity to obtain local control in these patients. Uncontrolled local disease, even in the presence of metastases, is associated with major morbidity that can significantly impair the remaining quality of life of a patient. Symptoms include pain, obstruction, incontinence, bleeding, discharge, neurological compromise and peripheral oedema. Patients with obstruction need to be managed empirically.¹⁷ With the availability of second-line chemotherapy with drugs such as oxaliplatin and irinotecan, local treatments such as surgical resection, cryotherapy, radiofrequency ablation, and hepatic arterial infusion also play a bigger role in achieving effective control of local tumours.

Radiation treatment needs to be fractionated appropriately, with multiple fields and manoeuvres undertaken to minimise small bowel presence within the irradiated volume. The dose delivered to the designated tumour volume needs to be of the order of 50–60 Gy.¹⁸ With such measures, the risk of radiation-induced bowel injury is small. Laser therapy¹⁹ and/or the placement of colonic stents²⁰ may also be a useful adjunct to radiotherapy in preventing the need for a defunctioning stoma.

The use of brachytherapy in locally advanced rectal cancers can contribute to improved local control and symptom relief in patients not amenable to surgery. Such brachytherapy can be used as a boost to external beam radiotherapy to increase the cytotoxic dose to the tumour, or delivered as sole therapy in patients with a short life expectancy.^{21,22}

What are the recommendations for inoperable rectal cancer?

Guideline — Inoperable rectal cancer	Level of evidence	Practice recommendation	Refs
Radiotherapy alone or chemoradiation should be considered in patients with locally advanced rectal cancer not amenable to surgery.	IV	Recommend	6–9, 16

19.4 Synchronous local and distant disease

Some of the most difficult decisions on treatment are in those patients diagnosed with both local and distant disease. Accordingly, their treatment often needs to be individualised.

When patients present synchronously with both a colorectal primary and liver secondaries, they can still be considered for potentially curative treatment.²³

Careful staging is important to accurately select such patients for a radical approach. Such investigations include CT imaging of the chest, abdomen and pelvis, MRI imaging of the pelvis, assessment of the liver with MRI or angio-CT and, where available, PET scanning.^{24–26} In these situations, resection of the primary disease generally takes priority, though in certain cases, patients may be considered for synchronous resection of both their primary and liver disease. If all gross disease has been resected, then patients should be considered for adjuvant therapy.

In patients with unresectable metastatic disease, aggressive treatment of the primary disease can often be appropriate to maintain control for the patient's remaining lifetime. Uncontrolled pelvic disease can lead to disabling tenesmus and bleeding, which can often be difficult to palliate. Significant symptom relief can be obtained with radiation therapy in 50–90% of patients with rectal bleeding, discharge or pain.^{17,27–29} In a recent series from MD Anderson hospital,³⁰ 55 patients with synchronous distant metastases from rectal cancer were treated with pelvic chemoradiation and no surgery. Eighty-one per cent had symptomatic pelvic control and 79% remained colostomy-free during their lifetime. Overall, 11% were alive at two years. Newer drugs such as oxaliplatin and capecitabine are under investigation as concurrent therapies with radiation in this setting.

19.5 Local recurrence

The incidence of local recurrence following resection of rectal cancer varies. It depends on tumour factors including stage, grade and vessel invasion, and external factors such as surgical technique and use of adjuvant therapies.^{31–33} Local recurrence rates of 3–50% have been recorded following apparently curative resection of rectal cancer.^{34,35} Median recurrence rates for T1, T2–3 and node-positive tumours were 8%, 16.3% and 28.6% respectively.³⁴

There are no randomised, prospective trials to act as guides for the management of locally recurrent rectal cancer. We have to rely on less robust evidence, such as retrospective analyses and uncontrolled prospectively documented series.

19.5.1 Assessment of the extent of local recurrence

There are four established methods of assessing the extent of local recurrence of rectal cancer: CT scan, MRI scan, PET scanning and endorectal ultrasound (ERUS).

CT scan is probably the most widely evaluated modality, with recent studies suggesting lesions as small as 2 cm can be detected reliably.³⁶ While initial reports claimed a remarkable 95% sensitivity at detecting a local recurrence,³⁷ later series show the sensitivity to be considerably lower at 69–88%.^{38–40}

There are difficulties in differentiating the appearance of normal postoperative changes (particularly in patients who have had previous radiotherapy) from recurrent cancer. Serial scans showing changes from a baseline are more sensitive than one-off scans.⁴¹

MRI scans were reported initially to be able to distinguish postoperative fibrosis from tumour recurrence more effectively than CT scans,⁴² and their accuracy has been confirmed by more recent data.⁴³

Probably the best currently available method of distinguishing fibrosis from recurrence is with PET scanning. This should be considered where available.²⁶

ERUS has been found to be similar in efficacy to CT in detecting local recurrence and can detect small extra-rectal recurrences before symptoms develop or there is endoluminal evidence of disease.^{44,45} Unfortunately, like CT and MRI, ERUS is unable to differentiate between normal perirectal lymph nodes and those harbouring recurrent cancer.⁴¹

19.5.2 Management of local recurrence

About 50% of patients with local recurrence of rectal cancer have disease confined to the pelvis.^{35, 46} The vast majority of local recurrences are inoperable and incurable. These patients are often in severe discomfort with cachexia and limited life expectancy. Their management is palliative and it should include consideration of radiotherapy and/or chemotherapy as well as adequate pain relief.

In patients who have not received previous pelvic radiotherapy, the use of palliative radiotherapy can relieve symptoms in the majority of cases, but the duration of relief is often short lived^{18,27-29} Such radiation may be combined with chemotherapy, given either concurrently or sequentially. In patients who have had previous pelvic radiotherapy, re-irradiation may be considered in special circumstances.⁴⁷ It is important that patients are involved in decision making and that their values are considered when deciding on the role of palliative radiotherapy.⁴⁸

A small number of recurrences may be salvaged with further local treatment. When local recurrence is not resected, five-year survival is negligible.⁴⁶ With major ablative surgery in highly selected cases, five-year survival can be as high as 37%.^{49,50} Therefore, in the absence of distant disease (after careful staging) or disabling comorbidities, surgical resection should be considered. In cases where radiotherapy has not been administered previously, the use of preoperative chemoradiation is to be recommended.⁵¹

Major surgery can result in a permanent end colostomy and ileal conduit. Despite this, improvement in quality of life has been reported following surgical removal of all pelvic organs (pelvic exenteration) in such patients.⁵² Although the above-mentioned reports support the use of radical surgical procedures, the lack of evidence based on randomised controlled trials as to their benefit precludes issuing broad recommendations regarding their use. Where contemplated, these procedures should be performed in specialised centres.

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