Chapter 21
Rectal Cancer

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Introduction

In 2014, an estimated 24,400 Canadians will be diagnosed with colorectal cancer and 9300 will die of the disease. Overall, colorectal cancer is the second leading cause of cancer death in men and the third most common cause of cancer death in women [1]. The death rate is declining in both sexes. Population-based screening has been shown to reduce mortality from colorectal cancer [2].

Presentation	Prognosis [3] 5-year overall survival (OS)
• Localized Disease (Stages I and II)	90 %
• Regional Disease (Stage III)	71 %
• Distant Metastasis (Stage IV)	13 %

The American Joint Committee on Cancer 7th edition is the current recommended Colorectal Cancer staging system.

In this chapter, the term rectal cancer refers to adenocarcinoma of the rectum, that is, adenocarcinoma arising at or above the anorectal junction (the pelvic floor) and at or below the rectosigmoid junction (where the taenia coli coalesce to form the confluent longitudinal muscle layer of the rectum).

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Definitions/Terminology

- **Localized Rectal Cancer**: rectal adenocarcinoma without distant metastases, which can be divided into early (T1-2N0) and advanced (T3-4 any N) disease
- **Locally Advanced Rectal Cancer**: a non-specific term that encompasses a range of pathology from bulky T3 tumours to those requiring multivisceral resection
- **Transanal Excision (TAE)**: localized excision of a rectal lesion; in general, a full-thickness, intact, disc of the wall with a 1 cm mucosal margin
- **Transanal Minimally Invasive Surgery (TAMIS)/Transanal Endoscopic Microsurgery (TEM)**: transanal excision of a rectal lesion with the use of a specialized video operating system; these systems include the establishment of a pneumorectum and provide access to the middle and upper rectum
- **Total Mesorectal Excision (TME)**: excision of the rectum and the mesorectum in the plane between the visceral mesorectal fascia and parietal fascia
- **Low Anterior Resection (LAR)**: a sphincter-preserving TME with colorectal or coloanal anastomosis
- **Anterior Resection (AR)**: a tumour-specific mesorectal excision, dividing the mesorectum and rectum 5 cm below the distal extent of the lesion, at a right angle to the long axis of the rectum
- **Abdominoperineal Resection (APR)**: TME with en bloc excision of the anus
- Positive Margin: tumour cells extending to the cut edge of a specimen. In a TME specimen, a circumferential resection margin (CRM) of $\leq$1 mm is considered positive. Quirke et al. have identified six modes of margin involvement: [4]
  - Direct extension
  - Discontinuous tumour spread
  - Lymph node involvement
  - Venous invasion
  - Lymphatic invasion
  - Perineural spread

Management

Localized Rectal Cancer

<table>
<tr><th>Clinical scenario</th><th>Workup</th><th>Surgical management</th><th>Follow-up [5]</th></tr>
<tr><td>Early Rectal Cancer (T1-T2, N0)</td><td rowspan="2">• History and physical:
– Assessment of preoperative continence, sexual function, neurologic and vascular symptoms
– Family history (cancer syndromes)
– Emphasis on DRE
• Labs:
– CEA
• Colonoscopy
• Imaging:
– CT chest/abdo/pelvis
– Pelvic MRI
– Endorectal ultrasound (ERUS)</td><td>• Upper/Middle Rectum:
– LAR
• Lower Rectum:
– TME or APR
*Select T1 cancers with favourable features may be considered for local excision (TAMIS/TEM)</td><td rowspan="2">• History & physical, CEA q6 months × 5 years
• CT chest/abdo/pelvis yearly × 3 years
• Colonoscopy after 1 year, unless complete colonoscopy not performed preoperatively, in which case it should be done within 6 months. Frequency of surveillance colonoscopies to be determined by findings. If normal, repeat in 5 years</td></tr>
<tr><td>Locally Advanced Resectable Rectal Cancer (T3-T4, N0 or N+ disease)</td><td>• Upper/Middle Rectum:
– CRT followed by LAR
• Lower Rectum:
– CRT followed by TME or APR
*Multivisceral resection as required to obtain R0 resection</td></tr>
</table>

DRE digital rectal exam, *LAR* low anterior resection, *TAMIS* transanal minimally invasive surgery, *CRT* chemoradiotherapy, *APR* abdominoperineal resection, *ERUS* endorectal ultrasound

Special Notes

- The likelihood of synchronous colon carcinoma is 3–5 % and synchronous neoplasia is 10–20 %.
- ERUS is the most accurate imaging modality for differentiating T1 from T2 tumours, but MRI is superior for more advanced T stages, N stage, assessment of the circumferential resection margin and response to neoadjuvant therapy [6, 7].
- PET scan is a useful adjunct in assessing response to neoadjuvant CRT, and has been shown to be predictive of survival (OS and DFS). It can also identify distant disease, and distinguish local recurrence from postoperative change [8].

- Laparoscopic surgery for rectal cancer has been evaluated in a number of randomized controlled trials, and has been shown to have short-term benefits compared with open surgery. The risk of incomplete TME specimen is higher with open resection [9]. The COLOR II trial demonstrated significantly higher rates of positive CRM with open resection of low rectal cancers [10]. The COREAN trial reported equivalent oncologic outcomes at 3 years [11].
- APR is indicated for cancer invading or very closely encroaching upon the external anal sphincter. Compared to anterior resection, APR is associated with higher rates of specimen perforation, circumferential margin positivity and local recurrence, and lower overall survival [12–14]. An extra-levator perineal approach, which may be facilitated by the prone jack-knife position, provides a superior oncologic resection to conventional APR [15, 16].
- Neoadjuvant CRT has been shown to significantly decrease lymph node yield after resection for rectal cancer, with some evidence that this mirrors tumour regression in response to treatment [17, 18]. The relevance of the 12 lymph node benchmark in this context has been called into question [19].
- Pathologic tumour regression grade (TRG) is a measure of response to neoadjuvant therapy, based on degree of fibrosis and percentage viable cells. TRG is correlated with outcome, with a greater degree of regression predicting better survival. [20]. The College of American Pathologists classifies treatment effect according to the following schema: [21]

Description	Tumour regression grade
No viable cancer cells	0 (complete response)
Single cells or small groups of cancer cells	1 (moderate response)
Residual cancer outgrown by fibrosis	2 (minimal response)
Minimal or no tumour kill; extensive residual cancer	3 (poor response)

- An analogous classification of radiologic TRG based on pre- and post-neoadjuvant MRI has been shown to predict disease-free survival (DFS) and overall survival (OS) [22]. The degree of tumour regression on post-treatment MRI was more closely correlated with survival than T stage.

Special Considerations

Local Excision for Rectal Cancer

Traditional criteria for transanal excision (TAE) have been expanded with the evolution of TAMIS/TEM:

1. **Curative resection of low-risk T1 lesions** [23]
   - T1N0
   - Well differentiated
   - No lymphatic, vascular or perineural invasion
   - Less than 4 cm in width
   - Less than 50 % circumferential
   - Within 15 cm of anal verge
- At least 1 cm margin of normal tissue surrounding the tumour is required.
- Tumour fragmentation is associated with a higher incidence of local recurrence. [24]
- Immediate salvage resection is indicated for adverse pathologic findings. The evidence indicates that the oncologic outcomes of immediate salvage resection are equivalent to primary resection [25, 26]. However, there is concern that local excision renders subsequent salvage more technically challenging, and in some circumstances may preclude sphincter-sparing reconstruction [27, 28].

2. **Palliation of T2/T3 lesions**
- For local control in patients who cannot tolerate radical resection

3. **Confirmation of complete pathologic response following neoadjuvant CRT**
- Excision of scar following complete clinical response can confirm the absence of residual disease, potentially avoiding resection [29, 30] (see below). Phase 2 trials to determine the oncologic safety of this approach are ongoing [31].

Recommended Margins

- Proximal—minimum 5 cm (gross margins)
- Distal
  - Upper and Middle rectum—minimum 5 cm (gross margins in the rectal wall and in the mesorectum)
  - Lower rectum—ideally 2 cm[a] (gross margins)
- Circumferential Radial Margin—minimum 1 mm (microscopic margins) [32][b]

Chemoradiation in Rectal Cancer

- Extraperitoneal location of the rectum allows for radiotherapy with minimal toxicity to intra-abdominal structures (e.g. small bowel)
- Radiotherapy reduces local recurrence rate by 50 % [35, 36]
- Neoadjuvant RT or chemoradiation (CRT) is indicated for T3-4 lesions, any N+, or threatened circumferential radial margin
- The MERCURY study identified a subset of patients based on MRI staging who have a favourable prognosis with surgery alone, allowing omission of RT [37, 38]. These good prognosis features include: CRM >1 mm, no evidence of extramural venous invasion, T1-T3 any N. The results are currently being validated in prospective RCTs, including a phase 2 pan-Canadian trial

Neoadjuvant vs. Adjuvant Chemoradiation [39–41]

• Advantages of neoadjuvant therapy: – Significantly lower local recurrence rate, no difference in overall survival – Possibility of tumour downstaging, down-sizing, and possibly increased rate of sphincter preservation – Lower rates of acute and chronic toxicity – Lower rate of anastomotic stricture – Higher treatment completion rate	• Disadvantage of neoadjuvant therapy: – Overtreatment of some patients

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Short- vs. Long-Course Radiotherapy [42, 43]
• Short-course RT = 25 Gy in 5 fractions followed by surgery in 1 week • Long-course CRT = 50.4 Gy in 28 fractions + 5FU followed by surgery in 8–12 weeks • No difference in overall survival, disease-free survival, local recurrence, or APR rates • Higher rate of pathologic downstaging with long-course CRT, including more complete pathologic responses • More acute toxicity with long-course CRT [44, 45] • Long-course CRT is standard of care in many North American centres, whereas short-course RT is widely practised in Europe
Complete Clinical Response After Neoadjuvant CRT
• Complete clinical response (cCR) to neoadjuvant CRT is associated with better outcome • cCR rates of 16–27 % reported in case series [46] • Limited data support a watchful waiting approach over radical resection in select cCRs: – Dutch study reports 2y OS 100 % and DFS 89 % in nonoperatively managed cohort [47] – Habr-Gama et al. report 94 % local control rate with watchful waiting approach, advocate close surveillance with immediate salvage in event of local recurrence [48] • Conflicting results from other centres indicate need for larger, prospective studies [49] • Promising case series suggest that local excision after cCR may be adequate [50, 51] • Radical resection remains the standard of care

[a]For low rectal tumours, a distal resection margin of 1 cm can be accepted to allow sphincter preservation. With appropriate technique and neoadjuvant therapy, a 1 cm margin is associated with rates of local recurrence and survival that are equivalent to wider margins [33].
[b]A positive CRM significantly increases the risk of local recurrence and is associated with decreased survival. In multivariate analyses, it has been identified as the single most important prognostic factor for local recurrence [34]

Locally Advanced Rectal Cancer (LARC) and Locally Recurrent Rectal Cancer (LRRC)

Workup	Perioperative treatment	Surgery
• History and physical: – Focus on urinary, gynecologic, neurologic symptoms, pain, lymphadenopathy • Labs: – CEA • Imaging: – CT chest/abdo/pelvis – MRI pelvis – PET or PET/CT—has been reported to change the management plan in 14 % of cases [52]	• Neoadjuvant CRT in primary disease • Evaluate for re-irradiation in previously irradiated pelvis [53] • Consider intraoperative radiotherapy if available and applicable [54] • Due to the high rate of distant failure, adjuvant systemic therapy is indicated	• En bloc resection of all involved structures to achieve an R0 resection margin [55, 56] • Early involvement of other surgical subspecialties (e.g. Urology, Orthopedics, Vascular)

CRT Chemoradiotherapy

Patterns of recurrence [57]	
Site	Comments
• Anastomotic recurrence • Inferior/perineal recurrence • Central recurrence (involving the rectum or urogenital structures)	• Amenable to resection
• Posterior recurrence	• Amenable to salvage resection when sacral involvement at or below S2
• Lateral recurrence	• May preclude resection with negative margins due to involvement of bony pelvis, major blood vessels and other lateral structures
Criteria for Unresectability [43]	
• Anatomic Involvement: – Above S2 or sacral ala – Acetabular involvement – Common or external iliac artery (relative) – Sciatic nerve or sciatic notch (relative) – Bilateral hydronephrosis (relative) • Biologic Factors: – Unresectable metastatic disease – Para-aortic lymph node involvement	• Patient Factors: – Refusal – Poor performance status – Unacceptable surgical risk • Technical Factors: – Inability to obtain a negative margin

Distant Metastatic Disease (Stage IV)

In patients with unresectable metastases, the median survival without systemic chemotherapy is 6–9 months. The addition of 5-fluorouracil (5-FU) based regimens improves survival to 12 months. Adding irinotecan or oxaliplatin to 5-FU extends survival to 20 months. More recently, with the identification of molecular targets and development of biologic agents, median survival has exceeded 30 months [58].

Workup	Surgery (referral to appropriate surgical subspecialty)	Follow-up
• History and physical • Labs: – CEA • Imaging: – CT chest/abdo/pelvis – MRI liver as indicated – US if ovarian metastases suspected – CT head/bone scan for symptoms – Consider PET/PET-CT to evaluate limited metastatic disease prior to planned resection [59]	• Liver: – Complete surgical resection with modern chemotherapy offers a 5-year overall survival up to 58 % [60–62] • Lung: – Complete surgical resection with modern chemotherapy offers a 5-year overall survival up to 55 % [63–65] • Peritoneum: – Cytoreductive surgery and HIPEC for colorectal metastases has a 5-year overall survival of 22–49 % [66] • Ovary: – Prophylactic oophorectomy is not routinely indicated, but bilateral oophorectomy is indicated if one ovary is involved • Brain: – Palliative resection may be indicated for carefully selected limited metastatic disease [67] • Bone: – Palliative radiotherapy	• Patients with potentially resectable disease undergoing chemotherapy should have imaging every 3 cycles to assess response • Monitor for toxicity depending on chemotherapeutic regimen used • CEA should be done only if patients do not have measurable disease on imaging • Patients undergoing palliation should only have blood tests and/or imaging as dictated by clinical condition

Special Notes

- In synchronous stage IV colorectal cancer, resection of the primary tumour has traditionally been discouraged in the absence of symptoms (e.g. bleeding, obstruction, perforation). This is based on the low proportion of asymptomatic primary tumours that progress to require intervention and the need for urgent systemic therapy in this population [68]. However, recent data question this dogma by demonstrating a survival advantage with resection of the primary in synchronous stage IV disease [69]. A prospective RCT is underway to help clarify the debate [70].

Landmark Trials

Study	Methods	Results
Heald et al. [71]	• Retrospective Review • *N* = 113 • Examination of Local Recurrence after TME	• LR = 0 % at 2 years with TME
Dutch Colorectal Cancer Group Trial Kapiteijn et al. [72]	• RCT • *N* = 1861 • Pre-op RT and TME vs. TME only	• LR: 2.4 % with pre-op RT and TME vs. 8.2 % TME only
Swedish Rectal Cancer Trial Gastrointestinal Tumour Study Group [23] Birgisson et al. [24]	• RCT • *N* = 1168 • Comparing pre-op RT and surgery vs. surgery alone	• LR: • 5 years: 11 % with pre-op RT vs. 27 % with surgery alone • 13 years: 9 % with pre-op RT vs. 26 % with surgery alone • OS: • 5 years: 58 % with pre-op RT vs. 48 % with surgery alone • 13-years: 38 % with pre-op RT vs. 30 % with surgery alone
German Rectal Cancer Trial Sauer et al. [25]	• RCT • *N* = 823 • Pre-op CRT vs. Post-op CRT	• LR: 6 % pre-op CRT vs. 13 % post-op CRT • No difference in 5-, 10-year OS • Toxicity (Grade 3/4): 27 % pre-op vs. 40 % post-op
NSABP R-03 Roh et al. [27]	• RCT • *N* = 267 • Pre-op CRT vs. Post-op CRT	• LR: 11 % in both arms
Polish Trial Bujko et al. [28]	• RCT • *N* = 316 • Pre-op CRT vs. short-course RT	• No difference in LR, DFS, sphincter preservation • Higher rate of pCR with pre-op CRT (16 % vs. 1 %) • Higher acute toxicity with pre-op CRT (18 % vs. 3 %)
Trans-Tasman Radiation Oncology Group (TROG) Trial Ngan et al. [29]	• RCT • *N* = 326 • Pre-op CRT vs. short-course RT	• No difference in LR, DFS, OS, sphincter preservation • Higher rate of pCR with pre-op CRT (15 % vs. 1 %)

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Study	Methods	Results
MERCURY study Taylor et al. [37]	• Prospective observational study • *N* = 122 • Surgery alone for "good prognosis" stage I, II, and III disease based on MRI, no pre-op or post-op RT	• Similar rates of LR, DFS, OS compared to other studies involving RT

RCT randomized controlled trial, *TME* total mesorectal excision, *CRT* chemoradiotherapy, *RT* radiotherapy, *LR* local recurrence, *CRM* circumferential radial margin, *OS* overall survival

Referring to Medical Oncology

1. ≥T3
2. ≥N1
3. Recurrent rectal cancer
4. Metastatic disease

Referring to Radiation Oncology

1. ≥T3
2. ≥N1
3. Recurrent rectal cancer
4. Ambiguous T staging (T2/T3) and suspected close circumferential margin
5. T1/T2 tumours if:
   (a) There is residual tumour or fragmentation after local excision
   (b) There are adverse features on final pathology of local excision

Referring to Multidisciplinary Cancer Conference (MCC)

Other indications not mentioned above:

1. Stage IV disease to assess treatment versus palliation
2. Patients with underlying inflammatory bowel disease and patients with documented or suspect familial cancer syndromes
3. Patients with significant medical co-morbidities that may preclude optimal treatment plans

Toronto Pearls

- There is strong evidence, including RCTs, that placing a loop ileostomy at LAR decreases clinical leak rates and re-operation rates [73]. This is advised for anastomoses within 3–4 cm of the pelvic floor
- The rate of anastomotic leak after LAR is most consistently associated with the level of the anastomosis. Achieving a tension-free anastomosis to the distal rectum or anus is facilitated by ligation of the IMA at its origin and separate ligation of the IMV at the inferior border of the pancreas
- A 5–6 cm colonic J pouch for patients undergoing LAR ameliorates the functional disturbance known as Low Anterior Resection Syndrome
- In pelvic exenteration, early ligation of the internal iliac vessels facilitates hemostasis
- When a vertical rectus abdominis myocutaneous (VRAM) flap is needed for reconstruction of the perineum, it is advised to take it ipsilateral to the ileoconduit, rather than the colostomy to avoid colostomy prolapse
- If a surgeon encounters an unexpected locally advanced rectal cancer in a curable patient and is not prepared to perform appropriate multivisceral resection, the procedure should be aborted, after possible creation of a stoma, and the patient referred for multidisciplinary consultation
- In the dissection of anterior rectal tumours, or in the event of a threatened CRM, Denonvillier's fascia should be taken with the rectum. Otherwise, it should be left intact in order to preserve autonomic nerve function

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