This guideline is a statement of consensus of the GI Disease Site Team regarding their views of currently accepted approaches to treatment. It is not intended to replace the independent medical judgement of the physician in the context of individual clinical circumstances to determine any patient’s care or treatment.
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Rectal Cancer
GI Practice Guideline

Overview

Approximately 180 patients with rectal cancer were referred to LRCP in 2006. The lifetime risk of this disease is about 5%, with the majority of cases occurring after the age of 50 years old. The North American average mortality rate is about 50%.

The primary treatment of rectal cancer is surgical resection. The present standard surgical procedures are low anterior resection and abdominoperineal resection with total mesorectal excision. Generally, at least 12 or more regional lymph nodes should be identified to minimize understaging. The specimen should be inked to allow assessment of the radial margins of resection. For mid to upper rectal cancers, the surgeon should document whether or not the gross tumor was above or below the peritoneal reflection as pelvic radiation is not routine for cancers above the peritoneal reflection. Transanal local excision should only be used in carefully selected cases (mobile, nonulcerating, well-differentiated tumors less than 4 cm diameter and within 8 cm of the anal verge; there should be no lymphovascular invasion and tumor should occupy less than one third of the bowel circumference.). There are no randomized trials of transanal local excision combined with chemoradiation versus standard (LAR, APR) surgery with or without chemoradiation. Local recurrence rates after transanal local excision and chemoradiation appear to be higher than after standard surgery with or without chemoradiation, especially for muscle-invading rectal cancers. Primary radiotherapy is usually reserved for medically inoperable patients since local control rates are often less than 40 percent.

Patients whose rectal cancers are not penetrating through full thickness of the rectal wall and have negative surgical margins and negative lymph nodes after LAR or APR do not routinely receive adjuvant treatment. For patients with muscle-invading rectal cancers that penetrate through the full thickness muscle wall (T3) or with any lymph nodes involved by metastatic cancer (N1 or greater), postoperative adjuvant chemotherapy and pelvic radiation has been the standard. This practice is being replaced by preoperative short course (one week) pelvic radiation followed by definitive surgery within two weeks post-radiation or by preoperative long course (five and a half to six weeks) combined chemotherapy and pelvic radiation followed by definitive surgery four to eight weeks post-radiation. Clinical trials are currently comparing the short course radiotherapy with the long course chemoradiation. Since short course preoperative radiation is not likely to lead to downstaging, long course preoperative chemoradiation would be more appropriate where one of the goals is to reduce the risk of APR.

There are significant advantages to the long course preoperative chemoradiation over postoperative treatment. While a survival advantage over postoperative chemoradiation
has not yet been demonstrated, the local pelvic recurrence rate is reduced from 13 percent
to 6 percent. In the German clinical trial, bowel function (urgency, soiling, frequency)
was better with preoperative chemoradiation than with postoperative chemoradiation.
Anastomotic stricturing occurred in 4 percent of patients after preoperative treatment
versus 12 percent with postoperative treatment. Severe acute and late side effects (Grade
3 or worse) occurred in 27 percent versus 40 percent (acute side effects) and in 14 percent
versus 24 percent (late side effects) with preoperative versus postoperative chemo-
radiation, respectively. Ninety-two and 89 percent of patients received the full course of
preoperative pelvic radiation and chemotherapy, respectively whereas; only 54 percent
and 50 of patients completed the full course of postoperative pelvic radiation and
chemotherapy, respectively. Twenty percent more patients (39% vs 19%) were able to
have sphincter preservation with preoperative versus postoperative chemoradiation when
the surgeon initially felt that APR was necessary. In summary, preoperative chemo-
radiation is better tolerated, locally more effective with fewer acute and long-term side
effects and a greater chance of sphincter preservation.

The main risk to preoperative chemoradiation is the possibility that the patient is
overstaged by radiologic and clinical assessment and receives chemoradiation, which
would not otherwise have been given (cancers that are both node negative and
penetrating less than the full thickness of the rectal muscle wall do not routinely receive
adjuvant treatment). Approximately 18 percent of patients were overstaged in the German
rectal cancer trial. Thus, patients being considered for preoperative treatment should have
preoperative endorectal ultrasound and/or MRI to assess depth of invasion (T3 or node
positive lesions would be suitable for preoperative treatment). Patients who have
radiologic T2 lesions but who wish to reduce the chance of APR would be suitable for
preoperative treatment.

**Investigations**

Initial presentation will be usually confirmed by endoscopy and biopsy. With Low lying
lesions require CT and Trans Rectal Ultrasound (TRUS) are helpful to determine T
status, upper rectal lesions require CT or Magnetic Resonance Imaging (MR), though MR
can be helpful for all rectal tumours.

Systemic disease should be addressed with physical exam, chest X-ray, CT abdomen or
ultrasound liver, CEA and routine blood tests to determine capacity for treatment (CBC,
liver function tests, Creatinine, LDH)

- Physical Exam with estimate of tumour circumference, size and distance from the anal
  verge
- Endoscopy and biopsy
- CT, TRUS and/or MR
• Chest X-ray
• Ultrasound abdomen or CT abdomen
• CBC, AST, Alk Phos. Bilirubin, Creatinine, CEA

### Staging
Request for review of outside slides, or special staining of internal pathology if there is suggestion of unusual features such as neuroendocrine histology.

### Treatment recommendations by Stage Groups

#### 0 Tis
1. Local excision or simple polypectomy.
2. Wedge resection for large lesions not amenable to local excision

#### I T1-2, N0, M0
1. Wide surgical resection (Total Mesorectal Excision) and anastomosis when adequate resection can be performed with sufficient distal rectum to allow anastomosis
2. Wide surgical resection (TME) with abdominal perineal resection
3. Local /trans-anal resection in selected patients (well differentiated, not fixed, clinically node negative, <50% circumference, <4 cm. < 10 cm. from anal verge

#### II, III T3-4, N0; T1-4, N1-2
Treatment can be divided into three phases: Surgery, Chemoradiotherapy, and Adjuvant Chemotherapy. Treatment should begin within 2-4 weeks of diagnosis.

### Standard treatment
1. Surgery, then 6-8 weeks later
2. Adjuvant Chemotherapy (1-4 cycles)
3. Chemoradiotherapy, then three weeks later,
4. Adjuvant Chemotherapy (0-4 cycles, total 4 when added to pre-radiation treatment, #2)

### Neoadjuvant treatment
Care in selection should include an assessment of whether or not a defunctioning colostomy or colonic stent is required before treatment. Surgery, medical oncology and radiation oncology all need consultation prior to initiation of treatment. Relative contraindications include active Inflammatory Bowel Disease, autoimmune disorders, and unstable angina.
1. Chemoradiotherapy, then 6-8 weeks later
2. Surgery, then 4-6 weeks later
3. Adjuvant Chemotherapy (4 cycles)

**Chemoradiotherapy**

5FU Continuous Infusion (CIV) 225 mg/M$^2$/day (optionally 180 mg/M$^2$/day for elderly or infirm) with concurrent three-field radiation 50.4 Gy in 28 fractions

**Adjuvant Chemotherapy**

Each of the following options consists of one cycle (to be repeated every four weeks for 4 cycles total):

1. 5FU 500 mg/M$^2$/day bolus IV for five days, or
2. 5FU 425 mg/M$^2$/day bolus IV (400 mg after radiation) plus leucovorin (folinic acid) 20 mg/M$^2$/day bolus IV, or
3. 5FU 225 mg/M$^2$/day CIV (200 after radiation) for 4 weeks (for patients with unacceptable myelosuppression).
4. FOLFOX: 5FU 400 mg/M$^2$, leucovorin 400 mg/M$^2$, Oxaliplatin 85 mg/M$^2$ on day 1, 5FU 2,400 mg/M$^2$ CIV 46 hours, repeat every 2 weeks, for high risk, young patients. 8 cycles (4 months). (ECOG 3201 demonstrated safety, though efficacy still unsure)

Dose adjustments are made at the discretion of the oncologist based on toxicity, usually by delaying treatment a week, or by making a dose reduction in one of more drugs. While dose reductions of 25% are common for 5FU, the neuropathy of Oxaliplatin can often be dealt with by reductions of 10%, and previous clinical trials at this centre have suggestions for adjustment.

**Treatment Benefits**

The use of post-operative chemotherapy and radiotherapy for rectal cancer has been well established over the last twenty years, and is outlined well in the CCO Practice Guideline. This meta-analysis established a reduction in local recurrence and mortality of 40-50%. One quoted study suggested local control improved from 12% to 30% and five year overall survival improved from 50% to 64%. The use of CIV chemotherapy during radiation was established by O’Connell, and the equivalency of chemotherapeutic protocols is apparent in the Intergroup 0144 study. Since the publication of the CCO Practice Guideline, several studies have demonstrated benefits of neoadjuvant therapy, so that it is now becoming the standard of practice. The benefits of neoadjuvant therapy shown by Saur *et. al.* are in the reduction of pelvic recurrence (11% to 7%, p=0.02) and long term complications such as stenosis (8.5% to 2.7%, p=0.001), as well as a reduction in sphincter loss (39% to 19%). In general, neoadjuvant chemoradiotherapy followed by surgery, and then adjuvant...
Chemotherapy, is quickly becoming the standard of care at LRCP, although most patients are still treated surgically first. It is hoped the percentage of patients receiving neoadjuvant therapy will increase over time.

Palliative resection

- Palliative resection (+/- radiotherapy) to prevent local recurrence and progression in selected patients
- Palliative radiotherapy in unresectable disease.
- Palliative chemotherapy as in Colon cancer

Metastasectomy

No clear evidence for the use of adjuvant therapy following metastasectomy, (although some evidence supporting use in hepatic mets). Should be assessed on an individual basis. Where neoadjuvant therapy is planned, oxaliplatin based treatment has less liver toxicity and post-operative mortality.

Liver

≤ 4 lesions and no other evidence of disease, refer for surgical resection, radioablation or cryotherapy and consider post-operative adjuvant therapy 20-40% five year DFS, with best results inpatients with long disease free interval, low CEA, good resection margins, low TNM stage with first surgery

Lung

Solitary metastasis best, single lobe, long disease free interval

Followup recommendations (following active treatment)

- History and physical exam every 3 to 6 months (stage II, III) for 3 years, every 6 months in years 4 and 5, then at discretion of the physician
- CEA every 3 months for 3 years
- Colonoscopy in first post-operative year, then once a year for patients with polyps, once every three to five years once free of polyps
- Flexible sigmoidoscopy every 6 months for patients who have not received radiation treatment
- CT scan abdomen, pelvis and chest annually for 3 years if curative surgery would be offered (ASCO 2005 Guidelines)

These follow-up recommendations may be passed over to the responsible family physician for the patient.

Patients with Stage IV disease followed according to need dictated by clinical course.
**Genetic Counselling**

Patients should be referred for genetic counselling after obtaining a family history or clinical history of one of the following risk factors:

**Risk Factors for Inherited Colorectal Cancer:**

1. Multiple cases in the family of the following cancers related to the Hereditary Non-Polyposis Colorectal Cancer (HNPCC) spectrum with at least one relative affected with colorectal or endometrial cancer. An age of onset less than 50 years, in closely related relatives and in more than one generation would raise the index of suspicion.

<table>
<thead>
<tr>
<th>Gastro-intestinal</th>
<th>colorectal</th>
<th>gastric</th>
<th>small bowel</th>
<th>hepatobiliary</th>
<th>pancreatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genito-urinary</td>
<td>endometrial</td>
<td>ovarian</td>
<td>kidney</td>
<td>ureter</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>sebaceous (adenoma or carcinoma)</td>
<td>brain</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2. Age at diagnosis of colorectal cancer less than 35 years.

3. Multiple primary cancers in one family member (see list above for tumour sites).

4. Family member with Familial Adenomatous Polyposis (FAP), or 10 or more adenomatous polyps.

5. Family member with a colonic adenoma or cancer with high microsatellite instability (MSI) and/or immunodeficiency.

6. Family member with a known mutation causing either HNPCC or FAP.
References

1. C. Germond AF, B.M. Taylor, S. Micucci, C. Zwaal and members of the Gastrointestinal Cancer Disease Site Group: Postoperative Adjuvant Radiotherapy and/or Chemotherapy for Resected Stage II or III Rectal Cancer


NCCN Guidelines:
NCCN Practice Guidelines in Oncology – v.2.2006
Rectal Cancer

**CLINICAL STAGE**
- T3, N0 or T any, N1-2
- Transabdominal resection
- pT1-2, N0, M0
- pT3, N0, M0 or pT1-3, N1-2

**PRIMARY TREATMENT**
- Preoperative continuous 5-FU/RT (preferred) (category 1 for node positive disease) or bolus 5-FU + leucovorin/RT or capcitabine/RT (category 2B)

**ADJUVANT TREATMENT\(^{a,t,1}\)**
- 5-FU ± leucovorin (category 1) or FOLFOX\(^{a}\) (category 2B)
- or Capcitabine\(^{a}\) (category 2B)

**T4 and/or locally unresectable**
- Continuous IV 5-FU/RT or bolus 5-FU + leucovorin/RT or capcitabine/RT\(^{h}\) (category 2B)

**PRIMARY TREATMENT**
- Resection, if possible
- Any T

**ADJUVANT TREATMENT\(^{a,t,1}\)**
- 5-FU ± leucovorin or FOLFOX\(^{a}\) (category 2B)
- or Capcitabine\(^{a}\) (category 2B)

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\(^{a}\)See Principles of Surgery (REC-A).
\(^{t}\)See Principles of Adjuvant Therapy (REC-B).
\(^{1}\)See Principles of Radiation Therapy (REC-C).
\(^{h}\)The use of FOLFOX or capcitabine is an extrapolation from the available data in colon cancer. Trials are still pending in rectal cancer.

**Data regarding the use of capcitabine/RT is limited and no phase III randomized data are available. Trials are pending. Kim, J-Sang, Kim, J-Sung, Cho, M, et al. Preoperative chemoradiation using oral capcitabine in locally advanced rectal cancer. Int J Radiation Oncology Biol Phys 2002;54(2):403-408.**

**Postoperative therapy is indicated in all patients who receive preoperative therapy, regardless of the surgical pathology results. An ongoing Intergroup trial compares 5-FU/leucovorin, FOLFOX, and FOLFIROI after surgery.**
## Rectal Cancer

### NCCN Practice Guidelines in Oncology – v.2.2006

<table>
<thead>
<tr>
<th>Clinical Stage</th>
<th>Primary Treatment</th>
<th>Adjuvant Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>T Any, N Any, M1</td>
<td>Continuous IV 5FU/ pelvic RT or bolus 5-FU + leucovorin/pelvic RT or Capecitabine/RT(^a) (category 2B)</td>
<td>5-FU ± leucovorin or FOLFOX + bevacizumab(^b) (category 2B) or FOLFIRI + bevacizumab(^b) (category 2B)</td>
</tr>
<tr>
<td>T Any, N Any, M1</td>
<td>Combination chemotherapy (FOLFOX + bevacizumab or FOLFIRI + bevacizumab)</td>
<td>Consider continuous IV 5-FU/ pelvic RT or bolus 5-FU + leucovorin/pelvic RT or Capecitabine/RT(^b) (category 2B)</td>
</tr>
<tr>
<td>T Any, N Any, M1</td>
<td>Staged or synchronous resection of metastases(^c) and rectal lesion</td>
<td>Surveillance (See REC-6)</td>
</tr>
<tr>
<td>T Any, N Any, M1</td>
<td>pT1-2, N0, M1</td>
<td>5-FU ± leucovorin × 6 mo or FOLFOX + bevacizumab(^b) × 4–6 mo (category 2B) or FOLFIRI + bevacizumab(^b) × 4–6 mo (category 2B)</td>
</tr>
<tr>
<td>T Any, N Any, M1</td>
<td>pT3-4, Any N or Any T, N1-2</td>
<td>5-FU ± leucovorin or FOLFOX(^b) (category 2B) or capecitabine(^b) (category 2B), then continuous 5-FU/RT or bolus 5-FU + leucovorin/RT (category 2B) or capecitabine/RT(^b) (category 2B), then 5-FU ± leucovorin or FOLFOX(^b) (category 2B) or capecitabine(^b) (category 2B)</td>
</tr>
</tbody>
</table>

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\(^a\) See Principles of Surgery (REC-A).
\(^b\) See Principles of Adjuvant Therapy (REC-B).
\(^c\) See Principles of Radiation Therapy (REC-C).

\(^b\) The use of FOLFOX or capecitabine is an extrapolation from the available data in colon cancer. Trials are still pending in rectal cancer.


\(^b\) The safety of administering bevacizumab pre- or postoperatively, in combination with 5-FU-based regimens, has not been adequately evaluated. Elderly patients are at increased risk of stroke and other arterial events.
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