EARLY STAGE RECTAL CANCER

Executive Summary

Early stage rectal cancer is a potentially curable illness. Surgery is the most critical component of the treatment for this malignancy. Over the past few decades, improvements in surgical technique, specifically the development of the total mesorectal excision (TME), have had a major impact on patient survival. Stage I rectal cancers are curable with surgery alone. The treatment of stage II and III rectal cancer is more complex and should involve a multidisciplinary approach. For stage II and III rectal cancer, neoadjuvant chemoradiation with IV 5-FU or oral capecitabine is the standard of care.

Public Health Relevance

Colorectal cancer is one of the most common, and deadly, malignancies; it has been estimated that worldwide there are 1.2 million new cases a year [1]. Globally, colorectal cancer is the fourth most common cause of cancer-related deaths in men and third in women, killing an estimated 320,600 men and 288,100 women annually [1].

In the developed world, the death rate from colorectal cancer has been decreasing, largely due to colonoscopy screening, that enable both the removal of precancerous polyps and the detection of early stage, curable disease. Because 90% of colon cancers occur in patients who are at least 50 years-old, in countries that are able to afford colonoscopy screening the recommendation for the general population is to begin at age 50[2].

Because of the expense of colonoscopy, population based screening programs are usually not feasible in many parts of the world. With poor access to health care added to that, colorectal cancer patients in low- and middle-income countries often present with more advanced stages of the disease.

In the United States, 40% of colorectal cancer patients have localized disease (stage I and II) [3], 36% are regionally advanced (stage III) and 20% have metastases at presentation [3].

Requirements for diagnosis, treatment, and monitoring

Diagnostics: Localized colorectal cancer often presents with one of the following symptoms: change in bowel habits, blood in the stools, abdominal discomfort, and weight loss. The symptoms of metastatic colorectal cancer depend on the site of metastasis depending on the site of metastasis (liver: RUQ abdominal pain, jaundice; bone: bone pain; lungs: chest pain, shortness of breath).
The primary mass in colorectal cancer can be diagnosed with a rectal exam, sigmoidoscopy or colonoscopy. During endoscopy a biopsy can be performed so that the diagnosis of cancer is confirmed pathologically.

A critical aspect of the evaluation of a colorectal cancer patient is establishing whether she has metastatic disease. In high resource health systems, computed tomography scan of the Chest, Abdomen and Pelvis is performed routinely. In resource-constrained settings systemic evaluation with abdominal and pelvic ultrasound is a less costly, commonly employed, option. Preoperative rectal cancer staging, which evaluates the T and N stage of the tumor, is also important in establishing the degree of loco-regional invasiveness of the tumor. Where available, it is performed by either rectal MRI or endoscopic ultrasound, complex and highly specialized methods that have limited availability in resource-constrained settings.

When chemotherapy is employed, laboratory evaluations play an important role in monitoring patient safety. A complete blood count (CBC) with differential assesses whether patients are myelosuppressed and neutropenic. A comprehensive metabolic panel monitors renal and hepatic function as well as electrolyte imbalances.

**Treatment:** Early stage rectal cancer is a potentially curable illness. Compared to early stage colon cancer, early stage rectal cancers have a higher risk of local recurrence. The treatment paradigm for rectal cancer has evolved to address this higher risk. Patients with locally advanced rectal cancers receive multidisciplinary care involving surgery, radiation and chemotherapy. In low-income countries, treatment of rectal cancer can be very challenging because of the complexity and cost of radiation, chemotherapy, imaging and supportive services.

As in colon cancer, surgery is the cornerstone of treatment for early stage rectal cancer. Locally advanced tumors are removed either by a sphincter-saving Low Anterior Resection (LAR) or Abdominoperineal Resection (APR). One of the biggest advances in the treatment of locally advanced rectal cancer was the development of the total mesorectal excision (TME). A TME involves a sharp dissection and complete removal of the mesorectum. The TME surgical approach reduces local recurrence rates from 12% - 25% to 5%- 6% [4-6]. In advanced health care systems, TME is the standard of care and, given the significant improvement in outcomes, sincere efforts to adapt this surgical procedure should be made worldwide.

Neoadjuvant chemoradiation was developed to address the high risk of recurrence associated with the disease and, where resources allow, it is the standard of care for patients with stage II and III rectal cancer. Patients with preoperatively staged tumors that are T1-2/N0 can be treated with surgery alone. Following surgery, if the pathology shows a higher stage, these patients are candidates for post-operative chemoradiation and adjuvant chemotherapy.

The evidence that chemoradiation was effective in the treatment of locally advanced rectal cancer initially came from the GITSG protocol GI-7175 [7]. This protocol randomized 227 patients into four groups: surgery alone, postoperative radiation, postoperative chemotherapy, or postoperative chemoradiation. The chemoradiation group had superior overall survival compared to the other groups and this established chemoradiation as the standard of care [8].
The question of whether chemoradiation should be given before or after surgery was addressed by the German Rectal Cancer Study [9]. This study found that neoadjuvant chemoradiation improved local control compared to post-operative chemoradiation. There was no survival difference between the two arms. Notably, neoadjuvant chemoradiation increased the number of sphincter-sparing surgeries and had less toxicity than post-operative chemoradiation [9]. The overall five-year survival rates were 76 percent and 74 percent, respectively (P=0.80). The five-year cumulative incidence of local relapse was 6 percent for patients assigned to preoperative chemoradiotherapy and 13 percent in the postoperative-treatment group (P=0.006).

The NSABP trial R-04 demonstrated that chemoradiation with capecitabine is equivalent to chemoradiation with 5-FU [10]. Capecitabine is an oral medication which is easier to administer than 5-FU continuous infusion, and has a different toxicity profile. A German trial corroborated these findings and suggested that capecitabine may be a little more effective than fluorouracil. 5-year overall survival in the capecitabine group was non-inferior to that in the fluorouracil group (76% [95% CI 67-82] vs 67% [58-74]; p=0.0004; post-hoc test for superiority p=0.05). 3-year disease-free survival was 75% (95% CI 68-81) in the capecitabine group and 67% (59-73) in the fluorouracil group (p=0.07). Similar numbers of patients had local recurrences in each group (12 [6%] in the capecitabine group vs 14 [7%] in the fluorouracil group, p=0.67), but fewer patients developed distant metastases in the capecitabine group (37 [19%] vs 54 [28%]; p=0.04).

One of the drawbacks of conventional long-course chemoradiation is that it is very expensive. One alternative to neoadjuvant chemoradiation is short-course radiation. In short-course radiation, patients receive 25 Gy in 5 fractions. This is followed by surgery 1 to 2 weeks later. The Polish Rectal Trial demonstrated that short-course radiation and long-course chemoradiation have equivalent local control and overall survival [11]. However, short-course radiation had less tumor downstaging and a lower pathological complete response rate than conventional long-course chemoradiation [11]. While short-course radiation is utilized in some European countries, it is still controversial in the United States.

Adjuvant 5-FU based chemotherapy is the standard of care in the developed world for patients who have undergone neoadjuvant chemoradiation. This recommendation is largely based on the successful use of adjuvant chemotherapy in colon cancer [12-14]. In addition, a recent trial demonstrated that rectal cancer patients receiving 8 cycles of adjuvant FOLFOX had improved disease-free survival compared to patients who received 8 cycles of adjuvant 5-FU/Leucovorin [15].

The choice of fluoropyrimidine, IV bolus or infusion fluoruracil or oral capecitabine is dependent upon local experience and resource-availability. In general, infusion and oral regimens have lower toxicity than bolus regimens as detailed in the metastatic colon cancer documents prepared by the task force.

**Administration:** Administration requires intravenous infusion capacity, and requires that patients have regular access to clinical care. In developed countries administration is usually performed in out-patient facilities, though in other settings, patients may be treated in in-patient
facilities. Antiemetics need to be available. Monitoring requires that clinicians have access to laboratory facilities, as well as the ability to recognize and address potential adverse events caused by the treatment itself. Importantly, in-patient facilities capable of supporting patients with severe infections and dehydration need to be readily available. Social and financial wellbeing can be impacted by treatment side effects and should be monitored and addressed as well.

**Systematic Reviews and Major Trials**

NB: Major trials relevant to the use of 5-FU +/- oxaliplatin can be found in the early stage colon cancer briefing and are not repeated here. Please also note that data concerning capecitabine is included in more depth in early stage colon cancer briefing as well.

*Surgical resection + chemoradiation vs surgical resection + chemotherapy alone*


**Purpose:** To determine survival and relapse rates by T and N stage and treatment method in five randomized phase III North American rectal adjuvant studies. **Patients and Methods:** Data were pooled from 3,791 eligible patients enrolled onto North Central Cancer Treatment Group (NCCTG) 79-47-51, NCCTG 86-47-51, US Gastrointestinal Intergroup 0114, National Surgical Adjuvant Breast and Bowel Project (NSABP) R01, and NSABP R02. Surgery alone (S) was the treatment arm in 179 patients. The remaining patients received adjuvant treatment as follows: irradiation (RT) alone (n = 281), RT + fluorouracil (FU) +/- semustine bolus chemotherapy (CT; n = 779), RT + protracted venous infusion CT (n = 325), RT + FU +/- leucovorin or levamisole bolus CT (n = 1,695), or CT alone (n = 532). Five-year follow-up was available in 94% of surviving patients, and 8-year follow-up, in 62%. **Results:** Overall (OS) and disease-free survival were dependent on TN stage, NT stage, and treatment method. Even among N2 patients, T substage influenced 5-year OS (T1-2, 67%; T3, 44%; T4, 37%; P<.001). Three risk groups of patients were defined: (1) intermediate (T1-2/N1, T3/N0), (2) moderately high (T1-2/N2, T3/N1, T4/N0), and (3) high (T3/N2, T4/N1, T4/N2). For intermediate-risk patients, those receiving S plus CT had 5-year OS rates of 85% (T1-2/N1) and 84% (T3/N0), which was similar to results with S plus RT plus CT (T1-2/N1, 78% to 83%; T3/N0, 74% to 80%). For moderately high-risk lesions, 5-year OS ranged from 43% to 70% with S plus CT, and 44% to 80% with S plus RT plus CT. For high-risk lesions, 5-year OS ranged from 25% to 45% with S plus CT, and 29% to 57% with S plus RT plus CT. **Conclusion:** Different treatment strategies may be indicated for intermediate-risk versus moderately high- or high-risk patients based on differential survival rates and rates of relapse. Use of trimodality treatment for all patients with intermediate-risk lesions may be excessive, since S plus CT resulted in 5-year OS of approximately 85%; however, 5-
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year disease-free survival rates with S plus CT were 78% (T1-2/N1) and 69%(T3/N0), indicating room for improvement.

Standard Regimens
Neoadjuvant 5-FU (or capecitabine) with radiation
Adjuvant 5-FU/Leucovorin or FOLFOX

NB: Leucovorin and calcium folinate are referred to in this document interchangeably.

Neoadjuvant Regimens

Chemoradiation with 5-FU
• Continuous infusion 5-fluorouracil (225 mg/m²/24 hours) Monday to Friday throughout the course of radiation or capecitabine as below are the optimal regimens but bolus 5FU is a reasonable alternative where the ability to safely deliver infusional 5FU or capecitabine is not available. No clinical trials have shown superiority of these two options over a bolus regimen but expert opinion and clinical trials data suggest lower toxicity.
  • Bolus regimen: 5FU 400 mg/m2 bolus IV + Leucovorin 20 mg/m2 IV for four days during weeks 1 and 5 of radiation

Chemoradiation with Capecitabine
• Capecitabine 825-1000 mg/m² twice daily Monday to Friday throughout the course of radiation

Adjuvant Regimens [after neoadjuvant treatment]

FOLFOX-6 Regimen for 8 cycles (4 months)
• Leucovorin 400 mg/m² IV on Day 1 of each 14 day cycle
• Fluorouracil (5-FU) 400 mg/m² IV bolus on Day 1 of each 14 day cycle
• Fluorouracil (5-FU) 1200mg/m² daily; continuous infusion over 46 hours (day 1 and 2 of each 14 day cycle)
• Oxaliplatin 85mg/m2 IV on Day 1 of each 14 day cycle

CapeOx (3-week cycle; 6 cycles)
• Capecitabine 1,000 mg/m² PO BID twice daily on Days 1-14 of each 21-day cycle
• Oxaliplatin 130 mg/m² over 2 hours on Day 1 of each 21-day cycle

FLOX (8-week cycle; four months)
• 5-FU 500 mg/m² IV bolus weekly for 8-week cycle
• Calcium folinate 500 mg/m² IV weekly for 6 weeks of each 8-week cycle
• Oxaliplatin 85 mg/m² IV on weeks 1,3,5 of each 8-week cycle
Capecitabine as a single agent
- Capecitabine 1,000-1,250 mg/m² twice daily for 14 days of each 21 day-cycle for 6 cycles-4 months

Modified de-Gramont regimen of adjuvant chemotherapy with 8 cycles of 5-FU and Leucovorin (4 months)
- Calcium folinate 400 mg/m² IV on Day 1 of each 14 day cycle
- Fluorouracil (5-FU) 400 mg/m² IV bolus on Day 1 of each 14 day cycle
- Fluorouracil (5-FU) 1200mg/m² daily; continuous infusion over 46 hours (day 1 and 2 of each 14 day cycle)

Roswell Park Regimen of adjuvant chemotherapy with 4 cycles of 5-FU and Leucovorin (4 months)
- Calcium folinate 500 mg/m² IV bolus on Day 1, 8, and 15 of each 28 day cycle (i.e. week 1, 2, and 3 of each 4 week cycle)
- Fluorouracil (5-FU) 500 mg/m² IV bolus on Day 1, 8, and 15 of each 28 day cycle (i.e. week 1, 2, and 3 of each 4 week cycle)

Mayo regimen of adjuvant chemotherapy with 4 cycles of 5-FU and Calcium folinate (4 months)
- Calcium folinate 20 mg/m² IV bolus administered on days 1-5 of each four week cycle
- Fluorouracil (5-FU) 425 mg/ m² on days 1-5 of each four week cycles

Note: it is acceptable to use low-dose calcium folinate, i.e. 20 mg/m² instead of higher doses. If radiation therapy is not available, adjuvant chemotherapy for 6 months becomes is likely to lead to benefits beyond surveillance alone.

Review of Benefits and Harms

Benefits
Chemotherapy in the neoadjuvant and the adjuvant settings decrease local recurrence and increase cure rates [See “Treatment” above for details]

Harms and Toxicity Considerations
Common
Frequent adverse effects of fluorouracil-leucovorin combination therapy are diarrhea and associated dehydration, neutropenia (uncommonly leading to infection in <2% of patients), anemia, and mucositis.[14,15,16] Palmar-plantar erythrodysthesia (hand-foot) syndrome is associated with fluorouracil and capecitabine, with an increased incidence of up to 60% for patients treated with capecitabine. This adverse effect typically resolves following treatment interruption.[17]
Oxaliplatin-containing regimens such as FOLFOX can lead to sensory neuropathy (24-92% of patients) which is often acute and reversible but may be persistent at high cumulative doses.[14] In one study, the FOLFOX regimen caused significant grade 3 neuropathy in 18% of patients.[18]

Patients treated with chemoradiation additionally can experience rectal discomfort and skin breakdown, females are at risk of vaginal stenosis and infertility. [9,16,19]

**Serious**

Diarrhea occurs in up to 50% of patients treated with fluorouracil or capecitabine. Diarrhea can be severe and may require hospital admission for IV fluid replacement, it is often dose-limiting. [14,16]

**Recommendations**

The reviewers recommend the incorporation of early stage rectal cancer treatment options into the WHO Model List of Essential Medicines, and recommend specifically that oxaliplatin and capecitabine be added to the core Essential Medicines List.

**Additions proposed for Section 8.2 of the EML**

Oxaliplatin
Capecitabine
References


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