ADJUVANT AND NEOADJUVANT MANAGEMENT OF COLORECTAL CANCER

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In 2013, colorectal cancer (CRC) was the third most common cancer in the United States and was the second leading cause of cancer-related deaths when both sexes were combined.\(^1\) Population-based screening for CRC, recommended in the United States since 1996, has facilitated early diagnosis of CRC. Indeed, approximately 80% of patients with CRC present with disease that is amenable to surgical resection of curative intent. Unfortunately, 10 to 50% of patients will experience disease relapse within 5 years after surgical resection, either locally or at a distant site.\(^2\) To decrease the risk of disease relapse, nonsurgical treatment modalities have been used as adjuncts to surgery. Adjunctive therapies can be administered before or after surgery and are termed neoadjuvant or adjuvant therapy, respectively. The therapeutic modalities can be broadly categorized as locally directed (e.g., radiation therapy [XRT]) or systemically directed (e.g., cytotoxic and/or targeted chemotherapy). The general principles that underlie surgical and adjunctive therapies include the following:

1. Surgery is most effective in the removal of localized primary tumor and associated regional lymphatic disease. But occult viable tumor cells, termed microscopic residual metastases, may reside in the body or in the circulation, which may be responsible for ultimate disease relapse despite complete surgical removal of gross disease.
2. Chemotherapy and XRT can be used as adjuncts to surgical resection to eliminate microscopic residual disease and reduce the risk of recurrence. These treatments destroy a fraction of the disease burden with each cycle. Their efficacy is maximized when tumor burden is minimized, typically after complete surgical resection.
3. Systemic chemotherapy shows a dose-response relationship. Maximum tolerated doses are typically administered in repeated cycles over a specific duration of time deemed optimal for eradication of tumor cells.
4. Neoadjuvant therapy offers several potential advantages [see Table 1].
5. Attention must be paid to treatment-related toxicities. The nature and the frequency of the toxicities associated with chemotherapy and radiation in patients of different age groups must be taken into consideration.\(^3\)

In this chapter, adjuvant and neoadjuvant therapies for both colon and rectal cancers are reviewed. Pivotal clinical trials that have provided the Level I evidence basis for current practice are summarized. The survival outcomes of CRC have significantly improved over past decades. The decision surrounding the use of neoadjuvant and adjuvant therapeutic modalities should consider the type and stage of the cancer, as well as the condition and comorbidities of the patient. The American Joint Committee on Cancer (AJCC) 7th edition CRC staging system [see Table 2] can be broadly summarized by stage I/II disease as node negative (i.e., local), stage III disease as node positive (i.e., locally advanced), and stage IV disease as metastatic (i.e., advanced).\(^4\) An extensive discussion regarding staging procedures is beyond the scope of this chapter. However, a thorough initial staging workup to determine the clinical stage of disease at diagnosis is critical for the selection of patients for neoadjuvant therapy; similarly, accurate assessment of the pathologic stage of disease at surgical resection plays a crucial role in the decision-making process of selection of adjuvant therapy.

Colon Cancer

The historical trials and rationale surrounding adjuvant therapy for colon cancer, stratified by disease stage, are discussed in Figure 1 [see Figure 1].

ADJUVANT CHEMOTHERAPY FOR STAGE III COLON CANCER

5-Fluorouracil/Levamisole

The chemotherapy agent 5-fluorouracil (5-FU) inhibits the enzyme thymidylate synthase, which is required for DNA synthesis. The North Central Cancer Treatment Group (NCCTG) performed one of the first prospective randomized trials investigating the use of adjuvant 5-FU in combination with levamisole, an antihelminthic drug with immunostimulatory activity. Patients with stage II/III CRC were randomized to surgery alone or to surgery plus adjuvant treatment with either levamisole only or levamisole plus 5-FU for 1 year. Improved 5-year disease-free survival (DFS) was observed for patients who received 5-FU/levamisole and, to a lesser extent, levamisole alone.\(^5\) Subset analysis demonstrated that patients with stage III colon cancer who received 5-FU/levamisole experienced a 40% reduction in the recurrence rate and a 33% reduction in the death rate compared with no adjuvant therapy, and the respective reductions were 2% and 6% for levamisole alone.\(^6\) These results were confirmed in a similarly designed randomized trial performed by the National Cancer Institute Intergroup Trial protocol 035. Based on the results from the above studies, the National Institutes of Health (NIH)
5-Fluorouracil/Leucovorin

Experimental studies showed that the cytotoxic effect of 5-FU can be modulated and potentiated by the addition of leucovorin (LV). LV works by stabilizing the 5-FU thymidylate synthase complex, thus increasing the cytotoxic activity of 5-FU. The combination of 5-FU and LV was initially demonstrated to be efficacious in the treatment of metastatic colon cancer. This observation subsequently led to studies investigating 5-FU plus LV in the adjuvant setting. In the National Surgical Adjuvant Breast and Bowel Project (NSABP) C-03 trial, patients with stage II or III CRC were randomly assigned to receive either 12 months of adjuvant 5-FU/LV or lomustine (MeCCNU)/vincristine (Oncovin)/5-FU (MOF, used in NSABP C-01). Patients who received 5-FU/LV experienced improved overall survival (OS) and DFS compared with patients receiving MOF. The subsequent NSABP C-04 trial randomized patients to receive adjuvant 5-FU/LV, 5-FU/levamisole, or 5-FU/LV/levamisole. This study demonstrated superior 5-year DFS with adjuvant 5-FU/LV versus 5-FU/levamisole (65% versus 60%; p = .04) and a trend toward improved 5-year OS (p = .07). The addition of levamisole to 5-FU/LV was not associated with additional survival advantage.

The International Multicenter Pooled Analysis of Colon Cancer Trials (IMPACT) further confirmed the benefit of 5-FU/LV in the adjuvant setting. This trial was a pooled analysis of three separate trials conducted in Italy, Canada, and France. Patients were randomized to surgery alone or surgery followed by 6 months of 5-FU/LV. The 3-year event-free survival (where events were defined as relapse, second tumor, or death) for patients with stage III colon cancer was 44% in the surgery-alone group but improved to 62% in the adjuvant chemotherapy group. The 3-year OS was also superior for patients who received adjuvant chemotherapy (76% versus 64%).

The Intergroup 0089 trial was another key trial that randomized patients to one of four treatment arms: 5-FU plus levamisole for 12 months (control arm), 5-FU plus high-dose LV for 8 months (Roswell Park schedule), 5-FU plus low-dose LV for 8 months (Mayo Clinic schedule), or 5-FU plus low-dose LV and levamisole for 6 months. After 10 years of follow-up, there was no significance difference in adjusted OS or DFS between the four treatment groups [see Table 3]. Thus, patients appear to derive similar survival benefit from 6 to 8 months of adjuvant 5-FU/LV compared with longer treatment of 5-FU plus levamisole, and the survival benefit was gained without the added toxicity of levamisole.

**Oxaliplatin**

Oxaliplatin is a third-generation platinum derivative that became available in the late 1990s. The addition of oxaliplatin to 5-FU/LV was immediately shown to be more efficacious than 5-FU for patients with metastatic colon cancer. The Multicenter International Study of Oxaliplatin/5-FU/LV in the Adjuvant Treatment of Colon Cancer (MOSAIC) trial was the first large, randomized trial to investigate the role of oxaliplatin in the adjuvant setting. Patients who underwent complete resection of stage II or stage III colon cancer (n = 2,246) were randomized to adjuvant folinic acid (LV)/5-FU/oxaliplatin (FOLFOX) or 5-FU/LV for 6 months. The 3-year DFS was significantly improved for patients...
receiving FOLFOX compared with 5-FU/LV (78.2% versus 72.9%; \( p = .002 \)). Updated results revealed 5-year DFS of 66.4% and 58.9% (hazard ratio [HR] = 0.78, \( p = .005 \)) and 6-year OS of 72.9% and 68.7% (HR = 0.80, \( p = .023 \)), both favoring FOLFOX over 5-FU/LV, respectively.\(^{17}\) In the United States, the NSABP C-07 trial compared the Roswell Park regimen of weekly bolus 5-FU/LV with or without oxaliplatin (FLOX regimen). Similar to the MOSAIC trial, the addition of oxaliplatin was associated with improved DFS.\(^{18}\) Based on these results, FOLFOX is currently recommended as the first-line adjuvant therapy after surgical resection in patients with stage III colon cancer.

**Figure 1** An algorithm for adjuvant treatment of colon cancer. High-risk features include T4 disease, obstruction or perforation at initial presentation, poorly differentiated tumor, presence of lymphovascular or perineal invasion, evidence of inadequate surgical resection, and evidence of close, indeterminate, or positive surgical resection margins. Adjuvant chemotherapy regimen options for high-risk stage II disease include 5-fluorouracil/leucovorin (5-FU/LV) or capecitabine. The addition of oxaliplatin should be individualized. Adjuvant chemotherapy regimen options for stage III disease include 5-FU/LV (folinic acid)/oxaliplatin (FOLFOX), bolus 5-FU/LV/oxaliplatin (FLOX), oxaliplatin (XELOX), single-agent capecitabine, and 5-FU/LV. MSI = microsatellite instability; MSS = microsatellite instability stable; MSI-L = microsatellite instability low; MSI-H = microsatellite instability high.

**Table 3** Disease-Free and Overall Survival for Intergroup 0089 Study\(^{13}\)

<table>
<thead>
<tr>
<th>Chemotherapy Regimens</th>
<th>DFS (%)</th>
<th>OS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5 yr</td>
<td>10 yr</td>
</tr>
<tr>
<td>5-FU/levamisole</td>
<td>55</td>
<td>45</td>
</tr>
<tr>
<td>5-FU/LV (Roswell Park schedule)</td>
<td>58</td>
<td>47</td>
</tr>
<tr>
<td>5-FU/LV (Mayo Clinic schedule)</td>
<td>60</td>
<td>49</td>
</tr>
<tr>
<td>5-FU/LV/levamisole</td>
<td>49</td>
<td>68</td>
</tr>
</tbody>
</table>

DFS = disease-free survival; 5-FU = 5-fluorouracil; LV = leucovorin; OS = overall survival.
Two new oral agents, UFT and capecitabine (Xeloda), were investigated as an alternative to continuous infusion of 5-FU in the adjuvant setting. UFT is a combination of oral uracil and the 5-FU prodrug tegafur. The NSABP C-06 trial compared UFT plus LV and showed that the combination achieved DFS similar to that of 5-FU/LV following the Roswell Park regimen. Capectabine preferentially generates fluorouracil in tumor tissue via a three-step enzymatic conversion. The Xeloda in Adjuvant Colon Cancer Therapy (X-ACT) trial evaluated capectabine in the adjuvant setting by randomizing 1,987 patients with resected stage III colon cancer to oral capectabine or bolus 5-FU/LV (Mayo Clinic regimen) for 6 months. DFS was equivalent in the two arms, but capectabine was associated with significantly less diarrhea, nausea/vomiting, stomatitis, alopecia, and neutropenia, although there was an increased risk of hand-foot syndrome and hyperbilirubinemia. More recently, capectabine combined with oxaliplatin (XELOX) was established as an adjuvant treatment regimen with a tolerable risk profile for stage III colon cancer in the trial NO16968 (XELOX in Adjuvant Colon Cancer Treatment [XELOXA]). In summary, FOLFOX and XELOX are currently regarded as equivalent in efficacy, and either regimen is recommended as adjuvant therapy after surgical resection of stage III colon cancer.

Irinotecan

Irinotecan, a topoisomerase I inhibitor, also became available in the mid-1990s and was shown to be effective in the treatment of metastatic CRC. Unfortunately, the addition of irinotecan to 5-FU/LV in the adjuvant setting was not associated with improved survival. Neither the Cancer and Leukemia Group B (CALGB) 89803 trial (bolus 5-FU plus LV versus irinotecan plus bolus 5-FU plus LV [IFL]) nor the Pan European Trial in Adjuvant Colon Cancer (PETACC-3) (continuous 5-FU plus LV versus continuous 5-FU plus LV plus irinotecan) was able to demonstrate an improvement in DFS or OS with the addition of irinotecan to a 5-FU/LV regimen. Based on these results, irinotecan is not recommended as adjuvant treatment of colon cancer.

Targeted Therapy

Bevacizumab and cetuximab are two targeted agents commonly used in combination with oxaliplatin- or irinotecan-based chemotherapy regimens for metastatic CRC. Bevacizumab (Avastin) is a humanized monoclonal antibody that targets the vascular endothelial growth factor (VEGF). Cetuximab is a chimeric human mouse monoclonal antibody that targets the epidermal growth factor receptor (EGFR). To date, they have not demonstrated any efficacy in the adjuvant setting: the Avastin Adjuvant (AVANT) trial failed to demonstrate improved DFS with the addition of bevacizumab to adjuvant FOLFOX, whereas the NCCTG failed to demonstrate improved DFS with the addition of cetuximab to adjuvant FOLFOX. Thus, neither bevacizumab nor cetuximab is recommended for the adjuvant treatment of colon cancer.

National Comprehensive Cancer Network Guidelines

In summary, the current National Comprehensive Cancer Network (NCCN) recommends 6 months of adjuvant chemotherapy following surgical resection for stage III colon cancer [see Figure 1]. Adjuvant therapy should begin as soon as the patient is medically stable, typically within 4 to 6 weeks after surgery. The standard of care treatment regimen is FOLFOX, but other treatment options include bolus 5-FU/LV/oxaliplatin (FLOX), XELOX, or single-agent capectabine or 5-FU/LV for patients felt to be inappropriate for oxaliplatin-based multiagent regimens. It is important for surgeons to be familiar with the common adverse effects associated with these common chemotherapy regimens [see Table 4].

Adjuvant Chemotherapy for Stage II Colon Cancer

Patients with stage II colon cancer typically face lower risks of disease relapse when compared with those with stage III disease. Many of the adjuvant trials discussed in the previous section enrolled patients with both stage II and III disease. Pooled and subgroup analyses of only stage II patients from large clinical trials have failed to show any improvement in DFS or OS with adjuvant chemotherapy. The International Multicenter Pooled Analysis of B2 Colon Cancer Trials (IMPACT B2) investigators pooled data from five different trials that randomized 1,016 stage II patients to surgery alone versus surgery plus adjuvant 5-FU/LV. The two groups did not differ in DFS or OS. Another pooled analysis of results from seven randomized controlled trials comparing 5-FU/LV or 5-FU/leavamisole with surgery alone showed similar findings.

However, there is a recent meta-analysis of 12 randomized controlled trials in which adjuvant chemotherapy demonstrated benefit in survival and in disease recurrence when given to patients with resected stage II disease: the 5-year OS and DFS HRs were 0.81 (95% CI 0.76 to 0.91) and 0.86 (95% CI 0.75 to 0.98), respectively.

Table 4 Common Toxicities Associated with Chemotherapeutic Agents Used as Systemic Therapy for Colorectal Cancer

<table>
<thead>
<tr>
<th>Systemic Therapy</th>
<th>Potential Common Toxicities</th>
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<tbody>
<tr>
<td>5-Fluorouracil (5-FU)</td>
<td>Fatigue, Gastrointestinal (nausea, diarrhea), Myelosuppression, Cardiovascular</td>
</tr>
<tr>
<td>Leucovorin (LV)</td>
<td>Gastrointestinal (diarrhea)</td>
</tr>
<tr>
<td>Oxaliplatin</td>
<td>Acute/chronic peripheral neuropathy, Fatigue, Gastrointestinal (nausea, diarrhea), Myelosuppression, Hypersensitivity</td>
</tr>
<tr>
<td>Capecitabine</td>
<td>Hand-foot syndrome, Fatigue, Gastrointestinal (nausea, diarrhea), Hyperbilirubinemia, Myelosuppression</td>
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Scientific American Surgery
The caveat is that many of the chemotherapy regimens in the trials included in this analysis are not currently recommended. Finally, the Quick and Simple and Reliable (QUASAR) trial represents one of the only sources of randomized data to demonstrate a benefit of adjuvant chemotherapy for stage II disease. Among 3,239 patients randomized to receive 5-FU/LV or observation alone after surgical resection, the relative risk of death with adjuvant chemotherapy versus surgery alone was 0.82 (95% CI 0.70 to 0.95, \( p = .008 \)), with an absolute improvement in survival of 3.6%. The relative risk of recurrence was 0.78 (95% CI 0.67 to 0.91, \( p = .001 \)). The authors concluded that adjuvant chemotherapy after resection of stage II colon cancer could improve survival, but the absolute benefit is small. Taken together, it is currently accepted that adjuvant chemotherapy provides a benefit in terms of survival among patients with stage II disease; however, the absolute benefit is small and has to be clearly balanced with potential side effects. In this context, biomarker research to further delineate and/or identify subgroups of patients who could benefit the most from the administration of adjuvant chemotherapy is a priority.

The use of combination regimens including oxaliplatin for stage II disease has also been examined. In a post hoc subgroup analysis of 569 patients with high-risk stage II disease randomized to adjuvant FOLFOX versus 5-FU/LV within the MOSAIC trial, there was no DFS or OS advantage for the addition of oxaliplatin to 5-FU/LV for stage II colon cancer. As a result of these findings, FOLFOX and XELOX are not considered the preferred adjuvant regimens for medically fit patients with stage II disease; however, the absolute benefit is small and has to be clearly balanced with potential side effects. In this context, biomarker research to further delineate and/or identify subgroups of patients who could benefit the most from the administration of adjuvant chemotherapy is a priority.

There have been increasing efforts to identify subgroups of patients with stage II colon cancer who may be at high risk for disease relapse and who may thus benefit from adjuvant chemotherapy. Indeed, both the American Society of Clinical Oncology (ASCO) and the NCCN currently recommend adjuvant chemotherapy for medically fit patients with high-risk stage II disease. High-risk or poor prognostic features are shown in Table 5 [see Table 5].

Additional molecular prognostic markers are currently being investigated for risk stratification. One of the most well-established prognostic biomarkers is microsatellite status, and multigene assays are becoming more widely available as additional prognostic tools.

### Table 5 High-Risk or Poor Prognostic Features of Patients with Stage II Colon Cancer

<table>
<thead>
<tr>
<th>Feature</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>T4 disease (i.e., invasion into adjacent organs)</td>
<td></td>
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<tr>
<td>Obstruction or perforation at initial presentation</td>
<td></td>
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<tr>
<td>Poorly differentiated tumors</td>
<td></td>
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<tr>
<td>Presence of lymphovascular invasion or perineal invasion</td>
<td></td>
</tr>
<tr>
<td>Evidence of inadequate surgical removal/pathologic assessment of lymph nodes (&lt;12 lymph nodes)</td>
<td></td>
</tr>
<tr>
<td>Evidence of close (&lt;2 mm or less), indeterminate, or positive surgical resection margin</td>
<td></td>
</tr>
<tr>
<td>Elevated carcinoembryonic antigen preoperatively</td>
<td></td>
</tr>
</tbody>
</table>

### Microsatellite Instability

Key genes responsible for DNA mismatch repair (MMR) function include MLH1, MSH2, MSH6, and/or PMS2. Mutations in these genes will result in deficiency of MMR proteins, thus leading to the accumulation of genetic errors in microsatellite regions, also known as microsatellite instability (MSI). In CRC, the deficient mismatch repair (dMMR) phenotype can result from inherited germline mutations or acquired somatic mutations in MMR genes. Patients with inherited mutations in MMR genes have a hereditary condition named Lynch syndrome (or hereditary nonpolyposis colon cancer [HNPCC]), which accounts for 3 to 5% of all cases of CRC. Somatic alterations of the MMR genes are secondary to hypermethylation of the MLH1 gene promoter and are associated with BRAF mutations. These mutations account for approximately 15% of sporadic CRC. Microsatellite status has prognostic significance. Patients with dMMR (or microsatellite instability high [MSI-H]) tumors have a better prognosis compared with patients with microsatellite instability stable tumors. In addition, some studies have demonstrated that patients with MSI-H CRCs do not benefit from 5-FU-based adjuvant therapy. In a pooled analysis, patients with dMMR CRCs had no improvement in DFS after receiving 5-FU-based adjuvant therapy (HR 1.10, 95% CI 0.42 to 2.91, \( p = .85 \)), whereas those with no deficiency in MSI-H CRCs had improved DFS (HR 0.67, 95% CI 0.48 to 0.93, \( p = .02 \)). In a subset analysis, dMMR patients who received adjuvant therapy experienced slightly reduced OS (HR 2.95, 95% CI 1.02 to 8.54, \( p = .04 \)). Therefore, because patients with stage II MSI-H colon cancer have a good prognosis and may not benefit from adjuvant 5-FU, the NCCN currently recommends that MSI testing be considered for all patients with stage II colon cancer, especially those who are candidates for adjuvant chemotherapy. Finally, MSI testing is also being increasingly performed as a screening test for the possibility of HNPCC (Lynch syndrome), particularly among those patients who are diagnosed before age 50.

### Multigene Assay

Several multigene assays have emerged as prognostic tools that can aid in the decision regarding adjuvant chemotherapy, including Oncotype DX Colon, ColoPrint, and ColoDx. The platforms used by these assays are fundamentally different with regard to the number of genes tested and the source of tumor tissue tested (archival versus fresh tumor). All assays calculate a recurrence score as an indication of the risk of relapse but rely on the clinician to translate the score to clinical decisions. The score has not demonstrated a predictive value for the use of adjuvant chemotherapy. The NCCN currently does not recommend the use of these emerging assays routinely to determine the use of adjuvant therapy in stage II disease.

### NCCN Guidelines

In summary, the role of adjuvant chemotherapy in patients with stage II disease remains a subject of debate, and clinicians must make an individualized benefit versus risk assessment. Adjuvant therapy should be considered...
for medically fit patients with high-risk disease. Although FOLFOX and XELOX are the preferred choice for adjuvant treatment of stage III colon cancer, they are not considered the preferred adjuvant regimens for high-risk stage II disease. The decision to add oxaliplatin should be individualized. On the other hand, patients with low-risk stage II colon cancer can be observed with close surveillance without adjuvant therapy, considered for treatment with 5-FU/LV or capecitabine, or enrolled in a clinical trial for the adjuvant setting.

**ADJUVANT CHEMOTHERAPY FOR STAGE I COLON CANCER**

Patients with stage I colon cancer have a favorable outcome, with 5-year OS of approximately 90%. Adjuvant therapy is not recommended for patients with stage I colon cancer.

**NEOADJUVANT CHEMOTHERAPY FOR COLON CANCER**

Neoadjuvant chemotherapy is currently not recommended for colon cancer; however, it is being considered for locally advanced disease in the clinical trial setting. The Fluoropyrimidine Oxaliplatin and Targeted Receptor Pre-Operative Therapy (FOxTROT) trial investigated the feasibility, safety, and efficacy of preoperative chemotherapy for colon cancer. A total of 150 patients with locally advanced tumors were randomly assigned 2:1 to receive neoadjuvant or adjuvant FOLFOX-type therapy. Of the 99 patients randomized to the neoadjuvant arm, 95 (95%) patients started and 85 (89%) completed neoadjuvant chemotherapy. Patients who received preoperative chemotherapy showed more tumor downstaging (two patients had a complete pathologic response), less apical lymph node involvement (1% versus 20%, \( p < .001 \)), less resection margin involvement (4% versus 20%, \( p = .002 \)), and greater tumor regression grade (31% versus 2%, \( p = .0001 \)) when compared with those receiving adjuvant chemotherapy. Preoperative chemotherapy for locally advanced colon cancer may be feasible, but further studies are needed to determine if neoadjuvant chemotherapy translates into long-term benefit.

**RADIATION THERAPY FOR COLON CANCER**

Radiation therapy has a potential role in highly selected patients with colon cancer. The Intergroup 0130 trial randomized patients with resected locally advanced colon cancer (tumor adherence or invasion of surrounding structures, T3N1 or T3N2) to receive adjuvant 5-FU with or without radiation therapy. The addition of adjuvant radiation was not associated with superior OS or DFS but increased the overall toxicity rates, although these findings are limited by slow accrual and inadequate power of the trial. Currently, the NCCCN recommends that radiation therapy be considered only for patients with T4 tumors penetrating to a fixed structure or for patients with recurrent disease.

**Rectal Cancer**

Unlike the case of colon cancer, neoadjuvant therapy plays a significant role in the treatment of rectal cancer. Clinical staging of rectal cancer, determined at the time of diagnosis and prior to any surgical pathology examination, must be accurately assessed because clinical stage is currently used to direct decisions regarding the surgical approach and the administration of neoadjuvant therapy. All patients diagnosed with rectal cancer should undergo a complete physical examination, baseline laboratory studies including carinoembryonic antigen (CEA), endoscopy with biopsy, computed tomography (CT) of the chest/abdomen/pelvis, and rectal endoscopic ultrasonography (EUS) and/or high-resolution pelvic magnetic resonance imaging (MRI). High-resolution MRI and EUS provide more accurate and detailed clinical TNM staging than CT, particularly the depth of tumor invasion (clinical T stage), nodal involvement (clinical N stage), and closeness of circumferential resection margin. The surgical therapy of rectal cancer has evolved significantly over time. Although transabdominal resection is the mainstay therapy for rectal cancer, transanal local excision is an option for selected low-risk early stage I rectal cancers. Total mesorectal excision (TME), defined by en bloc removal of the rectum and mesorectum with associated vascular and lymphatic structures, fatty tissue, and mesorectal fascia, has been associated with significantly lower pelvic recurrence rates when compared with uncontrolled conventional surgery (9% versus 16%, \( p = .002 \)). However, the local recurrence rate of resected rectal cancer with curative intent has historically ranged from 10 to 40%, and recurrent disease, often unsalvageable, negatively impacts OS and quality of life. Therefore, many randomized trials have evaluated the role of neoadjuvant and adjuvant treatments in decreasing the rates of local recurrence. We discuss below some of the landmark clinical trials in rectal cancer.

**ADJUVANT RADIATION THERAPY**

The role of adjuvant XRT has been evaluated by multiple randomized controlled trials. The NSABP R-01 study randomized patients with resected stage II or III rectal cancer to one of three treatment arms: surgery alone, postoperative adjuvant chemotherapy with 5-FU, MOF, or postoperative adjuvant XRT. Local recurrence decreased from 25% in the surgery-alone arm to 16% in the adjuvant XRT arm. There was no benefit in OS or DFS. This early trial showed that postoperative XRT could reduce local recurrence rates.

**ADJUVANT CHEMORADIATION**

The next trials tested whether the addition of chemotherapy to XRT can enhance the benefit from XRT alone. The Gastro-Intestinal Study Group (GIITSG) 7175 trial randomized 227 patients with resected stage II or III rectal cancer to four treatment arms: (1) no adjuvant therapy, (2) chemotherapy only (5-FU and semustine), (3) XRT only (40 to 48 Gy), and (4) radiotherapy and chemotherapy (combined modality). The results showed an advantage for combined-modality treatment over no adjuvant therapy in decreased local recurrence rates (11% versus 24%) and for improved DFS and OS (\( p = .01 \)). But increased acute toxicity was observed in the combined-modality arm (61%).
subsequently conducted a trial comparing adjuvant XRT (45 to 50.4 Gy) and adjuvant combined-modality chemoradiation (5-FU). After a median follow-up of 7 years, patients receiving adjuvant chemoradiation experienced significantly fewer local recurrences (13.5% versus 25.0%, \( p = .036 \)) compared with XRT alone. Furthermore, the NSABP R-02 was the largest randomized trial \( (N = 694) \) comparing postoperative adjuvant chemotherapy with or without XRT and again demonstrated that the addition of XRT to chemotherapy significantly decreased the local recurrence rate from 13% to 8% \( (p = .02) \). These trials led to the NIH 1990 consensus statement for patients with stage II or III rectal cancer to receive adjuvant XRT \( (50.4 \text{ Gy in 1.8 to 2.0 Gy fractions delivered over 6 weeks}) \) with concurrent 5-FU-based chemotherapy, followed by 4 months of 5-FU-based chemotherapy. To date, there are few data regarding evaluation of adjuvant chemotherapy regimens for rectal cancer, and treatment strategies have been extrapolated directly from colon cancer studies.

**Neoadjuvant Chemoradiation**

Combined-modality therapy was next considered in the neoadjuvant rather than the adjuvant setting. There are several advantages to neoadjuvant therapy in rectal cancer, including reduction in tumor size, thus facilitating sphincter preservation; decreased risk of XRT toxicity to small bowel, which may have fallen into the pelvis postoperatively; and avoiding delays in the delivery of postoperative adjuvant therapy due to surgical morbidity. The Swedish Rectal Cancer Trial was one of the first trials of neoadjuvant XRT. Patients with resectable rectal cancer were randomized to undergo preoperative XRT \( \text{(short course, 25 Gy delivered in five fractions in 1 week) followed by surgery or surgery alone.} \) Local recurrence was 11% in the neoadjuvant XRT group, compared with 27% in the surgery-alone group \( (p < .001) \). OS and DFS were also significantly higher in the neoadjuvant XRT group. One drawback of this trial is the high rate of local recurrence observed in the control arm, and this was attributed to the lack of surgical standardization and quality control. To address this, the Dutch Rectal Cancer Trial investigated the role of neoadjuvant XRT \( (5 \text{ Gy \times 5 days}) \) in the setting of quality-controlled TME surgery. In this trial, the local recurrence rate for TME group was 8.2%, compared with 2.4% with neoadjuvant XRT plus TME \( (p < .001) \); there was no difference in OS. Thus, the Dutch trial demonstrated the added benefit of neoadjuvant XRT in reduction of local recurrence even in the setting of TME surgery.

The German Rectal Cancer Trial compared the impact of preoperative versus postoperative chemoradiation in the setting of TME, randomizing 421 patients with resectable rectal tumors to one of these treatment arms. The preoperative treatment was given over 5.5 weeks, consisting of 50.4 Gy of radiation delivered in 1.8 Gy per day \( (5 \text{ days per week}) \) with concomitant 5-FU during the first and fifth weeks of radiation. Surgery was performed 6 weeks after completion of neoadjuvant therapy. One month after surgery, four cycles of adjuvant 5-FU were given. The postoperative treatment consisted of the same chemoradiation and chemotherapy regimens, except for the delivery of a boost to 54.0 Gy. The 5-year cumulative risk of local failure was 6% in the preoperative group compared with 13% in the postoperative group \( (p = .006) \). No difference was seen in distant recurrence, DFS, or OS, with 89% of preoperative and 50% of postoperative patients completing adjuvant chemotherapy.

Finally, preoperative XRT alone versus preoperative chemoradiation were compared in the Fédération Francophone de Cancérologie Digestive (FFCD) 9203 trial for clinical stage T3–4, Nx, M0 rectal cancers. Preoperative chemoradiation was more toxic than preoperative XRT \( (\text{grade 3/4 acute toxicity rate: 14.6% versus 2.7%; } p < .05) \), but patients who received preoperative chemoradiation were more likely to experience a complete pathologic response \( \text{(cPR) (11.4% versus 3.6%, } p < .05) \). The 5-year local recurrence rate was also lower in the preoperative chemoradiation group \( (8.1\% \text{ versus 16.5\%, } p < .05) \), and there was no impact on OS.

Based on these trials, the NCCN currently recommends neoadjuvant chemoradiation therapy for all patients with stage II or III \( (T3, T4, \text{ or any node-positive rectal cancer}) \) rectal cancer.

**Assessment of Response to Neoadjuvant Therapy**

Assessing tumor response to neoadjuvant therapy provides an opportunity to understand tumor biology. Tumor downstaging, clinical response \( \text{(CR)}, \) and pathologic response \( \text{(PR)} \) are terms that have been used to describe the degree of response to neoadjuvant therapy. Tumor downstaging occurs when the best pT-stage is lower than the postoperative stage, typically determined by imaging studies, is higher than the postneoadjuvant stage, determined either at the time of clinical reexamination \( \text{(clinical tumor downstaging)} \) or at the time of surgical pathology after resection \( \text{(pathologic tumor downstaging)} \). The overall reported rate of tumor downstaging after neoadjuvant chemoradiation is approximately 60%. Complete clinical response \( \text{(cCR)} \) is defined as the absence of clinically detectable tumor, based on physical/endoscopic examination and imaging studies, after completion of neoadjuvant therapy. The reported rate of cCR is approximately 20 to 30%. cPR is defined as the absence of viable tumor cells in the tumor bed, the mesorectum, or anywhere in the resected surgical specimen.
and other randomized trials, which had demonstrated the regimen used in the Swedish Rectal Cancer Trial within 5 to 10 days following completion of therapy. This (total of 25 Gy). Surgical resection is typically scheduled the United States and consists of 5 Gy delivered for 5 days course. Short-course XRT is more commonly used outside the United States, adjuvant chemotherapy or chemoradiation after tumor regression, local recurrence, and survival. The benefit of neoadjuvant combined-modality (chemotherapy and radiation) therapy prior to surgical resection. The benefit of adjuvant chemotherapy in these patients is largely extrapolated from data from clinical trials assessing the role of adjuvant chemotherapy in colon cancers. The European Organization for the Research and Treatment of Cancer (EORTC) 22921 trial examined the addition of preoperative or postoperative chemotherapy to preoperative radiotherapy in patients with clinical T3 or T4 resectable rectal cancer. The four treatment arms were preoperative XRT, preoperative chemoradiation, preoperative XRT plus postoperative chemotherapy, and preoperative chemoradiation plus postoperative chemotherapy. After 10 years of follow-up, the local recurrence rates were significantly lower in the latter three arms where chemotherapy was administered either pre- or postoperatively: 22.4% with preoperative XRT alone versus 11.8%, 14.5%, and 11.7%, respectively (p = .0017). No impact was observed on OS or DFS: the 10-year OS rates were 51.8% for all patients who received adjuvant chemotherapy and 48.4% for those who did not (HR 0.91, 95% CI 0.77 to 1.09, p = .32), whereas the corresponding 10-year DFS was 47.0% versus 43.7% (HR 0.91, 95% CI 0.77 to 1.08, p = .29). The adherence rate for the completion of chemotherapy was 82% in the preoperative group and 42.9% in the postoperative group. The authors concluded that adjuvant 5-FU-based chemotherapy after preoperative radiotherapy (with or without chemotherapy) does not affect DFS or OS. Therefore, more data are needed to support the benefit of adjuvant chemotherapy in the specific rectal cancer patient population that received preoperative radiotherapy with or without chemotherapy. Until then, the current NCCN recommends adjuvant chemotherapy (5-FU ± LV, FOLFOX or capecitabine ± oxaliplatin) for all patients with stage II or III rectal cancer, after neoadjuvant chemoradiation and surgery.

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The critical importance of accurate clinical staging cannot be overemphasized because it influences the decision to proceed with neoadjuvant treatment and the timing of surgery. Both neoadjuvant chemoradiation and adjuvant chemotherapy are currently advocated for patients with clinical stage II or III disease, whereas those with clinical stage I disease are treated with surgical resection only [see Figure 2].

Conclusion

Disease relapse can occur despite optimal surgical management of CRC, and both neoadjuvant and adjuvant therapy play a pivotal role in reducing this risk. Based on numerous clinical trials conducted over the past several decades, adjuvant chemotherapy is currently recommended for medically fit patients with high-risk stage II colon cancer and represents the standard of care in patients with stage III colon cancer. Radiation therapy has a limited role while the neoadjuvant approach is still under investigation. In contrast, patients with clinical stage II and III rectal cancer benefit from neoadjuvant combined-modality (chemotherapy and radiation) therapy prior to surgical resection. The benefit of adjuvant chemotherapy in these patients is largely extrapolated from data from colon cancer trials, whereas rectal cancer-specific data are being accumulated. Neoadjuvant and adjuvant therapies complement surgical resection in achieving optimal outcome in patients with CRC.
An algorithm for neoadjuvant and adjuvant treatment of rectal cancer. Neoadjuvant chemoradiation and adjuvant chemoradiation therapy regimen options are 5-fluorouracil (5-FU)/radiation therapy (XRT), 5-FU/leucovorin (LV)/XRT, and capecitabine (Xeloda)/XRT. Adjuvant chemotherapy regimen options are 5-FU/LV, 5-FU/LV (folinic acid)/oxaliplatin (FOLFOX), and oxaliplatin (XELOX). EUS = endoscopic ultrasonography; MRI = magnetic resonance imaging.

References