



Making sense of adjuvant chemotherapy in colorectal cancer

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Abstract: Surgical resection is the only curative treatment for locoregional colon cancer. The goal of adjuvant chemotherapy is to eradicate micro-metastatic disease and improve survival. This has been most clearly demonstrated in stage III (node-positive) disease, whereas benefit of adjuvant chemotherapy in stage II disease remains controversial. In stage III colon cancer, 6 months of adjuvant chemotherapy with oxaliplatin-based chemotherapy have been accepted as the standard for the last 15 years. The recent IDEA collaboration has challenged this in 2018; while overall was a negative non-inferiority study, pre-planned subset analyses do support that for patients with low-risk stage III disease, 3 months of XELOX (capecitabine and oxaliplatin combination) is non-inferior to 6 months. In stage II colon cancer, where the potential benefit of adjuvant chemotherapy is small, the emergence of biomarkers has helped in decision-making. Tumors with deficient mismatch repair protein (dMMR) do not benefit from 5-fluorouracil-based chemotherapy. For patients with high clinicopathological risk stage II disease with proficient mismatch repair proteins and good performance status, six months of adjuvant chemotherapy is still recommended. In the management of rectal cancers, where the risk of local recurrence is higher, chemoradiation (CRT) is often included as neoadjuvant or adjuvant therapy in the management of stage II and III rectal cancer. The benefit of adjuvant chemotherapy in rectal cancer has been extrapolated from adjuvant colon cancer studies with updated results from adjuvant rectal cancer studies demonstrating similar benefits. This review summarizes the current landscape of adjuvant therapy for patients with resected stage II and III colorectal cancer.

Keywords: Adjuvant chemotherapy; stage II; stage III; colorectal cancer

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Introduction

At diagnosis, surgical resection remains the mainstay of treatment for stage II and III colon cancers, with a 5-year overall survival (OS) of 80% and 60%, respectively. The goal of adjuvant chemotherapy is to eradicate micro-metastatic disease and improve survival. Over the last three decades, there have been multiple adjuvant chemotherapy trials conducted with the aim of improving survival. In this review, we discuss the evolution of adjuvant chemotherapy in the treatment of colorectal cancer and how the evidence impacts our clinical management today.

Colon cancer

Adjuvant chemotherapy in stage III colon cancer

In stage III colon cancer, 2- and 3-year disease-free survival (DFS) are accepted endpoints for clinical trials looking at the benefit of adjuvant therapy. This is based on the Adjuvant Colon Cancer End Points (ACCENT) collaborative group analysis which showed that 2- and 3-year DFS correlated with 5- and 6-year OS in colon cancer patients who received 5-fluorouracil (5-FU) based adjuvant chemotherapy (1). An update of this analysis showed that most relapses occur early (i.e., within 2 years

after surgery) and that recurrence rates were less than 1.5% per year after five years (2).

With regards to timing of adjuvant chemotherapy, the increased delay to adjuvant chemotherapy was associated with worse survival among patients with resected colorectal cancer. Meta-analyses have reported that a 4-week increase in time to adjuvant chemotherapy and a delay of adjuvant chemotherapy beyond 8 weeks after surgery were associated with decrease in OS (3). Therefore, it is recommended that adjuvant chemotherapy is initiated as soon as the patient is medically able, where feasible within 12 weeks.

Benefit of specific regimens

5-fluorouracil (5-FU)-based chemotherapy

In 1990, the benefits of adjuvant chemotherapy were first demonstrated in a pivotal trial by Moertel *et al.* The study demonstrated improved survival and decreased recurrence from adjuvant chemotherapy with 5-FU and levamisole administered for 12 months after surgery over surgery alone (4). Subsequent trials demonstrated that 5-FU combination with leucovorin (LV) was superior (5-7), with 6 months of therapy adequate to achieve similar OS benefits compared to 12 months (8). Survival advantages have been demonstrated both with Mayo Clinic regimen (daily 5-FU bolus for five days in a 28-day cycle, for 6 months) or the Roswell Park regimen (weekly 5-FU bolus for 6 weeks in an 8-week cycle, for 6 months). Toxicity profile differed however, with more stomatitis and neutropenia with the former, and diarrhea with the latter. Infusional 5-FU regimens have also been evaluated and found to be as efficacious as bolus regimens with less toxicities (9). In the X-ACT trial, oral capecitabine was established to be as convenient, safe and equally effective alternative to the Mayo Clinic regimen for stage III colon cancer (10). The oral fluoropyrimidine capecitabine generates 5-FU preferentially in tumor tissue by way of a three-step enzymatic cascade. The final conversion of 5-FU is catalyzed by thymidine phosphorylase, which is more active in tumor than healthy tissue.

Oxaliplatin-based therapies

Oxaliplatin was approved as part of adjuvant treatment for stage III colon cancer in 2004 based on a 3-year DFS endpoint. The benefit of adding oxaliplatin to 5-FU or capecitabine carries a 20% relative risk reduction for DFS, which translates into similar improvements in overall survival (11-13). In the landmark MOSAIC trial, the addition of oxaliplatin to 5-FU based chemotherapy contributed to an absolute improvement of 5-year DFS

rates and 6-year OS rates by 5.9% and 2.5% respectively (13). The XELOXA trial compared adjuvant capecitabine and oxaliplatin combination (XELOX) with bolus 5-FU/LV in stage III colon cancer, with a similar magnitude of benefit of DFS seen (11).

Regimens not recommended

Although irinotecan and oxaliplatin based regimens are thought to be equally effective in the metastatic setting, the incorporation of irinotecan to 5-FU based chemotherapy in multiple randomized, phase 3 studies was not superior to 5-FU alone in the adjuvant setting. The current evidence does not support the use of irinotecan-containing regimens in the adjuvant setting (14-17). Lack of benefit has also been observed with both anti-VEGF and anti-EGFR therapeutic antibodies in the adjuvant setting. In contrast to the trials with irinotecan-based chemotherapy, some of these trials even show worsened patient outcomes. Two randomized phase 3 trials compared a standard fluorouracil-oxaliplatin regimen to the same regimen plus bevacizumab during chemotherapy and continued for 1 year. In the AVANT study, addition of bevacizumab had no benefit, and even showed a significant reduction in OS (18). Similarly, the PETACC-8 and N0147 trials randomized patients with KRAS wild type tumors to receive FOLFOX with or without cetuximab (19,20). Both trials showed no survival benefit with the addition of cetuximab but potential harm in the cetuximab arm in N0147. Therefore, irinotecan-based chemotherapy, anti-VEGF and anti-EGFR therapies are not recommended as adjuvant treatment.

Duration of adjuvant chemotherapy

As discussed earlier, six months of oxaliplatin-based chemotherapy had been accepted as the standard for the last 15 years. However, cumulative doses of oxaliplatin increases the risk of long-term sensory neuropathy which can be debilitating. This led to the investigation of whether a shorter duration of adjuvant chemotherapy for colon cancer would lessen toxicities but provide similar survival benefit. The International Duration Evaluation of Adjuvant Therapy (IDEA) collaboration enrolled 12,834 patients with stage III colon cancer in six phase 3 trials in 12 countries (21). All patients were randomly assigned to either three or six months of adjuvant chemotherapy with either FOLFOX or XELOX (CAPOX). The primary endpoint of 3-year DFS did not meet the prespecified cut-off for noninferiority in the overall population. However, non-inferiority was observed in certain subgroups. In the pre-specified subgroup analysis according to treatment

Table 1 Clinicopathological definitions of “high risk” stage II colon cancer from expert groups

High-risk features as per ASCO [2004], ESMO [2013] and NCCN [2018] guidelines (25-27)
T4 primary tumor
Inadequately sampled lymph nodes (ASCO <13, NCCN and ESMO <12)
Poorly differentiated tumors, that are not MSI-H
Bowel perforation
Lymphovascular invasion
Perineural invasion
Additional high-risk features
NCCN/ESMO: bowel obstruction
NCCN: positive surgical margins
MSI-H, microsatellite instability-high.

(XELOX *vs.* FOLFOX), six months of adjuvant FOLFOX was superior to three months, with a difference in DFS rate of 2.4% (73.6% *vs.* 76.0%). Among patients who received XELOX, three months of XELOX was non-inferior to six months for all stages combined. Specifically, in the low-risk (T1-3, N1) subgroup, the DFS for three months of XELOX was noninferior to six months of XELOX (HR, 0.85; 95% CI, 0.71–1.01). However, in the high-risk (T4 and/or N2) subgroup, DFS for three months of FOLFOX was inferior to six months of FOLFOX (HR, 1.20; 95% CI, 1.07–1.35) (21). The study also showed that shorter duration of chemotherapy was associated with lower rates of adverse events and peripheral neuropathy compared to longer duration of chemotherapy.

The results of the IDEA collaboration have led to a change in practice whereby in low-risk stage III disease (T1-3, N1), the duration of adjuvant oxaliplatin-based chemotherapy may be reduced to three months. In high-risk stage III disease (T4 and/or N2), six months of adjuvant chemotherapy with an oxaliplatin-based doublet chemotherapy remains the standard (22). A shared-decision making approach and discussion about the risks and benefits of adjuvant chemotherapy with the patient is encouraged.

Application in clinical practice

Adjuvant chemotherapy is recommended in stage III colon cancer. It should be initiated within 12 weeks from surgery, earlier if medically able. In low-risk stage III disease (T1-3, N1), the length of adjuvant chemotherapy

can be three months (particularly, if XELOX is used) or six months, after discussion with the patient about the risks and benefits of adjuvant chemotherapy and its duration. In high-risk stage III disease (T4 and/or N2), six months of adjuvant chemotherapy with an oxaliplatin-based doublet chemotherapy is still recommended.

Adjuvant chemotherapy in stage II colon cancer

As compared to stage III disease where adjuvant chemotherapy is universally recommended, the decision for adjuvant chemotherapy for patients with stage II disease remains challenging. Surgery alone offers excellent outcomes and the small benefit for adjuvant chemotherapy in unselected patients, when weighed against toxicities, inconvenience and cost makes it difficult to justify this recommendation for all patients (23).

Clinicopathological markers of prediction

The analysis of survival outcomes by American Joint Committee on Cancer (AJCC) shows that patients with stage IIB or IIC (T4 disease) are inferior in outcomes compared to stage IIIA (T3 disease) (24). Thus, the recommendation for consideration of adjuvant chemotherapy despite the lack of direct evidence from randomised controlled trials is based on extrapolating the relative benefits of adjuvant therapy in stage III disease (25). Currently, there is uniformity in what many international clinical guidelines recognise as high-risk clinicopathologic features in selecting patients with stage II colon cancer for adjuvant treatment. These features include less than 12 lymph nodes (LNs) identified at surgery, T4 tumor, poorly differentiated tumor [excluding microsatellite instability-high (MSI-H) tumors], presence of bowel obstruction or perforation, and presence of lymphovascular invasion. Definitions of “high-risk” stage II colon cancer from expert groups are outlined in *Table 1*. Although these factors are associated with a poorer prognosis, they are not predictive of chemotherapy response.

5-FU-based chemotherapy in stage II colon cancer

Many trials have investigated the benefit of adjuvant chemotherapy in stage II colon cancer. A meta-analysis of five studies with 1,016 patients from the IMPACT B2 investigators, a pooled analysis of seven trials with 3,302 patients, and an analysis of the Surveillance, Epidemiology, and End Results (SEER) database of 3,151 stage II patients have shown no benefit with adjuvant therapy in stage II

disease (28-30). Contrary to these studies is the Quick and Simple and Reliable (QUASAR) study, which showed a modest (~4%) absolute benefit despite a 20% relative reduction in the risk of recurrence and death (23). In this study, patients with stage II colon cancer were randomized to receive 5-FU chemotherapy or observation after surgery. It has been shown in previous trials that a minimum of 13 lymph nodes should be sampled to stage a colon cancer as node negative (31), and one major criticism of the study is that more than 60% of patients had less than 12 lymph nodes resected.

Oxaliplatin-based chemotherapy

The utility of oxaliplatin-based chemotherapy in stage II disease is based on a subgroup analysis from the MOSAIC study. In patients with stage II disease, the DFS benefit for FOLFOX compared to 5-FU/LV alone was approximately 3.5%. This benefit exceeded 5% in patients with stage II tumors with clinical high-risk features (undifferentiated tumors, T4, perforation, obstruction, fewer than 10 lymph nodes identified and lymphovascular invasion) (32). Further updates of the study demonstrated a significant 6-year OS benefit for patients with stage III, but not for stage II disease when an oxaliplatin-based regimen was used as adjuvant therapy (13).

Molecular biomarkers of prediction

MMR genes (*MLH1*, *MSH2*, *MSH6* and *PMS2*) are required for the correction of nucleotide base mispairings that occur during DNA replication (33). This may be due to a consequence of a germline mutation (as in Lynch Syndrome), or more commonly an epigenetic silencing of MMR in sporadic colorectal cancers (34). MMR deficient cells accumulate errors during DNA replication, which lead to formation of abnormalities in short sequences of nucleotide bases called microsatellites (35). MMR status can be identified with immunohistochemistry through loss of expression of MMR proteins, and is highly concordant (>95%) with MSI testing using polymerase chain reaction (PCR), in which dMMR corresponds to high-degree MSI (MSI-H) (36). MSI-H or dMMR status are used as prognostic and predictive molecular biomarkers in stage II disease. Approximately 20% of stage II colon cancers have dMMR phenotype, and this is a prognostic marker of a more favourable outcome (37). These patients receive no benefit from fluoropyrimidine-based adjuvant therapy (38,39). Routine testing of MSI status should be performed

for all patients with stage II colon cancer to select patients with excellent prognosis and spare them from adjuvant 5-FU chemotherapy (26).

The uptake of gene expression signatures to guide adjuvant treatment decisions to avoid overtreatment is considered mainstream in breast cancer and there have been efforts to do the same in colon cancer. Of these multi-gene assays (40), Oncotype DX colon have been studied the most extensively—while these assays can identify a subset of stage II patients with increased risk of disease recurrence, they have a limited role in predicting the true benefit of adjuvant therapy (41-43).

Of the biomarkers being studied for risk stratification of disease recurrence, circulating tumour DNA (ctDNA) holds the most promise. Seventy-nine per cent of patients with detectable ctDNA after oncological resection experienced disease recurrence, compared to only 9.8% of those without detectable ctDNA, independent of known clinical high-risk features (44). If validated in larger phase III clinical trials, ctDNA may allow for a non-invasive approach of determining disease recurrence and identifying patients who are most likely to benefit from adjuvant therapy.

There is growing importance of using immune score (Immunoscore) as a prognostic factor for early-stage colon cancer. Immunoscore is the calculation of the mean of the four percentiles obtained for CD3+ and CD8+ T cell counts at either the tumor center or invasive margin. From an analysis of 3,539 patients with early stage colorectal cancer, Immunoscore was validated as a prognostic assay for recurrence-free survival, DFS and OS. It identified a subgroup of high-risk patients as the risk of recurrence at 3-years was significantly reduced in patients with a low Immunoscore compared with those who had a high Immunoscore (45). Its applicability in practice to guide clinical decisions will need to be evaluated in prospective studies.

Application in clinical practice

For patients with stage II colon cancer, 5-FU-based chemotherapy is recommended for 6 months if the tumor has high-risk clinicopathological features. There is minimum benefit with the addition of oxaliplatin. MSI or MMR status should be checked in all stage II tumors to select patients (with MSI-high or dMMR status) who may not benefit from adjuvant chemotherapy. Currently, there is insufficient evidence to recommend the routine use of multigene assays in colon cancer, ctDNA or Immunoscore to determine the need of adjuvant therapy. A shared

decision-making approach should be used for patients with stage II colorectal cancer, weighing the risks versus benefits of treatment for each individual.

Adjuvant chemotherapy in the elderly

The median age of patients at diagnosis of colon cancer is 70 and there is a need to comprehensively evaluate elderly patients to estimate individual risk/benefit ratios for adjuvant treatment. Many clinical trials enrol younger patients and conclusions drawn from treating elderly patients are dependent on subgroup analyses. A constraint of the pooled data is selection bias, in that presumably more fit elderly were enrolled on the individual clinical trials, and the fact that less than 1% of the trial participants were in their 80s.

Stage III colon cancer

Multiple population studies have shown that adjuvant therapy is beneficial in older patients. The SEER-Medicare Databases included more than 7,000 patients above 65-year-old with stage 3 colon cancer and found a survival benefit for the use of 5-FU/LV (HR 0.70; $P < 0.001$) (46). SEER-Medicare and NCCN Outcomes Databases showed a survival benefit for adjuvant chemotherapy even in patients 75 years and older (HR 0.60; 95% CI, 0.53–0.68) (47).

The ACCENT database reported a reduced benefit to the addition of oxaliplatin to 5-FU in the adjuvant setting in patients ≥ 70 years of age (48). Using the National Cancer Database with more than 100,000 patients with stage III colon cancer, Margalit and colleagues found that low-risk patients older than 72 years (defined by IDEA collaborators as T3 and N1) and high-risk patients (T4 or N2 disease) older than 85 years did not benefit from doublet chemotherapy; suggesting that omission of oxaliplatin can be considered in IDEA low-risk patients older than 72 years old (49). Subset analyses looking at patients ≥ 70 years of age in both the NSABP C-07 and MOSAIC trials both found that there was no survival benefit with the addition of oxaliplatin to 5-FU/LV chemotherapy (47,50). However, support for the addition of oxaliplatin in elderly patients who would fit entry criteria for adjuvant clinical trials come from pooled individual patient data from patients with stage III colon cancer in NSABP-C08, XELOXA, X-ACT and AVANT showed DFS benefit for the addition of oxaliplatin to 5-FU-based chemotherapy (HR 0.77, $P < 0.014$) (51).

Stage II colon cancer

In average risk stage II disease, the QUASAR study showed

no benefit for adjuvant chemotherapy amongst patients > 70 years old (23). Given the low absolute benefit in the general population, it is reasonable to omit adjuvant treatment in this group of older patients. A survival benefit for fluoropyrimidine-based adjuvant chemotherapy was not observed in an analysis from the linked SEER/Medicare database of 24,847 patients aged 65 and older who underwent colectomy for stage II colon cancer, even in those with high-risk features (52). As with the general population, older patients with dMMR are considered at low-risk for recurrence and do not benefit from adjuvant therapy.

Application in clinical practice

There is great heterogeneity in physical function among older adults and chronologic age alone cannot be relied upon to make treatment decisions. Overall, 5-FU/LV as adjuvant therapy appears to benefit all patients with stage III disease, regardless of age. However, the evidence of benefit for the addition of oxaliplatin in patients above 70 is much less consistent and should not be the rule. In terms of toxicities, it has been shown that patient age had no impact on toxicities such as nausea, diarrhea, stomatitis, but elderly patients do have an increased risk of hematological toxicities (53).

Rectal cancer

The risk of pelvic recurrence in rectal cancer is higher than those with colon cancer due to the close proximity of the rectum to pelvic structures, absence of a serosa surrounding the rectum and technical difficulties associated with obtaining wide surgical margins at resection. Due to this, locoregional therapy such as CRT is often included as neoadjuvant or adjuvant therapy in the management of stage II and III rectal cancer. Unlike colon cancer, clinical staging (using imaging and endoscopy findings) is used to direct the recommendations for pre- or post-operative therapy in rectal cancer and this remains a challenge due to the risk of under-staging or over-staging the tumor. Therefore, careful patient selection with respect to particular treatment options and the use of sequenced multi-modality therapy with chemotherapy, radiotherapy and surgery is required. Other than T1 stage rectal cancer, total mesorectal excision (TME) is routinely performed as it has been shown to decrease local seeding and subsequent recurrences (54).

Adjuvant therapy for resected rectal cancer (with no prior neoadjuvant treatment)

The role of adjuvant CRT was proven when two studies

demonstrated that 5-FU-based chemotherapy plus radiation was more effective than radiation or surgery alone in preventing local and distant recurrence (55,56). It has also been shown that prolonged infusion of 5-FU was superior to bolus administration during radiation therapy, with a 3-year DFS advantage. In clinical practice, capecitabine administered twice daily at 825 mg/m² on days of radiation has become a widely accepted substitute for continuous infusion of 5-FU after two phase 3 trials confirmed the non-inferiority of capecitabine as a radiosensitizer compared to 5-FU (57,58). The addition of oxaliplatin to neoadjuvant CRT have been studied in multiple phase 3 randomized controlled trials and have not been shown to provide additional benefit, and therefore, should not be recommended at this time (59-61).

The toxicities associated with adjuvant radiotherapy led to the German Rectal Trials group investigating the timing of radiation therapy with respect to surgery. Patients who underwent pre-operative combined-modality therapy had a lower rate of local recurrence (6% *vs.* 13% at 5 years), improved acute and chronic toxicities and higher rate of sphincter preservation, establishing neoadjuvant CRT as a standard of care for stage II and III rectal cancer. Long-term follow up confirmed the improvement in local control in pre-operative CRT in 10 years (62). The main disadvantage of pre-operative radiotherapy is the possibility of over-treating early-stage tumors that do not require adjuvant radiation. Given that neoadjuvant CRT is now commonplace, post-operative CRT is usually reserved for those with clinical stage I rectal cancer who were upstaged after pathologic review of the surgical specimen.

Adjuvant chemotherapy following neoadjuvant treatment

Historically, the benefit of adjuvant chemotherapy in rectal cancer has been extrapolated from adjuvant colon cancer studies (MOSAIC and NSABP C-07) (13,63). Although many studies have attempted to answer the question of benefit of the addition of adjuvant chemotherapy following standard of care neoadjuvant CRT followed by curative resection, the data has been conflicting. In a meta-analysis of 1196 patients who received 5-FU based adjuvant chemotherapy (5-FU/LV, capecitabine or XELOX) after pre-operative therapy and surgery, survival and rate of distant recurrences were not improved in stage II and III rectal cancers (64). The PETACC-06 study as well which randomized patients to capecitabine with radiotherapy before surgery, followed by capecitabine after surgery *vs.* XELOX and radiotherapy

before surgery, followed by XELOX after surgery showed no difference in 3-year DFS (65). The ADORE and CAO/ARO/AIO-04 studies (5-FU/LV *vs.* FOLFOX) suggest otherwise (66,67). Both the ADORE and the CAO/ARO/AIO-04 trials showed a significant advantage in DFS of combined fluorouracil and oxaliplatin-based adjuvant chemotherapy compared with fluorouracil alone. The 3-year DFS reported in these studies were similar to those reported in the MOSAIC and NSABP C-07 adjuvant colon cancer studies. Critics argue that because neither of these two trials had an observational group, the benefit of adjuvant combination chemotherapy remains unknown. In the long-term results from the ADORE study, the 6-year OS remains similar in both 5-FU/LV and FOLFOX arms but in the subgroup analysis, patients with ypN2 and minimally regressed tumor benefited from FOLFOX over 5FU/LV (66). These results suggest that the subgroup of patients (ypN2 or minimally regressed tumors) may benefit from oxaliplatin-based adjuvant chemotherapy. Factors contributing to the difficulty of proving efficacy of adjuvant chemotherapy in rectal cancer include inaccurate baseline staging, inclusion of lower stage tumors in these trials, poor compliance to chemotherapy, varied timing of surgery in different trials, suboptimal regimens and variable control arms (68). We currently await results from clinical trials which are changing the treatment paradigm of rectal cancer with total neoadjuvant therapy and risk-adapted strategies to reduce toxicities from the current state of trimodality therapy in this disease.

Application in clinical practice

In the era of neoadjuvant CRT in the treatment of rectal cancer, adjuvant chemotherapy is generally recommended for stage II and III rectal cancers. The choice of regimen should be based on initial clinical staging, predicted circumferential resection margin (CRM) status and pathological evaluation of the surgical specimen. For higher-risk patients, an oxaliplatin-based doublet such as FOLFOX or XELOX may be considered. 5-FU/LV, or capecitabine are alternatives in other cases, especially for patients whose cancer responded to neoadjuvant treatment. The length of adjuvant chemotherapy should be for four months when pre-operative CRT is administered.

Conclusions

The benefits of adjuvant chemotherapy have been most clearly demonstrated in stage III colon cancer with

oxaliplatin-based doublet preferred over single agent fluoropyrimidines in younger patients with no other competing co-morbidities. We know that shorter duration of oxaliplatin exposure reduces toxicities and the IDEA collaboration has provided evidence that in low-risk stage III patients, three months of oxaliplatin exposure with XELOX, has no detrimental effect in survival compared to six months of treatment. In stage II colon cancer, clinicopathologic risk factors and MMR status are used to guide decisions for adjuvant therapy. As the absolute benefit from adjuvant therapy in stage II disease is small, a discussion on the risks *vs.* benefits of adjuvant therapy and the choice of agent is warranted. In rectal cancer, adjuvant chemotherapy is recommended after neoadjuvant CRT and surgery in stage II and III disease. The choice of regimen should be based on initial clinical staging, predicted circumferential resection margin (CRM) status and pathological evaluation of the surgical specimen.

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Footnote

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