ADJUVANT THERAPY FOR COLORECTAL CANCER

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Abstract

Patients with resected colon cancer (stage III [T1 to T4, N1-N2] or high-risk stage II [T3 or T4, N0]) or stage II/III rectal cancers (T3 or T4, N0-2) are at significant risk of local and distant failure, with reduced survival due to microscopic residual disease. To reduce this risk, adjuvant therapy has been the standard of care for both cancer populations, as stated in the 2005 Guidelines for the Prevention, Early Detection and Management of Colorectal Cancer developed through Cancer Council Australia's Clinical Guidelines Network. This review provides an update to the guidelines. Patients, with resected stage III colon cancer should, where possible, be offered six months of adjuvant chemotherapy. The optimal regimen is oxaliplatin-5FU or -capecitabine, based on relevant clinical factors. For patients with resected stage II colon cancer, adjuvant 5FU-based chemotherapy should be considered for those at particularly high risk of relapse. For patients with stage II/III rectal cancer, treatment approaches include: (i) short course radiotherapy and immediate total mesorectal excision; or (ii) neoadjuvant chemoradiotherapy (with 5FU infusion or capecitabine) followed by TME. Post-operative adjuvant chemotherapy should be offered to all medically fit patients. At present, there are no markers to identify patients who may not require neoadjuvant chemoradiotherapy or who can avoid surgery.

Approximately 70-80% of newly diagnosed cases of colorectal cancer (CRC) undergo curative resection, however 40% of these develop incurable recurrent disease due to undetected micrometastases. In particular, patients with stage III (T1 to T4, N1-2) or Dukes’ C colon cancer have a five-year survival rate of between 44-88%, with a three-year disease-free survival (DFS) ranging from 45 to 52%. Those with stage II (T3 or T4, N0) or Dukes B colon cancer have a five-year survival rate of between 45-60% and three-year DFS of 64–75%. The inability to cure all such patients is a direct consequence of residual disease left behind after surgery. Over the last two decades, adjuvant chemotherapy has been offered to such high risk patients with the aim to decrease relapse and improve overall survival (OS) by attempting to eliminate this microscopic residual disease.

Patients with rectal cancer are at even greater risk of local recurrence following surgery alone, relative to the more proximal colon primaries. In particular, tumours that have penetrated the rectal wall (T3 or T4) and/or with nodal involvement (N1-2) are at increased risk of local or distant relapse, with recurrence rates up to 25-65%. A positive circumferential resection margin (CRM) (tumour ≤1mm of resection margin) is an important independent prognostic marker, accounting for up to 85% of local recurrences, and correlates with lymphovascular/perineural invasion and nodal involvement. Hence the optimum strategy to improve the outcome of rectal cancer patients must address the problems of local and distant recurrence. Multimodality treatment comprising total mesorectal excision (TME), with chemotherapy and radiotherapy, has been the standard of care for locally advanced (stage II and III) rectal cancer. The current nomograms include preoperative short course RT or preoperative chemoradiotherapy (CRT), followed by TME and adjuvant chemotherapy, and in limited patients, post-operative CRT, with adjuvant chemotherapy. These approaches have dramatically reduced local recurrence, however approximately one-third of patients will expire from their disease within five years.

This article will review the current data and practice regarding the adjuvant treatment of both colon and rectal cancers, and will serve as an update beyond the 2005 Guidelines for the Prevention, Early Detection and Management of Colorectal Cancer, developed through Cancer Council Australia’s Clinical Guidelines Network and approved by the National Health and Medical Research Council (NHMRC). Adjuvant therapy of resected colon cancer

Adjuvant chemotherapy is offered to high risk patients with the aim of decreasing relapse and improving OS by attempting to eliminate this microscopic residual disease. Its benefits must outweigh the risks from chemotherapy-related toxicities. For over two decades, it has been offered to patients with stage III disease as standard therapy, a practice reinforced by two recent meta-analyses. In the case of patients with stage II disease, the role of adjuvant therapy is controversial given the difficulty in identifying patients at the highest of risk who would benefit the most from adjuvant therapy. The recognised poor prognostic markers for patients with stage II disease include: (1) poorly differentiated histology; (2) obstruction or perforation at presentation; (3) lymphovascular invasion; (4) less than 12 lymph nodes retrieved during primary resection; and (5) T4 disease (with invasion into adjacent organs). The issues regarding treating patients with stage II disease will be addressed below.

Adjuvant chemotherapy for resected stage III colon cancer (T1-4, N1-2, M0)

Adjuvant chemotherapy has been the standard of care
for stage III disease for the last two decades. Initial efforts
concentrated on the evaluation of 5-fluorouracil (5FU)-
based regimens and 5FU biomodulation, and more recently
the evaluation of oral 5FU produgs.11 12 Two recent meta-
analyses have shown a significant reduction in mortality by
biomodulation of 5FU.13-14 Subsequent large randomised
trials have demonstrated that a weekly 5FU-low dose
leucovorin (LV) regimen is preferred, based upon efficacy
and toxicity relative to alternative regimens, or the use of
5FU-Levamisole with six months as the optimal duration of
therapy. The randomised phase III X-ACT trial has also
demonstrated the equivalent efficacy, and near superiority
of the oral 5FU produg, capecitabine, (24 weeks, 1250
mg/m² b.i.d, days 1-14, 1 week rest) relative to six months
bolus 5FU-LV as adjuvant therapy for stage III colon
cancer, both in terms of survival parameters, toxicity and
pharmacoeconomics.15

The advances in the treatment of metastatic disease,
including oral 5FU produgs, oxaliplatin, irinotecan and
the biologicals (including epidermal growth factor receptor
[EGFR] and anti-vascular endothelial growth factor [VEGF]
monoclonal antibodies), have led to these agents being
evaluated in patients with stage III disease. The evidence will
be summarised in the sections below. It must be noted that
during this time, three year DFS rate has been validated as
an appropriate endpoint for adjuvant trials given its strong
correlation with five-year OS,25 and recently six-year OS.26
In modern adjuvant trials, six or seven years may now be
required to demonstrate OS improvements.27

**Oxaliplatin and 5FU or Capecitabine**

The efficacy of oxaliplatin plus 5FU in the adjuvant setting
was demonstrated by two pivotal trials - the MOSAIC,28
and the more recent NSABP C07 trials.29 In the MOSAIC
trial, 2246 patients who had stage II or III colon cancer were
randomised to receive a combined bolus/infusional 5FU
regimen (LV5FU2) alone, or with oxaliplatin (FOLFOX4),
for six months. The primary end point was DFS.28 A total
of 1123 patients were randomly assigned and on final
analysis reported in 2009, the five-year DFS rates were
73.3% and 67.4% in the FOLFOX4 and LV5FU2 groups
respectively (HR =0.80; P <0.005). Six-year OS rates were
78.5% and 76.0% in the FOLFOX4 versus LV5FU2 groups
respectively (HR =0.84; P <0.05). The corresponding six-
year OS rates for patients with stage III disease were 72.9%
and 68.7%, respectively (HR =0.80; P <0.005). There was
no difference in OS seen in the stage II population.30

The NSABP C07 trial, published in 2007, randomised
2492 patients with stage II and III colon cancer to either
5FU 500mg/m², plus LV 500mg/m², both IV weekly for
six weeks during each eight-week cycle (Roswell Park
regimen) for three cycles, or the same 5FU-LV regimen
with oxaliplatin 85 mg/m² IV administered on weeks one,
three and five of each eight-week cycle for three cycles.29
The additional benefit provided by oxaliplatin in terms of
DFS, as observed from the MOSAIC trial, was confirmed.29

A subsequent study, the NO1998 trial, compared
capcitabine plus oxaliplatin (XELOX; oxaliplatin 130mg/
m² on day one plus capcitabine 1000 mg/m² b.i.d on
days one to 14, every three weeks for 24 weeks) with
bolus 5FU-LV (Mayo Clinic for 24 weeks or Roswell Park
for 32 weeks) in patients with stage III colon cancer.31
The three-year DFS rate was 70.9% with XELOX and
66.5% with 5FU-LV (HR =0.80, P <0.005). XELOX is thus
considered an additional adjuvant treatment option for
these patients.31

The efficacy of adjuvant oxaliplatin therapy has also been
evaluated in the elderly. A subgroup analyses of the NO1998
trial above, demonstrated reduced risk of recurrence in all
groups receiving oxaliplatin, including patients <65 years
of age and those ≥65 years of age, however in the latter
group the trend was not significant.31 A post-hoc analysis
of the NSABP C07 trial also demonstrated that oxaliplatin
significantly improved OS in patients younger than age 70
(HR, 0.80; P<0.05), but no positive effect was evident in
older patients.32

**Irinotecan and 5FU**

Despite the activity of irinotecan in the treatment of
advanced CRC, randomised phase III trials in the adjuvant
setting (including CALGB 89803, PETACC3 and ACCORD
2 trials) have failed to demonstrate an added benefit
relative to 5FU-LV alone.33-36

**Biological agents + combination adjuvant
chemotherapy**

In the metastatic setting, the antiangiogenic agent,
bevacizumab, a monoclonal antibody to VEGF, and the
EGFR monoclonal antibodies, cetuximab and panitumumab,
have shown added benefit when added to conventional chemotherapy backbones, whether
oxaliplatin-,30 or irinotecan-based,37 or 5FU-LV.38-39
However, recent phase III trials in the adjuvant setting have
demonstrated that these biological agents provide no
additional benefit and may actually be detrimental when
added to a chemotherapy backbone, usually oxaliplatin-
5FU.

For these have included the NSABP C08 and AVANT
trials for bevacizumab and the NCCCTG-N0147 trial for
cetuximab.40-42 The mechanisms for this lack of synergy
with chemotherapy and the biological agents in this setting
are not clear, but may be explained by the induction of
therapy resistance mechanisms by VEGF or EGFR
inhibition; this has been discussed elsewhere.43

In terms of bevacizumab, two large relevant trials await
reporting: the QUASAR 2 study, randomising patients to
capcitabine +/- bevacizumab; and the ECOG E5202,44
discussed below. Cetuximab is being further assessed in
the PETTAC-8 trial. The FoxTROT trial evaluating FOLFOX
or XELOX ± panitumumab is also to be reported.45

**Adjuvant therapy of patients with resected
stage II colon cancer**

**The case for and against?**

In the case of patients with stage II disease, the role of
adjuvant therapy is controversial given the difficulty in
identifying patients at the highest risk who would benefit
the most from adjuvant therapy whilst avoiding potential
toxicity in patients who would not benefit.15

The efficacy of systemic adjuvant chemotherapy for patients
with stage II cancer has still not been confirmed.11 The
previously reported analyses from the IMPACT-B group,46
the pooled analysis of the NSABP C01–4 trials,47 and the
large phase III QUASAR trial,43 have been inconsistent. In terms of modern combination therapy, there is relevant data from the MOSAIC and the NSABP C07 trials, above, in patients with stage II disease. In terms of the MOSAIC trial, 899 patients with stage II disease were randomised,30 and with a median follow-up of 6.8 years, the five-year DFS was 79.9% versus 83.7% (HR =0.84, P>0.05) and the six-year OS 86.8% versus 86.9% (P >0.05).30 From the NSABP C07 trial, 29% overall had resected stage II disease and the four year DFS was 81% versus 84.2% in favour of oxaliplatin-5FU.29

A recent Cochrane analysis considered all randomised trials or meta-analyses containing data on stage II colon cancer patients undergoing adjuvant therapy versus surgery alone; overall 8642 patients were considered.40 In terms of the effect of adjuvant therapy, the pooled relative risk ratio for OS was 0.96 (95% CI 0.88-1.05), and for DFS 0.83 (95% CI 0.75-0.92). Hence the benefit was in terms of DFS only.40

Thus the overall the benefits of adjuvant systemic chemotherapy in patients with stage II patients are modest, but should be discussed in those with high risk features. The co-morbidities and likelihood of tolerating adjuvant systemic chemotherapy should be considered as well.43

**Identifying high risk stage II patients**

Given the modest benefit for adjuvant therapy in such patients, there is an urgent need to better characterise high risk patients who would gain the greatest benefit. At present the identifiers of high risk relate to the tumour as well as clinical factors, as listed above, albeit inconsistently.15 Considerable effort has been directed to identify molecular prognostic and predictive factors. However, as expected, there is considerable heterogeneity in terms of the cohorts evaluated, prospective versus retrospective analyses, and analytical methodology. The markers evaluated thus far include aneuploidy/tetraploidy DNA, 18q allelic loss, as well as microsatellite status (MS), p53, Kras, BRAF and thymidylate synthase.50-54 A detailed review of these molecular factors with regard to stage II disease has been published recently.55

**MSI**

The assessment of microsatellite instability (MSI), which serves as a marker for DNA mismatch repair (MMR) system function, has emerged as a useful tool for risk stratification of patients with stage II colon cancer. It seems clear, by retrospective studies and meta-analyses, that patients with stage II and III tumours classified as MSI-High (MSI-H) or defective MMR [dMMR], have a better prognosis, independent of adjuvant therapy, relative to MS-Stable tumours.56-58 While the prognostic importance of MSI has been confirmed, its importance in predicting response to adjuvant chemotherapy is unclear.51 However, it appears from two retrospective studies that patients with dMMR do not benefit from adjuvant 5FU therapy.59,60 Based on the body of current data, with the caveat that MSI status is still to be validated prospectively as a predictive biomarker, the current NCCN guidelines recommend that where adjuvant therapy is being considered in patients with stage II disease, MSI status must be assessed and those with MSI-H tumor should not be offered 5FU-based therapy.17,44

It is unclear whether this also applies to oxaliplatin-5FU adjuvant regimens. A recent study investigated the clinical implication of MSI-H/dMMR and p53 expression in 221 patients with resected colon cancer (13 stage II and 108 stage III disease) who received post-operative FOLFOX therapy.61 The study observed that MMR status was not associated with DFS or OS, and thus adding oxaliplatin to adjuvant chemotherapy may overcome the negative impact of 5-FU on colon cancers with MSI-H/dMMR.51 There is also preclinical evidence that MSI-H/dMMR tumour cells may be equally sensitive to oxaliplatin and possibly more sensitive to irinotecan.62

**18q Allelic Imbalance (18qAI)**

Chromosome 18q, contains the tumor suppressor genes deleted in colon cancer and the SMAD4 gene, which are lost in the oncogenic development of CRC.63 The allelic loss of 18q is manifested as a loss of heterozygosity (LOH). The 18qLOH or 18 allele imbalance (18qAI) have been correlated with a poorer prognosis in patients with stage II and III disease, albeit inconsistently.64,65 The recently closed ECOG E5202 study had randomised stage II patients, stratified by MSI status and 18q allele imbalance, to observation for low risk patients (MS-S or MSI-Low with retention of 18q or MSI-H) and high risk patients (MS-S/18qLOH or MSI-L/18qLOH) to FOLFOX4 +/- bevacizumab. It was closed early following the reports that demonstrated the lack of benefit of bevacizumab in the adjuvant setting. We are still awaiting its final analysis.14

**Gene expression approaches**

Quantitative gene expression assays have been evaluated to assess recurrence risk, though with less utility for the benefits from chemotherapy in patients with stage II disease. There are at present, two commercially available gene expression classifiers (Colprint and Oncotype DX) that have been developed and subsequently validated to prognostically classify patients with early stage colon cancer at high risk of relapse, rather than to determine their predictive ability in terms of outcomes from adjuvant chemotherapy.66,67 Others have also been reported and are or are being validated.68,69

**Adjuvant therapy of rectal cancer**

As stated above, patients with rectal cancer are at greater risk of local recurrence following surgery alone relative to the more proximal colon primaries.4 An increased risk of local or distant relapse is observed, especially in tumours that have penetrated the rectal wall (T3 or T4) and/or with nodal involvement (N1-2).5 A positive circumferential resection margin (CRM) (tumour ≤1mm of resection margin) is also an important independent prognostic marker, accounting for up to 85% of local recurrences.6-8 Hence the optimum strategy to improve the outcome of rectal cancer patients must address the problems of local and distant recurrence.9

Multimodality treatment comprising of TME, with chemotherapy and radiotherapy, have been the standard of care for locally advanced (stage II and III) rectal cancer, as discussed in the 2005 Australian guidelines.3 The current treatment nomograms will be discussed below, and include preoperative short-course radiotherapy or preoperative CRT followed by TME and adjuvant chemotherapy, and in select...
patients post-operative CRT with adjuvant chemotherapy. These approaches have dramatically reduced local recurrence, however approximately one-third of patients will still die from their disease within five years. Current work is also now being directed towards identifying low risk patients who may avoid pre-operative radiotherapy or even surgery.

Current treatment nomograms for rectal cancer

Short-course preoperative radiotherapy (25Gy in 5 fractions) followed by TME

The advantages for preoperative radiotherapy include possible tumour downstaging, reduction of radiation field size and hence toxicity, and increasing radiosensitivity of the well-oxygenated un-manipulated tumour bed. Three meta-analyses have confirmed that preoperative radiotherapy is associated with a reduced local recurrence rate and reduction in cancer-specific mortality relative to surgery alone, which extended to 10 years. Short intensive course preoperative radiotherapy appeared to be as effective as longer schedules. The pivotal Dutch Colorectal Cancer Group phase III trial, confirmed the benefit of preoperative radiotherapy (25Gy in five fractions) followed by TME one week later relative to TME alone in terms of local recurrence rate. Follow-up data at five years, reported in 2007, had demonstrated that local recurrence was 5.6% versus 10.9%, respectively (P<0.001), but there was no OS difference. As expected, short-course radiotherapy followed by immediate TME had not induced downstaging of the primary.

Short-course preoperative radiotherapy (25Gy in 5 fractions) followed by TME versus TME and selective post-operative CRT

As TME reduces the risk of local recurrence, it was suggested that the role of preoperative radiotherapy needed to be reassessed. The MRC-C07 trial had compared short-course preoperative RT (25Gy/5 fractions) versus immediate surgery, with selective postoperative CRT (45Gy/25 fractions with concurrent 5FU) in patients with positive resection margins. Overall, 1350 patients were randomised and the primary outcome measure was local recurrence. At four years follow-up, there was a 61% reduction in the relative risk for local recurrence in patients receiving preoperative radiotherapy (HR =0.39, P<0.0001), with an absolute difference at three years of 6.2% (4.4% versus 10.6%). The relative improvement in DFS was 24% for pre-operative radiotherapy (HR 0.76, P<0.05).

Preoperative (long-course) CRT versus short course preoperative radiotherapy

This has been directly compared in three randomised phase III trials. A Polish study randomised 316 clinical stage T3–T4 rectal cancer patients to short-course radiotherapy (25Gy/5 fractions) plus TME one week later, versus long-course CRT (50.4Gy plus bolus 5FU–LV) plus surgery. The primary endpoint was sphincter preservation. There was no difference between the arms in terms of survival, local recurrence, late toxicity or sphincter preservation. The rates of positive CRM involvement though, were lower in the CRT arm (4% versus 13%, P<0.05). A smaller Lithuanian phase III trial (n =83) compared the downstaging post-long-course CRT versus short-course radiotherapy. The former resulted in a significant greater tumoural downsizing and downstaging (P>0.05), but there was no difference in the R0 resection rates.

The third study is the Australian TROG 01.04 trial that randomised 326 patients to short-course radiotherapy (5x5 Gy) versus long-course preoperative CRT (with daily bolus 5FU-LV, weeks one and five), followed by surgery and post-operative adjuvant chemotherapy. The primary endpoint was local recurrence, which was not statistically significant between the arms 7.5% versus 4.4%, respectively. Nevertheless, in patients with distal tumours, long-course CRT did appear to be associated with lower rates of local recurrence. There were no differences between the arms for distant recurrence, relapse-free survival, OS or late toxicity.

Based on current evidence, pre-operative long-course CRT, where downstaging effects are more pronounced, may be preferable, particularly for patients with distal or low rectal tumours or those with threatened radial margins. For patients with small, relatively proximal tumors for whom the duration of therapy is an important consideration, short-course preoperative radiotherapy appears to be appropriate.

Preoperative CRT versus postoperative CRT

The comparison between preoperative and postoperative CRT has been addressed by two pivotal phase III trials, updated since the guidelines. The first is the German CAO/ARO/AIO-94 trial which randomised 800 patients with clinical stage T3/T4 or node-positive disease with OS as the primary endpoint. The initial results from 2004 were confirmed when updated in 2012. At a median follow-up of 134 months, OS at 10 years was approximately 60% in both arms (P>0.05), and there were no significant differences for DFS and 10-year cumulative incidence of distant metastases. However, the 10-year cumulative incidence of local relapse was 7.1% versus 10.1% in the pre and postoperative CRT arms, respectively (P<0.05).

The NSABP R 03 trial, reported in 2009, randomised patients with T3–T4 or node-positive rectal cancers to either: (i) preoperative therapy - weekly bolus 5FU-LV for six weeks, followed by CRT (50.4Gy/28 fractions with bolus 5FU-LV). Patients then proceeded to surgery followed by 24 weeks of weekly 5FU-LV; or (ii) post-operative therapy - surgery followed by CRT (50.4Gy/28 fractions with bolus 5FU-LV) and then followed by 24 weeks of weekly 5FU-LV. The trial was closed prematurely, with only 267 of the planned 900 patients recruited. In the preoperative arm, sphincteric preservation occurred in 48%, compared with 39% of patients in the postoperative group (P>0.05). The five year DFS for the preoperative group was significantly higher (65% versus 53%; P<0.05). Thus preoperative CRT is preferred to postoperative CRT.

The optimal chemotherapy backbone for concurrent long course pelvic radiotherapy

5FU-based therapy: Infusion and oral 5FU prodrugs

The use of continuous infusion 5FU over bolus 5FU has become the standard of care in the CRT treatment of...
rectal cancers, primarily for its low toxicity profile.\textsuperscript{85} Two randomised phase III studies have now confirmed the equivalent efficacy of capecitabine as a radiosensitizing agent in preoperative CRT. A German phase III trial randomised patients to either: (i) preoperative CRT 50.4Gy plus capecitabine (825mg/m\textsuperscript{2} b.i.d), days 1-38 and post-surgery capecitabine 1250mg/m\textsuperscript{2} day b.i.d days one–14, q3 weeks for five additional cycles; or (ii) preoperative CRT 50.4Gy with infusional 5-FU and post-surgery four additional cycles of bolus 5FU.\textsuperscript{86} At a median follow-up of 52 months, the local recurrence rate was equal (capecitabine 6% versus 5-FU 7%, P>0.05), but with significantly fewer patients developing distant metastases in the capecitabine arm (18.8% vs 27.7%; P<0.05).\textsuperscript{87} The five-year OS rate was 75.7% for the capecitabine group and 66.6% for the 5FU group (P>0.05).\textsuperscript{86}

The second, the NSABP R-04 trial, was a 2x2 factorial design randomising patients to continuous infusion 5FU during preoperative RT versus capecitabine (825mg/m\textsuperscript{2} b.i.d) on the days of radiotherapy only, and the second randomisation was with and without oxaliplatin.\textsuperscript{88} In terms of the capecitabine versus 5FU, no differences were seen with regards to pathological complete response (pCR), tumour downstaging, or sphincter-sparing surgery. Local recurrence and overall survival have yet to be reported.\textsuperscript{88}

It thus appears that capecitabine is a reasonable alternative to infusional 5FU as a radiosensitiser in pre-operative CRT, especially in those patients seeking an oral regimen or where a central venous access device is not preferred.

The utility of other chemotherapy agents and biologicals concurrent with long-course radiotherapy

With the advances in systemic therapy in advanced CRC, there has been considerable effort to increase the effectiveness of CRT in terms of pathological downstaging, and systemic control. At this stage, based on trials discussed below, there has been no change from the 5FU (infusion or oral prodrug) chemotherapy backbone for CRT.

1. Oxaliplatin

There have been five reported phase III trials evaluating oxaliplatin with 5FU backbone versus 5FU alone as part of preoperative CRT. The STAR-01,\textsuperscript{89} NSABP-R04,\textsuperscript{86} and the PETACC-6,\textsuperscript{80} trials all demonstrated the absence of additional benefit for tumoral pathological response or downstaging, but with an increased rate of toxicity. The German CAO/ARO/AIO4-04,\textsuperscript{81} showed that patients who received oxaliplatin with 5-FU during CRT relative to 5FU alone had a pathological complete response (pCR) of 17.6% versus 13.1% (P<0.05). The Accord 12/0405-Prodige 2 trial of oxaliplatin plus capecitabine versus capecitabine during CRT, demonstrated a similar trend: 19.2% versus 13.9% (P>0.05).\textsuperscript{92} To date, no DFS or OS advantage has been demonstrated. At this stage oxaliplatin cannot be a standard of care in preoperative CRT.

2. Monoclonal antibodies to VEGF and EGFR

Phase I and II trials of bevacizumab,\textsuperscript{79,86} and cetuximab,\textsuperscript{97-98,100} or panitumumab,\textsuperscript{101-102} have been combined with neoadjuvant CRT. The reported pathological response rates range from 0-25%, not providing a significant advantage in this regard, but associated with increased gastrointestinal toxicity and issues with wound healing.\textsuperscript{80,103-104} Thus the use of monoclonal antibodies cannot be considered as standard of care in preoperative CRT.

Current issues regarding the adjuvant therapy of rectal cancer

The role of post-operative adjuvant therapy patients undergoing neoadjuvant CRT or radiotherapy treatment

The role of post-operative adjuvant therapy in patients treated in the neoadjuvant setting is unclear. It is standard practice to offer patients adjuvant therapy to reduce distant disease failure and improve OS. The optimal regimen and whether some patients, based upon pathological response or baseline stage, can be spared treatment is unclear. The only trial to evaluate this question was the EORTC Radiotherapy Group Trial 22921, which randomised patients to preoperative radiotherapy, preoperative CRT, preoperative radiotherapy plus postoperative chemotherapy, or preoperative CRT plus postoperative chemotherapy.\textsuperscript{10} This showed no significant difference in OS or DFS between those that received post-operative chemotherapy versus those who did not (P>0.05).\textsuperscript{10} However, it must be noted that 43% of patients only completed the planned postoperative chemotherapy.\textsuperscript{105}

Several retrospective series have shown that patients post-neoadjuvant CRT who achieve a pCR may have no, or minimal benefit from adjuvant chemotherapy.\textsuperscript{106-107} A post-hoc analysis of patients who underwent neoadjuvant CRT or radiotherapy and post-operative chemotherapy from the EORTC 22921 trial above, demonstrated an improved DFS and OS in those with resected pT0-2 versus pT3-4 disease (P<0.05).\textsuperscript{108} Thus patients that have tumoural downstaging post CRT or radiotherapy do benefit from adjuvant chemotherapy,\textsuperscript{108} an observation confirmed by others.\textsuperscript{108-110} For treatment non-responders, it is not clear if additional 5FU chemotherapy or even multi-agent chemotherapy improves their poor outcomes.\textsuperscript{111} Prospective data are required.

Hence at present, adjuvant chemotherapy should be offered to all medically fit patients with locally advanced, completely resected rectal cancer post-preoperative CRT or short-course radiotherapy. However, it is not clear which patients derive the most benefit from this approach. Patients treated with pre-operative CRT should have four months of a 5FU-LV or capecitabine regimen, and those post short-course radiotherapy a six month course postoperatively. If there is nodal disease at baseline or in the resected specimen, they should be offered an oxaliplatin-5FU/capecitabine based regimen, unless contraindicated.\textsuperscript{105}

Role of TME after pre-operative CRT

Overall, approximately 15-20%,\textsuperscript{89,92,112} of patients achieve a pCR at the time of TME post CRT, which is associated with substantially improved local control, distant control and DFS.\textsuperscript{92,113-116} A recent meta-analysis, involving 16 studies and 3363 patients, evaluated the long-term outcomes of patients found to have a pCR post neoadjuvant CRT.\textsuperscript{113}
Overall, 1263 had a pCR with a mean local recurrence rate of 0.7% (range 0-2.6%). Compared with non-responders, a pCR was associated with fewer local recurrences (OR 0.25; P<0.005), reduced distant failure (P<0.001), and a greater OS (OR 3.28, P<0.005) and DFS (OR 4.33, P<0.001) at five years. At present, there are no available predictive biomarkers that identify patients most likely to undergo a pCR post-neoadjuvant therapy.\(^{117}\)

Given these outcomes of pCR, some have advocated avoiding surgical resection totally in very select patients achieving clinical CR (cCR) post neoadjuvant CRT. However, the ability to predict cCR using clinical parameters is not robust.\(^{118}-119\) The evidence is based upon a number of retrospective trials or prospective series,\(^{120}-126\) without randomised data. A recent systematic review of 30 publications (9 series, 650 patients) evaluated a non-operative approach after CRT.\(^{127}\) Overall the cCR rates varied from 10.9 to 56%.\(^{117}\) The most recent Habr-Gama series,\(^{123}\) reported a loco-regional failure rate of 4.6%, with five-year OS and DFS of 96% and 72%, respectively. These variable results reflect the significant heterogeneity in study design, including aspects of baseline and post-treatment staging, the definition of cCR and the nature of follow-up. The avoidance of TME requires, at the least, long-term prospective observational and randomised studies. Validated methods are also required to distinguish residual scar from viable tumor and document residual mesorectal deposits. Current MRI,\(^{128}-129\) or PET,\(^{130}-132\) imaging data have been inconsistent in this regard. A number of European prospective trials are evaluating this question.

**Novel alternative neoadjuvant approaches**

These include intensifying systemic chemotherapy prior to neoadjuvant CRT or radiotherapy and surgery in an effort to reduce systemic failure, especially as 20%-40% of patients do not receive post-operative adjuvant chemotherapy.\(^{10, 84}\) A Phase II trial in high risk patients (distal lesions, threatened CRM, cT4 or cN2),\(^{133}\) and a prospective study,\(^{134}\) have evaluated an induction oxaliplatin-capetabine combination pre-CRT. The studies have observed reduced toxicity,\(^{134}\) higher response rates with favourable survival parameters.\(^{133}\) Phase III trial data are required to validate the utility of such induction chemotherapy.

Other approaches have been to identify patients with low risk disease at baseline, who can proceed with surgery alone without neoadjuvant therapy. There is retrospective evidence indicating that there is a subgroup of patients with early T3N0 disease who may not benefit from additional therapy, apart from surgery.\(^{135-136}\) The MERCURY study evaluated 374 patients with stage I–II rectal cancer, who underwent baseline high resolution pelvic MRI imaging.\(^{137}\)

Overall, 33% of these patients were deemed to have good prognosis, based upon predicted clear CRM (T2-T3a/b disease), and thus underwent surgery alone. The five-year DFS for stage II–III patients in this category was 85%, with a 3% local recurrence rate.\(^{137}\) There is also the current US Intergroup PROSPECT phase II/III trial, evaluating the need for pre-operative radiotherapy in patients with mid to high rectal tumors who are candidates for TME with sphincter preservation. Patients are randomised to a standard arm of neoadjuvant CRT with 5FU, followed by TME and adjuvant chemotherapy. In the experimental arm, patients will receive neoadjuvant chemotherapy alone with FOLFOX, but will only receive post-operative radiation therapy if they have a <20% pathological response to chemotherapy.\(^{138}\)

**Conclusions**

In conclusion, adjuvant therapy is recommended for patients with resected stage III colon cancer. Patients, based on fitness and preference, with completely resected stage III cancer, should be offered six months of adjuvant chemotherapy, which optimally should start within eight weeks of surgery. The optimal regimen is oxaliplatin in combination with 5FU-LV or capcitabine, based on relevant consideration of the therapeutic ratio, especially in regard to neurotoxicity, and perhaps age. Patients not considered suitable for oxaliplatin should be offered 5FU-LV or capcitabine.\(^{52}\) Current trials are now investigating the optimal length of therapy i.e. three versus six months, and the additional benefit of the EGFR monoclonal antibody panitumumab, (the FOxTROT trial).\(^{43}\)

In terms of patients with resected stage II disease, adjuvant chemotherapy may be discussed with patients at high risk of disease relapse, based upon clinico-pathological factors discussed above and while considering the patients’ comorbidities, age and the risk of therapy-related toxicity. MSI status must be assessed for those patients being considered for adjuvant therapy. Those with a MSI-H tumor should not be offered 5FU-based therapy.\(^{17, 44}\) The utility of oxaliplatin-based therapy in this setting is controversial, given the marginal benefit and greater risk of toxicity. Where available, commercial gene expression classifiers may also be considered to further classify patients based on risk of relapse. However, at this stage they cannot identify patients who are likely to respond to therapy.

For patients with stage II/III rectal cancer (T3 or T4 and/or with nodal involvement [N1-2]), the optimal strategy is to reduce local and distant recurrence. Current treatment approaches may include: (i) short-course radiotherapy and immediate TME (especially in proximal tumours); or (ii) long-course neoadjuvant CRT (with 5FU infusion or capecitabine) followed by TME. Post-operative adjuvant chemotherapy should be offered to medically fit patients. Postoperative CRT therapy may be preferred, for example where patients who have undergone surgery for very small or proximal T3 tumors, or tumors that are either T2/3. In these circumstances, post CRT and adjuvant chemotherapy should be considered if unexpected nodal involvement or a positive margin is identified. At present, there are no validated markers that can identify patients who may not require neoadjuvant radiotherapy, or who can be safely spared surgery post CRT or radiotherapy, though these are areas of active research. In an effort to increase pCR, the intensification of neoadjuvant chemotherapy is also being evaluated.

**References**

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