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*TOPIC HIGHLIGHT*

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# Adjuvant therapies for colorectal cancer

Suzanne Kosmider, Lara Lipton

Suzanne Kosmider, Lara Lipton, Department of Medical Oncology and Clinical Haematology, Western Hospital, Footscray 3011, Victoria, Australia
Correspondence to: Lara Lipton, MBBS, FRACP, Consultant Gastrointestinal Oncologist Western Hospital, Gordon Street, Footscray 3011, Victoria, Australia. lara.lipton@mh.org.au
Telephone: +61-3-83456666 Fax: +61-3-83456445
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## Abstract

The management of colon and rectal cancer has changed dramatically over the last 25 years. The use of adjuvant therapies has become standard practice in locally advanced (stage Ⅲ and selected stage Ⅱ) colorectal cancer. Improved surgical techniques, chemotherapeutics and radiotherapy are resulting in higher cure rates and the development of agents targeting proliferative and angiogenic pathways offer further promise. Here we explore risk factors for local and distant recurrence after resection of colon and rectal cancer, and the role of adjuvant treatments. Discussion will focus on the evidence base for adjuvant therapies utilised in colorectal cancer, and the treatment of sub-groups such as the elderly and stage Ⅱ disease. The role of adjuvant radiotherapy in rectal cancer in reduction of recurrence will be explored and the role and optimal methods for surveillance post-curative resection with or without adjuvant therapy will also be addressed.



**Key words:** Colon cancer; Rectal cancer; Chemotherapy; Radiotherapy; Adjuvant treatment

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## INTRODUCTION

Colorectal cancer (CRC) is the most common internal malignancy in men and women of western societies and its incidence is rapidly increasing in Asia. Colon cancer affects men and women almost equally, whilst rectal cancer is more common in men, female:male ratio 1:1.3[1]. Colorectal cancer is uncommon under the age of 50 years, with a median age at diagnosis of 70. Globally, the age-standardized incidence rate (ASR) is 20.1 per 100 000 males and 14.6 per 100 000 females. There are notable differences in incidence rates of developed versus developing countries. In the Western world, the ASR is 40.0 in males and 26.6 in females; however, in developing nations, the rates are 10.2 and 7.7, respectively[2].

The main risk factors for CRC development are advancing age and a family history of the disease. About 2%-4% of cases are related to known genetic syndromes including Familial Adenomatous Polyposis (FAP) and hereditary non-polyposis colorectal cancer (HNPCC). Another 25% have a family history without an identified genetic predisposition[3]. Other relevant lifestyle factors include diet, weight and physical activity[2]. Approximately one-third of affected persons will present with disease involving local lymph nodes (stage Ⅲ), and another third with lymph node negative disease (Stage Ⅰ or Ⅱ)[4]. About 30% of people have metastatic (stage Ⅳ) disease at diagnosis (Table 1)[5].

## THE RISK OF CANCER RECURRENCE AFTER RESECTION OF COLORECTAL CANCER

After curative surgical resection, a proportion of those treated will relapse, predominantly with distant metastatic disease. Fifty to 60% of persons with Stage Ⅲ and 25% with Stage Ⅱ disease will relapse within 5 years[6]. This is due to the presence of micrometastatic disease at the time of surgery. Such disease can potentially be eradicated with the use of adjuvant therapies. The risk of relapse may be estimated by assessing the clinical and histologic features of the cancer. Poor risk clinical features include higher TNM stage (Table 1), elevated preoperative carcinoembryonic antigen (CEA), insufficient lymph node sampling (< 10 nodes), and presentation with colonic perforation or obstruction[7]. Metastasis to regional lymph nodes is the factor most strongly predictive of outcome following complete surgical resection[7]. Other factors have consistently been implicated as of prognostic value, but remain to be validated in prospective trials. These include the histological grade of the cancer, lymphovascular invasion, residual tumour following neo-adjuvant therapy for rectal cancer, and microsatellite instability (MSI)[7]. There is no prospective evidence to suggest these factors aid assessment of disease free and overall survival, or serve as predictive factors for adjuvant therapy benefit.

**Table 1A TNM staging system for colon cancer with AJCC stage grouping[57]**

| AJCC stage | TNM category |
|---|---|
| Stage 0 | Tis, N0, M0 |
| Stage I | T1, N0, M0<br>T2, N0, M0 |
| Stage ⅡA | T3, N0, M0 |
| Stage ⅡB | T4, N0, M0 |
| Stage ⅢA | T1-T2, N1, M0 |
| Stage ⅢB | T3-T4, N1, M0 |
| Stage ⅢC | Any T, N2, M0 |
| Stage Ⅳ | Any T, Any N, M1 |

**Table 1B TNM staging system for colon cancer[57]**

| | Tumour stage (T) | Nodal stage (N) | Metastasis (M) |
|---|---|---|---|
| X | Primary tumour can not be assessed | Nodal metastasis can not be assessed | Distant metastasis can not be assessed |
| 0 | No primary tumor identified | No nodal metastasis | No distant metastases |
| is | Carcinoma *in situ* (tumour limited to mucosa | | |
| 1 | Involvement of submucosa, but no penetration through muscularis propria | 1-3 pericolic/ perirectal nodes involved. | Distant metastases |
| 2 | Invasion into, but not penetration through, muscularis propria | 4 or more pericolic/ perirectal nodes involved | |
| 3 | Penetration through muscularis propria in o subserosa (if present), or pericolic fat, but not into peritoneal cavity or other organs. | | |
| 4 | Invasion of other organs or involvement of free peritoneal cavity | | |

Evidence suggests that cancers displaying MSI have a better prognosis stage for stage compared to microsatellite stable cancers and that persons with such cancer may not benefit from adjuvant 5-FU chemotherapy; however, the literature regarding the latter remains conflicting[8,9].

## ADJUVANT CHEMOTHERAPY FOR COLON CANCER

### *Cancer stage*

Lymph node involvement in colon cancer (stage Ⅲ) remains the strongest predictor for distant relapse. Adjuvant chemotherapy with 5-FU given intravenously for 6 mo in combination with leucovorin calcium (LV) decreases the relative risk of death by 30% in stage Ⅲ colon cancers when compared to surgery alone. This equates to a greater than 10% absolute risk reduction[10]. With newer chemotherapy regimens the absolute risk reduction may be even greater (Figure 1). Controversy still exists over the role of adjuvant chemotherapy for those with Stage Ⅱ disease, of whom 75% are cured with surgery alone. Relative risk reductions in these patients are much the same as in stage Ⅲ; however, given the lower risk of relapse, the absolute improvement in 5 year survival is 2%-5%[5,11,12]. Patients with Stage Ⅱ disease with poor prognostic features include those with < 10 lymph nodes sampled at surgery, T4 tumours (Table 1), bowel obstruction or perforation at presentation, lymphovascular invasion or high histological grade. Current practise is to consider adjuvant chemotherapy for high-risk patients, particularly when of young age and/or without major co-morbidities.

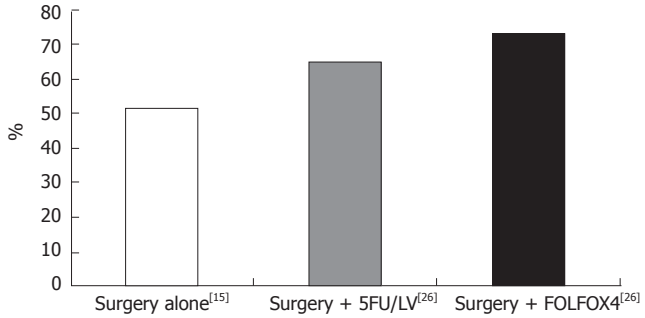


**Figure 1** Three year disease free survival in stage Ⅲ colon cancer.

### *Adjuvant therapy in the elderly*

Historically, many adjuvant chemotherapy clinical trials have excluded patients over 75 years of age, and as such, the data regarding the risks and benefits of adjuvant treatment in the elderly are limited. A pooled analysis of over 3000 patients treated with adjuvant 5-FU chemotherapy for stage Ⅱ or Ⅲ colon cancer investigated the effect of age on overall survival and time to tumour recurrence[13]. No significant interaction was observed between age and the efficacy of treatment. The incidence of toxicity was not increased among the elderly (defined as age > 70 years), except for leukopenia in one study in which 5-Fluorouracil (5-FU) was used in combination with levamisole[13]. The observed benefit of 5-FU adjuvant therapy in the 65 plus age range has been addressed in several recent reports. No statistical difference in survival benefit was observed between patients under and over the age of 70 with the use of oxaliplatin and 5-FU adjuvant chemotherapy in a randomised study which included patients up to 75 years of age[14]. Neither was there a difference in the rates of hematologic and non-hematologic toxicity. As such, fit elderly patients with little co-morbidity should not be excluded from adjuvant therapy on the basis of age alone.

## CHEMOTHERAPEUTIC AGENTS AND TOXICITIES

### *5-FU and its derivatives*

In the 1980's, 5-fluorouracil based chemotherapy was shown to provide a survival advantage over best supportive care in metastatic CRC[15]. This formed the rationale for its use as an adjuvant therapy in randomised trials. Adjuvant

**Table 2 Common adjuvant chemotherapy regimens for colon cancer**

| Chemotherapy Regimen | Drugs | Route | Dosage | Cycle length and number |
|---|---|---|---|---|
| Mayo Regimen[58] | 5-FU/LV | iv | 5-FU, 425 mg/m$^2$ per day d 1-5<br>LV 20 mg/m$^2$ per day d 1-5 | 28 d<br>6 cycles |
| Roswell Park[59] | 5-FU/LV | iv | 5-FU 500 mg/m$^2$ per day weekly × 6<br>LV 500 mg/m$^2$ per day weekly × 6 | 8 wk<br>4 cycles |
| Xeloda[24] | Capecitabine | oral | 1250 mg/m$^2$<br>BD × 14 d | 21d<br>8 cycles |
| FOLFOX 4[31] | 5-FU/LV<br>Oxaliplatin | iv | Oxaliplatin 85 mg/m$^2$ d 1<br>LV 200 mg/m$^2$ per d d 1-2<br>5-FU 400 mg/m$^2$ per day d 1-2<br>5-FU, 600 mg/m$^2$ per d CVI over 22 h, d 1-2 | 14 d<br>12 cycles |
| FLOX[32] | 5-FU/LV<br>Oxaliplatin | iv | Oxaliplatin 85 mg/m$^2$ wk 1, 3, 5<br>LV 500 mg/m$^2$ wk 1-6<br>5-FU 500 mg/m$^2$ wk 1-6 | 8 wk<br>3 cycles |

CVI: Continuous venous infusion; LV: Leucovorin calcium; iv: intravenous.

5-FU in combination with levamisole showed a significant increase in 5 year survival over surgery alone[16]. Cancer recurrence was decreased by 41% ($P < 0.0001$) and overall mortality was reduced by 33% ($P = 0.006$)[16]. 5-FU with the addition of LV was then shown to be superior to 5-FU/levamisole in both disease-free survival ($P = 0.037$) and overall survival ($P = 0.0089$)[17]. A randomised study comparing high versus standard dose LV showed no added benefit in overall survival or recurrence rates for high dose therapy, and resulted in higher rates of toxicity[18]. The standard duration of 5-FU chemotherapy for colon cancer is 6 mo with patients treated for 12 mo showing no extra benefit[19].

Different methods of administration of 5-FU have also been investigated with infusion of 5-FU resulting in greater response rates than bolus, with a slight survival advantage in the metastatic setting[20]. This benefit has not translated into increased survival in the adjuvant setting[21,22]. Infusion of 5-FU is well tolerated, but requires the insertion of an indwelling venous catheter and the use of an infusion pump, both of which add to patient inconvenience. Capecitabine, an oral fluoropyrimidine, is converted to fluorouracil by thymidine phosphorylase, an enzyme active in colorectal tumour tissue and has a relatively predictable and favourable toxicity profile in most people. It is an established alternative to 5-FU/leucovorin in the metastatic setting, with equivalent progression free and overall survival[23]. In a randomised equivalence trial comparing bolus 5-FU and leucovorin with capecitabine in the adjuvant treatment of stage Ⅲ colon cancer, capecitabine showed equivalent disease free survival with no increase in adverse events[24]. Capecitabine provides a convenient oral alternative to bolus 5-FU therapy for those able to tolerate and comply with an oral regimen[24].

5-FU and its oral equivalents share a common side-effect profile with predominant gastrointestinal toxicities including nausea, mucositis and diarrhoea. Neutropenia and nausea are more commonly seen with the bolus 5-FU regimens. Infusion of 5-FU and oral capecitabine have higher rates of hand-foot syndrome (erythema, dryness and cracking of palms and soles), diarrhoea and mucositis. The treatment related mortality rate among patients treated with 5-FU is 0.5%[25]. 5-FU is degraded through the enzyme dihydropyrimidine dehydrogenase (DPD) as the initial and rate-limiting step in pyrimidine catabolism. Patients with an inherited deficiency or significantly decreased DPD activity may develop life-threatening toxicity following exposure to 5-FU with severe mucositis, granulocytopenia, neuropathy and death[26]. The toxicity results from decreased drug clearance, and prolonged drug exposure. It has been estimated that approximately 3%-5% of the Caucasian population and 8% of the African-American population have DPD activity less than 95% of normal[27]. While this lowered level of activity may not result in life threatening 5-FU toxicity, it can result in grade 3/4 toxicities in a significant number of patients[28]. Thus, although in the majority of persons a safe therapeutic agent, careful monitoring, especially in the early stages of treatment with 5-FU is warranted and dose reductions not infrequently necessary.

### *Oxaliplatin*

Although platinum derivatives such as cisplatin are inactive in CRC, oxaliplatin, a third-generation platinum analogue has impressive activity in combination with 5-FU and LV in stage Ⅳ disease and is among the most effective agents for metastatic CRC[29,30]. The combination has been evaluated in phase Ⅲ studies for adjuvant treatment of stage Ⅱ and Ⅲ colon cancer, using two differing regimens, FOLFOX4 and FLOX (Table 2). Both are of the same duration (24 wk), but differ in the cumulative dose of oxaliplatin and in the need for continuous infusion of 5-FU. Both showed superiority over 5-FU/LV therapy, with an absolute improvement in 3 year disease free survival in the range of 6%-8% for Stage Ⅲ disease, and 2%-3% for stage Ⅱ disease[31,32]. Oxaliplatin in combination with 5-FU and leucovorin is now the standard of care for stage Ⅲ colon cancer in patients of good performance status.

The major toxicity of oxaliplatin is peripheral sensory neuropathy of two distinct types. An acute neurotoxicity includes cold-related dysesthesia, which may last days after administration, and is transitory in nature. The use

**Table 3 Rates of local recurrence according to stage at diagnosis, surgical management and the inclusion of radiotherapy for rectal cancer (%)**

| Stage at diagnosis | Surgery alone[41] | Total mesorectal excision[42] | TME plus radiotherapy[42] |
|---|---|---|---|
| Stage I | 14 | 0.7 | 0.5 |
| Stage II | 22 | 5.7 | 1.0 |
| Stage III | 46 | 15 | 4.3 |

TME: Total mesorectal excision.

of calcium and magnesium infusions may reduce the incidence and intensity of acute oxaliplatin reactions such as pharyngeal spasm and intense cold-related dysesthesia[33]. Oxaliplatin may also cause a sensory neuropathy with increasing cumulative dose, which, in a small number of cases, may be irreversible. In one study of the commonly used FOLFOX4 regimen (Table 2), 12% of patients experienced grade 3 neuropathy (paresthesia interfering with function and severe objective sensory loss) at the end of 12 cycles, which decreased to 1% at one year follow-up[31]. Neutropenia is more common with regimens that include oxaliplatin over 5-FU alone.

The efficacy and safety of targeted therapies in the adjuvant treatment of CRC is currently under investigation. Trials incorporating bevacizumab (an angiogenesis inhibitor) with oxaliplatin based chemotherapy are currently recruiting subjects[34].

### Adjuvant therapy for rectal cancer and reducing local and distant recurrence

The treatment of rectal cancer differs from that of colon cancer in several respects. In cancers that are T3 or T4, N1 or low in the rectum, surgical resection alone may be associated with relatively high rates of loco-regional recurrence. Depending on the stage of rectal cancer at diagnosis, local relapse occurs in up to 50% of patients at a median time of 12 mo following surgery (Table 3)[35]. Local relapse with involvement of pelvic nerves, bone or other organs by tumour can cause significant pain, as well as sphincter, bladder and sexual dysfunction. Salvage surgery with the intent of cure is rarely possible. Distant metastatic disease commonly occurs in extra-hepatic sites and relapse free survival after hepatic metastectomy is poorer than that of colon cancer. Therefore, adjuvant treatment in rectal cancer has two aims, control of distant and local relapse. Radiotherapy and systemic chemotherapy are used in the management of T3-T4, node positive and very low rectal cancers[36]. Strong evidence exists for the impact of surgical technique on local control. Total mesorectal excision (TME), the precise anatomical excision of the rectum with an intact mesorectum, is the current standard of care and has been associated with reduced rates of local relapse over previous surgical methods (Table 2)[37].

### Preoperative staging

In a number of countries neo-adjuvant (pre-operative) radiotherapy is routinely used. The aims of pre-operative radiotherapy are to maximise the likelihood of a complete surgical resection, to downstage the primary cancer allowing sphincter preserving surgery and to decrease the risk of locoregional (pelvic) cancer relapse.

A potential disadvantage of such treatment is the potential for over-treating early stage tumours (T1 or T2). Hence, accurate pre-operative staging is vital. The best modalities to assess rectal tumour invasion and nodal stage (T and N score) have been investigated. For tumour invasion through the muscle wall (T score), MRI appears statistically superior to CT. The sensitivity for MRI is 97% and the specificity 98%; for CT, the sensitivity is 70% and the specificity 85%[38]. CT has a relatively high false-positive prediction of pelvic floor and piriform muscle invasion[38]. Preoperative evaluation of nodal status is still problematic, and other imaging tools including transrectal ultrasound (TRUS) have been evaluated. The results of a meta-analysis on the accuracy of preoperative imaging suggests that there is no significant difference between MRI and TRUS with respect to assessment of nodal status, but that CT scanning is inferior[39]. The sensitivity for CT, TRUS, MRI and MRI with endo-rectal coil are 52%, 71%, 65% and 82%; for specificity 78%, 76%, 80% and 83%; and for accuracy 66%, 74%, 74% and 82%, respectively[40].

### Radiotherapy

A number of radiation schedules have been used in both trial and practice. Short course pre-operative radiotherapy consisting of 20 Gy given in five fractions over five days has been used with the aim of reduction in local recurrence. Long-term follow up of the Swedish Rectal Cancer Trial comparing such radiotherapy followed by surgery over surgery alone shows lower local recurrence rates in the radiotherapy arm (9% *vs* 26%)[41]. In this trial, patients did not uniformly undergo TME. The Dutch Colorectal Cancer group conducted a similar trial incorporating short course pre-operative radiotherapy but all patients underwent TME with lower recurrence rates again seen in the radiotherapy arm (2.4% *vs* 8.2%, $P < 0.001$)[42]. The presence of cancer cell hypoxia may be an important cause of resistance to radiation therapy, so irradiating tissue not rendered hypoxic by previous surgery may result in improved local control[43]. A German trial compared 4 wk of preoperative chemoradiotherapy using 50.4 Gy in 28 fractions combined with a five day continuous infusion of 5-FU (1000 mg/m$^2$ per day) during the first and fifth wk of radiotherapy, with the same regimen given post operatively for locally advanced rectal cancer (T3/4 or node positive)[44]. All patients underwent TME. Preoperative treatment resulted in a halving of the local recurrence rate at 5 years over post-operative treatment (6% *vs* 13%, $P = 0.006$) and was associated with reduced toxicity including acute and chronic diarrhoea and anastomotic strictures. There was no difference in overall survival between the two groups[44].

### Chemotherapy considerations in rectal cancer

5-FU may be administered as a radiation sensitiser. Infusion 5-FU for the duration of radiotherapy has been compared to bolus 5-FU in randomised trials with the continuous infusion resulting in superior local and distant

disease free survival[17,45]. Low dose oral capecitabine during radiotherapy has also been investigated. In a randomised phase Ⅱ trial of capecitabine versus infusion of 5-FU during pre-operative radiotherapy, no statistically significant difference in complete pathological response rates at surgery were noted. Tumour down-staging was statistically higher with capecitabine therapy (77% *vs* 50%, $P = 0.009$) and the combination of radiotherapy and capecitabine was well tolerated[46]. These findings suggest preoperative chemoradiation with oral capecitabine may be equivalent to continuous 5-FU[47]. Persons diagnosed with node positive disease on pre-operative staging, or at histological examination of the resected tumour should be considered for adjuvant (post-operative) 5-FU therapy to eradicate micrometastatic disease. As with colon cancer, the duration of the chemotherapy should be 6 mo, which includes the period of chemotherapy given concurrent with radiotherapy. Phase Ⅱ data exists for the role of oxaliplatin in combination with 5-FU in the treatment of rectal cancer with a high pathological complete response rate, but more toxicity than 5-FU used alone[48].

### *Surveillance post-curative resection and/or adjuvant therapy in CRC*

Despite adjuvant treatment, 30%-40% of patients with stage Ⅲ and up to 25% of stage Ⅱ colorectal cancer patients will develop locoregional recurrence, or distant metastasis. Up to 8% will develop a new primary CRC within 4 years[49]. The relapse rate for CRC is highest in the first 2 years, and falls to < 5% at 5 years, with 80% of relapses occurring within 3 years[6]. As such, the frequency of clinical review should be maximal in this time period. Surveillance aims to improve outcome by detecting isolated and resectable cancer recurrences (hepatic, pulmonary or anastomotic) or a new primary CRC. The method and intensity of surveillance after primary treatment remains controversial. Although increased detection of early recurrence at a potentially curable stage could improve survival, frequent imaging and biochemical investigations incur cost and possibly concern for the patient. Often surveillance detects incurable recurrences, months before symptoms develop[50-52].

Recent meta-analyses have addressed intensive versus simple follow-up strategies[50-52]. Intensive strategies incorporate some form of abdominal imaging (usually CT), whilst simple strategies rely on history and examination alone, reserving imaging to investigate clinical symptoms of recurrent disease. Both strategies incorporate monitoring of CEA. In all meta-analyses, those with more intensive surveillance were more likely to undergo surgery with curative intent for metastatic or recurrent disease[53]. The most recent American Society of Clinical Oncology (ASCO) guidelines regarding surveillance after potentially curative therapy for colorectal cancer reflect the changing attitude towards the role of routine CT imaging (Table 4)[6]. A pelvic CT should be included in rectal cancer patients, especially if they have not had radiotherapy. There is less evidence for performing chest CT, than for liver imaging. However, as pulmonary metastasis are common in rectal cancer, often occurring without CEA elevation, it may be more useful in these patients, particularly as pulmonary recurrences have represented the largest proportion of resectable metastasis in several trials[54,55]. Regarding endoscopy, a number of guidelines exist. All patients should have a pre or peri-operative colonoscopy. For persons without specific familial risk, a repeat colonoscopy should be performed at 1-3 years, and if normal, once every 5 years thereafter. Those with high-risk genetic syndromes should be followed more frequently. Flexible sigmoidoscopy every 6 mo for 5 years is recommended for patients with rectal cancer who have not undergone pelvic radiotherapy (further discussion of post-surgical follow up is provided in the final review of this topic review series by Gan *et al*).

**Table 4 2005 ASCO Guidelines for post-treatment surveillance[6]**

| Year post diagnosis | History and physical review | CEA level | CT scan chest and abdomen | Colonoscopy |
|---|---|---|---|---|
| Yr 1 | 3-6 monthly | 3 monthly | Yearly | |
| Yr 2 | 3-6monthly | 3 monthly | Yearly | |
| Yr 3 | 3-6 monthly | 3 monthly | Yearly | Colonoscopy |
| Yr 4 | 6 monthly | At review | Nil | |
| Yr 5 | 6 monthly | At review | Nil | |

CEA: Carcinoembryonic antigen.

## CONCLUSION

Currently, adjuvant therapy for colorectal cancer is based on the clinical features at presentation including co-morbidities and histologic features of the cancer. Although a number of genetic and biochemical markers of prognosis have been suggested, none have, as yet, been proved robust enough in prospective trials, to guide clinical practice[56]. Future research should aim to identify additional prognostic factors to accurately predict benefit from adjuvant treatment and allow individual tailoring of therapy. Important issues, which need to be addressed, include (1) selection of patients with stage Ⅱ disease who would benefit from adjuvant therapy, (2) which patients with node-positive colon cancer would be adequately treated with 5-FU based therapy, and thus could be spared the potential neurotoxicity associated with oxaliplatin therapy? (3) How many cycles of oxaliplatin constitute adequate therapy? (4) What is the role of oxaliplatin in adjuvant treatment for rectal cancer?

Therapies targeting pathways involved in colorectal carcinogenesis have an increasing role to play in the management of metastatic colorectal cancer in combination with more traditional chemotherapy agents. Of particular interest are agents directed against tumour growth factors, their receptors and down-stream pathways. Bevicuzimab, a monoclonal antibody directed against circulating vascular endothelial growth factor and cetuximab and panitumimab, agents targeting the epidermal growth factor receptor, have been used in combination with chemotherapy in advanced colorectal cancer with promising results. Trials are underway to define their role in the adjuvant setting. Although much has been

achieved in the adjuvant management of colorectal cancer there is room for ongoing improvement in all areas to increase the chance of cure for each individual treated.

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