Review:

Adjuvant therapy for colorectal cancer – is there a place for a Northern Ireland study?

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SUMMARY

Survival from colorectal cancer has not improved over the last four decades despite advances in surgery and anaesthesia. The answer to the question whether adjuvant chemotherapy and radiotherapy will improve survival from the disease can only come from randomised, controlled trials. In the future, immunotherapy and gene therapy may be of benefit but these are still many years from the clinical arena. We believe that current evidence suggests that patients with Dukes’ B and C colorectal cancer should be entered into trials of adjuvant therapy. This evidence is reviewed below along with estimates of the impact that adjuvant therapy would have on the outcome from this disease in Northern Ireland.

There are approximately 600 new cases of newly-diagnosed pathologically proven colorectal carcinoma in Northern Ireland annually.1 This disease accounts for an average of 440 deaths yearly in our community.2 Colorectal cancer is the second most common cause of death from malignancy in adults in this population. The Northern Ireland colorectal cancer register has found that the proportion of tumours using Dukes’ staging was as follows: Dukes’ A 4%, Dukes’ B 50%, Dukes’ C 28%, Dukes’ D 18%.

These figures were calculated using the Astler-Coller Modification of Dukes’ staging:3 A – mucosal (ie intramucosal and submucosal), B – into or through the colonic muscle wall, C – one or more lymph nodes involved, and D – distant metastases present. Survival figures for colorectal cancer have not improved over the last few decades despite advances in medical care. Using the above version of Dukes’ staging, five-year survival figures 4 are: A – virtually 100%; B – range 30%-85%, average 70%; C – range 30%-60%, average 45%; and D – under 5%.

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Potentially curative surgery is possible in around 75% of new cases of colorectal cancer, but long-term follow-up reveals that around half of these “cured” patients will develop incurable recurrence of colorectal cancer. There is no indication for adjuvant treatment in Dukes’ A colorectal cancer. The hazards of currently available therapies outweigh the benefits in a disease with 98-100% five-year survival. Equally, patients with Dukes’ D or incurable disease cannot receive adjuvant therapy but may benefit from additional therapy after palliative surgery. This may result in improvements in both survival time and quality of life.

There are approximately 600 cases in Northern Ireland annually. From the stage distribution above we expect there to be about 470 cases in the Dukes’ B and C groups. Estimates of five year survival applied to the projected 470 cases per annum in Duke’s B and C would give a five year mortality overall of 40%.

We believe that patients with Dukes’ B and C colorectal cancer should be enrolled in a randomised, controlled trial of adjuvant therapy. This would entail treatment arms of modulated 5-fluorouracil chemotherapy for colon cancer and radiotherapy and chemotherapy for rectal cancer. Statistical calculations show that a trial of 520 patients (260 per treatment group) will have 80% power to detect a statistically significant 30% relative reduction in mortality with adjuvant therapy (P<0.05; two-tailed). This would represent a mortality in the treatment groups of 28% compared to 40% and is approximately equivalent to the long term survival of one in every eight patients who currently die within five years.

Although some Dukes’ B and C stage patients are currently offered adjuvant therapy in Northern Ireland, this remains a very small proportion (<10%) of the total. Northern Ireland is an ideal area for a trial of adjuvant therapy in colorectal cancer as we have one of the highest incidences of this cancer in the world, and our population has low rates of immigration, emigration and mobility compared to the rest of the United Kingdom, allowing excellent follow-up; clinical trials are possible without dissipation of patients between health authorities, hospitals and regions because of our small size, and easy communication between consultants. At present adjuvant therapy is not often offered to suitable patients.

It is anticipated that the necessary sample size of a minimum of 520 patients could be accrued in Northern Ireland within three years. A larger multicentre trial would greatly increase the number of patients and a national study is currently being proposed by the United Kingdom Co-ordinating Committee on Cancer Research which will have multiple arms of varying chemotherapy regimens. However, recent experience has shown that local recruitment from Northern Ireland into national studies in colorectal cancer such as the AXIS trial of intraportal chemotherapy and the Medical Research Council trial of chemotherapy in advanced colorectal cancer is very low.

Chemotherapy

Previous trials have shown that 5-fluorouracil, either singly or in combination with other agents is the most effective adjuvant systemic chemotherapeutic agent. This substance is a prodrug which is metabolised in place of uracil or
orotate in the de-novo or salvage pathways of generation of uridine nucleotides producing a cytotoxic insult through effects on translation, transcription, mitosis or DNA synthesis.\textsuperscript{8} Folinic acid in combination with 5-fluorouracil is more effective than 5-fluorouracil alone due to inhibition of thymidylate synthetase.\textsuperscript{9} A combination of 5-fluorouracil and folinic acid would be administered according to the 48-hour infusion regime used by the ICRF medical oncology department at St Bartholomew's Hospital.\textsuperscript{10} Chemotherapy should commence at two weeks postoperatively unless there are wound or other postoperative complications and must occur within six weeks of surgery. Folinic acid is administered at 200mg/m\textsuperscript{2} (maximum dose 350mg) by intravenous infusion in 250ml normal saline over two hours. This is followed by an intravenous bolus of 400mg/m\textsuperscript{2} 5-fluorouracil in 100ml normal saline over 15 minutes followed by an intravenous infusion of 400 mg/m\textsuperscript{2} 5-fluorouracil in 1000ml normal saline over 18 hours. The above regimen is given on two consecutive days as an in-patient and repeated every two weeks for a total of eight courses (sixteen days of in-patient stay over four months).

The original report of this regimen showed a low incidence of toxicity. In 64 patients with advanced adenocarcinoma, none had toxic effects greater than WHO Grade II, 9\% developed mucositis, 12\% diarrhoea and 3\% significant neutropaenia. No dose-reduction was necessary and 97\% of treatments were given as planned. It is expected that these figures will be even better when given in an adjuvant setting, as has already been the experience in the Northern Ireland Centre For Clinical Oncology. When this regimen was used in Belvoir Park Hospital as adjuvant treatment for colorectal cancer, gastrointestinal upset occurred in under 10\% of cases and significant neutropaenia has not occurred. The 48 hour infusion schedule results in much lower toxicity and emergency hospital admissions than schedules using daily bolus injections.

Data from Austria from a randomised trial on the use of modulated 5-fluorouracil in advanced disease suggests that chemotherapy often results in mild to moderate gastrointestinal symptoms\textsuperscript{6} but does not result in a decrease in quality of life scores. Indeed, in patients with poor quality of life from symptoms of their disease before treatment, there was an improvement with chemotherapy.

\textit{Radiotherapy}

The area most at risk of local recurrence of rectal cancer below the peritoneal reflection is the posterior pelvis. Radiation enteritis is avoided by using fields limiting high radiation doses to this volume. Prone positioning to prevent irradiation of loops of small bowel will also decrease complications. The treatment fields should centre on the site of the resected tumour and include the lateral pelvic nodes. The postoperative radiotherapy should commence as soon as possible but must be within six weeks of resection. The dosage ranges suggested are 40-50 Gy delivered in 20-25 daily fractions over a four to five week period and may precede or run concurrently with chemotherapy.

\textit{Summary of Previous trials}

One half of patients with colorectal cancer die with distant disease.\textsuperscript{5} The disease is systemic and occult micrometastases are commonly present in patients who have undergone apparently complete tumour resection. Dissemination often occurs before the primary tumour becomes clinically apparent and this
characteristic has prevented improvements in cure rates despite advances in surgical and anaesthetic techniques. In order to improve the prognosis by eliminating micrometastases, a number of investigations have studied adjuvant chemotherapy but its value in colorectal cancer remains unclear. Many trials have taken place, with great variation in the use of randomisation, patient numbers, particular chemotherapeutic regimens and the duration of follow-up.

Chemotherapy trials

Chemotherapy trials in colorectal cancer using 5-fluorouracil alone have demonstrated it to be the best single agent. However, large studies by the Veterans Administration Surgical Adjuvant Group\(^\text{11}\) and Central Oncology Group\(^\text{12}\) demonstrated only minor activity. Overall, single agent chemotherapy with 5-fluorouracil has given a reduction in mortality of 10% at best. The Veterans Administration Surgical Adjuvant Group later administered low-dose intravenous 5-fluorouracil plus oral lomustine.\(^\text{13}\) They demonstrated prolonged disease-free survival in Dukes’ C patients but no improvement in overall survival. The Gastrointestinal Tumour Study Group\(^\text{14}\) studied the use of 5-fluorouracil plus lomustine with or without BCG immunotherapy against BCG alone, and against controls. They found no improvement in survival and the further problem that lomustine was associated with increased risk of leukaemias. The South West Oncology Group\(^\text{15}\) compared 5-fluorouracil and lomustine with or without BCG against controls and found no survival benefit at seven years. The National Surgical Adjuvant Breast and Bowel Project (NSABP)\(^\text{16}\) compared adjuvant 5-fluorouracil, lomustine and vincristine against BCG and controls, and demonstrated an 8% improvement in survival after five years.

Windle et al\(^\text{17}\) compared adjuvant 5-fluorouracil with levamisole against levamisole alone and controls. After eight years, they found improved survival in Dukes’ C patients with combination chemotherapy. Levamisole is an anti-helminthic drug with immunostimulatory properties and has been used as adjuvant cancer treatment in the last two decades either alone, or with radiotherapy or chemotherapy,\(^\text{18}\) but with unclear results on survival. The European Organisation for Research and Treatment of Cancer group demonstrated recently that by itself it has no adjuvant effect in colonic cancer,\(^\text{19}\) although it is standard practice in the USA to combine levamisole with 5-fluorouracil in treatment of colorectal cancer. The mechanism of action of levamisole is unclear and 5-fluorouracil alone may be responsible for the observed effects on survival in trials on the combination of 5-fluorouracil and levamisole.\(^\text{20}\)

The North Central Cancer Treatment Group (NCCTG)\(^\text{21}\) compared 5-fluorouracil plus levamisole against levamisole and controls. They also showed increased survival with combination chemotherapy in Dukes’ C patients. A larger intergroup study was performed to confirm these results and enrolled three times more patients.\(^\text{22}\) They showed that this combination chemotherapy increased survival in Dukes’ C patients by 33% and decreased recurrence by 41%. Levamisole alone was no better than the untreated controls. There was no clear benefit in patients with Dukes’ B disease. The addition of folic acid to 5-fluorouracil resulted in improvements in response, quality of life and survival in the NCCTG study in advanced colorectal cancer.\(^\text{23}\) There is also considerable discussion on the best route for administering adjuvant chemotherapy –

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intrahepatic, intraperitoneal, intraportal or intravenous. Of these, the latter two are of most current interest. Hepatic metastases are the commonest cause of failure following surgery for colorectal cancer and these presumably arise from haematogenous spread via the portal vein. Portal infusions are an attempt to target the chemotherapy to the liver and to limit toxicity. These are usually given in conjunction with heparin for a short period of about a week. The treatment is well tolerated without significant hepatic toxicity but results have been very conflicting. Taylor et al showed significant improvement in survival following portal vein infusions of 5-fluorouracil particularly in Dukes’ B lesions. The NSABP conducted a similar, but much larger trial of seven day portal vein infusion of 5-fluorouracil versus no postoperative adjuvant treatment in Dukes’ A, B and C disease. They observed an 8% improvement in survival with intraportal 5-fluorouracil but no reduction in clinically detectable hepatic metastases. The Large Bowel Cancer Project failed to reveal any improvement in survival or incidence of liver metastases with intra-portal 5-fluorouracil and heparin infusion. There is no evidence currently that portal-vein infusion is superior to systemic intravenous administration. The NSABP recently reported a trial designed to evaluate the efficacy of folinic acid-modulated 5-fluorouracil in adjuvant therapy of Dukes’ B and C colon cancer. They found that folinic acid and 5-fluorouracil treatment significantly prolongs disease-free survival with a 32% reduction in mortality risk compared to a control group randomised to receive lomustine, vincristine and 5-fluorouracil. Further evidence that modulated 5-fluorouracil may be beneficial came in a meta-analysis of nine randomised prospective clinical trials with 1381 patients with advanced colorectal cancer; this demonstrated a 23% objective response rate with folinic acid and 5-fluorouracil.

Radiotherapy Trials

The object of adjuvant radiotherapy is to prevent the further growth of cancer cells not removed at the time of surgery. Radiotherapy results in cytotoxicity principally by damaging DNA, thereby interfering with the ability of cells to reproduce. It was initially thought that adjuvant radiotherapy after surgery for rectal cancer would reduce the risk of local recurrence and thereby improve survival rates. The incidence of pelvic recurrence is variable, with figures of 10% to 40% commonly quoted. The risk of recurrence increases with worsening Dukes’ stage. The first site of recurrence found at re-operation is often the general area of the primary cancer and studies have also shown that prevention of recurrence in the area of the primary tumour is associated with a decreased incidence of distant metastase. Pelvic recurrence may be associated with both microscopic extension of tumour to the lateral resection margins and metastases in unresected pelvic wall lymph nodes. The following studies examined the outcome after curative surgery with or without postoperative radiotherapy in Dukes’ B or C colorectal cancer. The Gastrointestinal Tumor Study Group showed a 9% increase in five year survival and 4% reduction in both local and extrapelvic recurrence with adjuvant radiotherapy. The National Surgical Adjuvant Breast and Bowel Project showed a 3% decrease in five year survival, 9% improvement in local recurrence and 5% worsening in extrapelvic recurrence with radiation. The Denmark study showed that radiotherapy caused no change in five year survival, a 2% decrease in local recurrence and a 2% increase in extrapelvic
recurrence. The Netherlands study\textsuperscript{38} showed a 10% decrease in five year survival, 9% improvement in local recurrence and 12% worsening in extrapelvic recurrence. Overall, these studies have shown that radiotherapy as the sole adjuvant therapy, given either pre- or post-operatively, will reduce pelvic recurrence but not markedly influence either survival rates or extrapelvic recurrence.\textsuperscript{29} Reduction in pelvic recurrence is worthwhile as this is often difficult or impossible to control, and symptoms are often severe and result in a very poor quality of life.

**Combined radiotherapy and chemotherapy trials**

The failure of adjuvant chemotherapy to lower pelvic recurrence and of adjuvant radiotherapy to lower extrapelvic recurrence or mortality rates has resulted in establishment of trials of adjuvant combination therapy. The following studies examined the outcome after curative surgery and post-operative radiotherapy with or without chemotherapy in Dukes’ B and C colorectal cancer. The Gastrointestinal Tumor Study Group\textsuperscript{35, 39} trial had five year survivals of 43% with surgery alone, 52% with adjuvant radiotherapy and 59% with combination radiotherapy and chemotherapy. The local recurrence rates were 24%, 20% and 11% respectively and extrapelvic recurrence rates 34%, 30% and 26%. The NCCTG trial\textsuperscript{40} had five year survival of 47% for adjuvant radiotherapy and 58% for adjuvant combination therapy. The local recurrence rates were 25% and 14% respectively, and extrapelvic recurrence rates 46% and 29%. Another study,\textsuperscript{41} however, showed no significant improvement in survival with combination chemotherapy and radiotherapy over one or other of the adjuvant modalities alone. The combinations of radiotherapy and chemotherapy used in the trials described were fairly well tolerated. The risks of serious late morbidity such as enteritis and treatment-related mortality were broadly similar to those of patients treated with radiotherapy alone.

**Conclusion**

Previous trials of adjuvant therapy in colorectal cancer have suggested a modest survival benefit. Recent evidence shows that modulation of 5-fluorouracil with folinic acid results in greater efficacy with acceptable toxicity. We believe that a local, randomised, controlled trial can accrue sufficient patients to allow us to demonstrate whether adjuvant therapy of colorectal cancer using modulated 5-fluorouracil provides worthwhile improvement in survival in this common disease.

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