Adjuvant chemotherapy for stage II colorectal cancer: who should receive therapy and with what?

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Introduction

The article provided by Van Cutsem et al. [1] eloquently demonstrates that there is clear and definitive evidence for the use of adjuvant chemotherapy in stage III colorectal cancer patients after surgery, with a proportional reduction in the odds of dying from colorectal cancer of 25–30% and an absolute survival benefit in the order of 7–12%. A more controversial question has been the efficacy and cost-effectiveness of this treatment in stage II colorectal cancer, where no lymph node metastases are detected. In this review we will discuss the history of adjuvant therapy for stage II disease, explain the shortfalls of previous analyses, and outline the emerging new evidence that may bring some clarity to our decision-making.

History of adjuvant chemotherapy for stage II colorectal cancer: subgroup analysis from single trials

Despite significantly different recurrence and survival rates, most randomised studies to date have recruited both stage II and III patients (see Table 1), often with pre-planned subgroup analyses, in an attempt to determine the efficacy of chemotherapy by stage. For example the intergroup trial (INT-0035 [2]), described in the previous article [1], evaluated both stage II ($n=318$) and stage III ($n=929$) patients. This trial did confirm the benefit of bolus 5-fluorouracil (5-FU)/levamisole (LEV) in stage III colon cancer patients with a 41% reduction in risk of recurrence ($P<0.0001$) and a 33% reduction in mortality ($P=0.006$). However, in the final analysis, despite there being a 31% decreased recurrence rate in the stage II patients, this did not achieve significance ($P=0.10$) [3]. This is likely a consequence of the decreased event rate in this population.

As a result of the INT-0035 trial, the National Institutes of Health (NIH) published a consensus statement suggesting that the bolus 5-FU/LEV combination should be utilised as standard therapy for patients with stage III colon cancer following surgical resection. The UK Kings Fund Forum followed this with a similar recommendation. Clearly there was no statistically significant data from this trial to support the use of adjuvant chemotherapy in stage II disease.

Shortly after this trial, concern was raised about the use of levamisole; its potential to cause allergic reactions and its possible lack of efficacy. In order to test leucovorin (LV) as an alternative 5-FU-modulator, the International Multicentre Pooled Analysis of Colon Cancer Trials (IMPACT) collated data from five individual trials that compared 5-FU/leucovorin

Table 1
Staging and survival of colorectal cancer[a]

TNM system				Approximate 5-year survival (%)	Dukes' classification
Stage	T stage	Lymph nodes (N)	Metastasis (M)		
0	T0	N_0	M_0		
I	T1	N_0	M_0	97	A
	T2	N_0	M_0	90	
II	T3	N_0	M_0	78	B
	T4	N_0	M_0	63	
III	Any T	N_1	M_0	56–66	C
	Any T	N_2	M_0	26–37	
IV	Any T	Any N	M_1	1%	D

[a] T*is*, Carcinoma in situ: T_1 tumour invades sub-mucosa; T_2 tumour invades muscularis propria: T_3 tumour invades through muscularis propria into subserosa, or into nonperitonealised pericolis or perirectal tissues; T_4 tumour directly invades other organs or structures, and/or perforates visceral peritoneum.
N_0: No regional lymph node metastasis; N_1: metastasis in 1–3 regional lymph nodes: N_2: metastasis in 4 or more regional lymph nodes.
M_0: no distant mestastasis; M_1: distant metastasis.

(LV) versus operation alone in stage II ($n=1016$)/ stage III ($n=1487$) colon cancer patients in 1995. They demonstrated that 3-year overall survival (OS) for all stages combined was improved for bolus 5-FU/LV chemotherapy compared with surgery alone (83% versus 78%; $P=0.03$) [4]. However, as for the intergroup study, subsequent analysis of the stage II patients alone ($n=1016$) showed that the 5-year OS was not significantly different with the addition of adjuvant chemotherapy (82% versus 80%), giving a hazard ratio (HR) for death of 0.86 (90% confidence interval (CI): 0.72–1.07; $P=0.13$) [5].

In an attempt to clarify the situation with respect to 5-FU modulation, the intergroup study (INT-0089) randomised 3759 patients (80% stage III and 20% high risk stage II) to various combinations of 5-FU +/– LV +/– LEV. For stage III disease only, the 5-FU/LEV arm (without LV) was inferior, suggesting that LV should be used as the 5-FU modulator and levamisole should no longer be part of the adjuvant schedule. Again, none of the analyses of the small number (approximately 700) of stage II patients showed any significant differences. The paper concluded that 6 months' adjuvant therapy including 5-FU and LV but not LEV should be considered standard for stage III colon cancer [6]. The results of the first part of the Quick and Simple and Reliable (Quasar) trial also confirmed the lack of efficacy of LEV in stage III disease and suggested that low-dose LV is as effective a modulator as high-dose LV [7].

More recently, adjuvant chemotherapy trials in colorectal cancer have concentrated on the use of oral pro-drugs of 5-FU, infusional 5-FU and the integration of the novel agents irinotecan and oxaliplatin.

Results of the X-ACT study were presented at the American Society of Clinical Oncology (ASCO) 2004 meeting. An oral fluoropyrimidine pro-drug, was compared with the bolus 5-FU/LV Mayo regime in the adjuvant treatment of stage III only colon cancer. Capecitabine proved to be at least equivalent to 5-FU/LV with a trend towards superiority in terms of 3-year disease-free survival (DFS) and statistically significantly better results in terms of relapse-free survival. However, this trial did not include any stage II patients, which means that extrapolating capecitabine use into this setting is difficult [8].

Infusional 5-FU regimes have been compared with bolus regimes for efficacy and toxicity profiles. It is postulated that, because the doubling time of colon cancer is slow, with infusional regimes one is likely to kill a greater proportion of cells as they cycle through the S-phase than would be possible with bolus regimes. In addition, because the peak serum concentration of drug is likely to be lower with infusion, some toxicities may be ameliorated. Andre and colleagues [9] randomised 905 stage II (43%) and III (57%) colon cancer patients (in a 2×2 factorial fashion) to semi-monthly LV5FU2 (LV 200 mg/m^2 as a 2-h infusion followed by 400 mg/m^2 bolus 5-FU then 600 mg/m^2 22-h continuous infusion 5-FU, all repeated on day 2), or bolus 5-FU/LV (LV 200 mg/m^2 over 15 min and bolus 5-FU 400 mg/m^2 over 15 min daily for 5 days 4-weekly) and 24 versus 36 weeks of treatment. After 41 months median follow-up there were no significant differences between the regimens or durations in terms of DFS or OS for either stage II or stage III disease, but overall toxicities were significantly decreased in the infusional arms ($P<0.001$) [9]. Similarly, a UK study with 716 stage II (42%) and stage III (58%) patients has suggested equivalent 3-year OS for 12 weeks of protracted infusion of 5-FU (300 mg/m^2/d) and 6 months of bolus 5-FU/LV (Mayo); again with decreased grade 3/4 diarrhoea and stomatitis in the infusional arm [10]. It appears clear from these trials that it is easier to demonstrate no difference between arms when one is looking at stage II disease than it is to detect statistically significant differences.

Finally, the novel agents oxaliplatin (OX) and irinotecan are now being assessed in the adjuvant setting. The MOSAIC trial, published last year, compared 2-weekly infusional 5-FU/LV/OX (FOLFOX) with infusional 5-FU/LV alone (LV5FU2 – deGramont regime) in the adjuvant treatment of 2246 stage II ($n=899$) and III ($n=1347$) colon cancer patients. Final results demonstrate that 3-year DFS (all stages together) is improved with the addition of OX compared with 5-FU/LV alone (78.2% (95%CI: 75.6–80.7) versus 72.9% (95%CI: 70.2–75.7); $P=0.002$) with a relative reduction in risk of recurrence of 23% [11]. However, subgroup analysis did not reveal a statistically significant improvement in DFS for the stage II patients treated with oxaliplatin (HR 0.80; 95%CI: 0.56–1.15) with DFS rates at 3 years follow-up of 87.0% and 84.3%, respectively. This is perhaps again a consequence of the relative lack of events in the stage II patients (67 in the 5-FU/LV-alone arm and 56 in the oxaliplatin arm, in terms of DFS). The 4-year follow-up results, presented at the ASCO-GI meeting in January 2005, showed that the DFS gap for stage II patients had widened a little with 85.1% 4-year DFS in the OX+ arm and 81.3% 4-year DFS in the OX– arm [12]. Perhaps, with further follow-up and more events, this may achieve significance. The most worrying toxicity from oxaliplatin was a 12.4% rate of grade 3 peripheral sensory neuropathy.

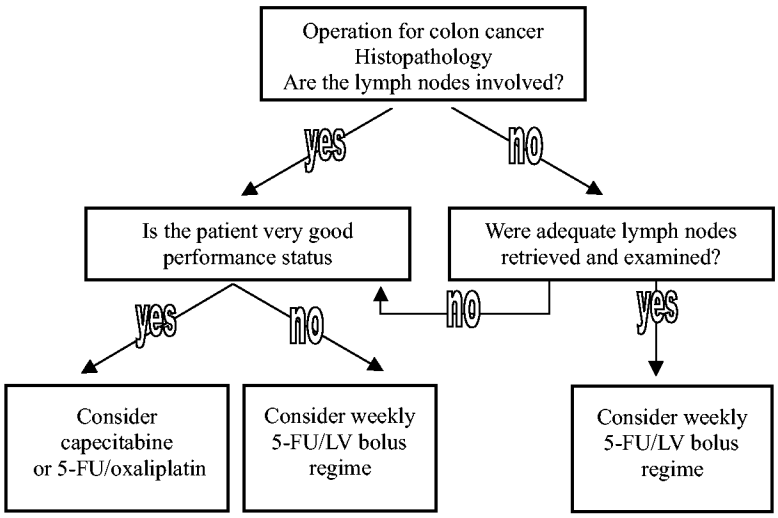

Fig. 1. A possible decision pathway for stage II and stage III colon cancer adjuvant therapy based on current data.

However 12 months after cessation of therapy, the frequency of grade 3 neuropathy had decreased to 1.1%. However this should still remain a strong consideration when making judgements about adjuvant therapy, particularly in patients with stage II disease, the vast majority of which will be cured by surgery alone.

The same promising results have not been repeated so far with irinotecan (IR) combination regimes in the adjuvant setting. An irinotecan/bolus 5-FU combination (the so-called IFL regime) is not recommended because of its high toxicity, excessive treatment-related deaths and lack of evidence of efficacy benefit [13]. Also, preliminary results of trials combining IR with infusional 5-FU (the PETACC-3 study and ACCORD-02) have suggested no statistically significant improvement in DFS [14,15].

In conclusion, the routine use of adjuvant chemotherapy for stage III colorectal cancer is now advocated, as demonstrated in the previous article [1]. The decision about specific regimen/combination of drugs is taken by the individual physician for a particular patient, and is dependent upon a number of factors including age and co-morbidity of the patient, expected toxicity profiles and, in some cases, financial constraints (see Fig. 1 for possible decision paradigm).

Adjuvant chemotherapy for stage II colorectal cancer: pooled analyses from multiple trials

The proportion of new colorectal cancer patients with stage II disease appears to be increasing, possibly as a consequence of screening programmes and better public education. However it is clear that there is still relatively little solid evidence from individual trials to advocate adjuvant chemotherapy for stage II colon cancer. This dilemma has arisen because most trials in the past included and statistically amalgamated stage II and stage III cancers. As we have already demonstrated from the individual trials presented, there are significantly fewer recurrences and deaths among the stage II patients. This means that a far higher number of stage II than stage III patients must be entered into a study to be able to detect a small absolute difference in recurrence or survival to satisfy the *a priori* power calculations. Unfortunately the reverse has generally been true, with stage II patients usually comprising only 20–40% of the total number of patients randomised. This dramatically reduces the probability of demonstrating a clear effect in early stage disease, where absolute benefits are likely to be small.

Because of the difficulties associated with relatively fewer numbers of stage II patients included in individual trials, pooled sub-group analyses of early stage patients from many trials have been attempted. The National Surgical Adjuvant Breast and Bowel Project (NSABP) group were the first authors to collate their data from four separate trials [16]. This was not a true meta-analysis but a relative estimation of the benefits of adjuvant therapy from all of the studies with combination of the best arm of each study compared with the worst. They suggested similar, if not better, proportional reductions in HRs for recurrence and mortality and as great a relative increase in DFS for stage II cancers as those observed for stage III. However, a number of criticisms were

levelled at this analysis, including heterogeneity in the experimental chemotherapy regimes used and a lack of any individual study employing either a 5-FU/LV test arm (felt to be the ' gold standard') or a surgery-alone control arm.

The IMPACT investigators also re-analysed the pooled stage II results from their five adjuvant chemotherapy trials comprising 1016 stage II patients in total, randomised to 5-FU/LV ($n=507$) versus observation ($n=509$). In the 1999 analysis, despite the longer follow-up compared with the earlier analysis [6] they found only a trend towards better outcome in the treated group, with no statistically significant difference between 5-FU/LV treatment and observation, with respect to 5-year OS (HR 0.86, 90%CI: 0.68–1.07) or event-free survival (HR 0.83, 90%CI: 0.72–1.07; $P=0.137$) [17].

Most recently, Gill and colleagues [18] performed a pooled analysis of seven 5-FU-based adjuvant therapy trials for stage II and III colon cancer. In this analysis, all of the trials experimental arms included bolus 5-FU for 6 or 12 months; and modulation either with LV (5 trials) or LEV (2 trials). Overall 51% of the patients received bolus 5-FU-based therapy daily for 5 days, 4-weekly (dose range 340–450 mg/m^2) and 49% had no adjuvant therapy. Numbers randomised into the separate trials ranged from 247 to 926. Of the 3302 patients analysed, 1440 (43.6%) were diagnosed with stage II cancer. In a multivariate analysis, adjuvant therapy produced a beneficial treatment effect across all subsets. However, on univariate analysis, adjuvant treatment did appear to benefit stage III patients to a greater degree than stage II patients. For example, the increase in 5-year DFS for stage II disease patients was 72–76% (an absolute benefit of 4%; $P=0.049$) with chemotherapy compared with surgery alone; whereas stage III patients benefited from an increase in 5-year DFS of 48–65% (if they had 1–4 nodes positive) or 23–40% (for those with 5 or more nodes involved) – an absolute benefit of 17%. The stage II patients did not appear to benefit significantly in terms of 5-year OS (80 versus 81%, $P=0.1127$).

After consideration of all the pooled data presented above, the American Society of Clinical Oncology published recommendations last year that stated that there was ' no evidence for a statistically significant survival benefit from adjuvant chemotherapy for stage II patients and that the routine use of adjuvant chemotherapy for medically fit patients with stage II colon cancer patients was not recommended' [19].

Quasar 1: an appropriately powered single trial for stage II patients

The pooled data presented above are consistent with a trend towards better outcome for stage II patients with adjuvant therapy. However, they are not conclusive as the numbers included in each individual pool are still too small to detect a true benefit for this population. Statisticians have estimated that between 3000 and 4000 patients would have to be randomised in order to provide sufficient power to detect absolute differences in recurrence or survival of 3–4%.

The Quasar 1 trial randomised colorectal cancer patients for whom the indication for adjuvant therapy was uncertain, to receive bolus 5-FU-based adjuvant therapy or observation alone after an R0 colorectal cancer resection (specific 5-FU regimes are detailed in ref. [20]). The exact definition of an uncertain indication was left to the individual clinician' s discretion. However, as presented at ASCO 2004, 92% of the 3239 patients randomised had stage II disease ($n=2980$). Taking all 3239 patients into consideration, 5-year recurrence rates in the treatment versus observation arms were 22.2% and 26.2% respectively (relative risk 0.78; 95%CI: 0.67–0.91; $P=0.001$). Analysing the stage II patients separately, there was a 3–4% absolute improvement in OS at 5 years ($P=0.04$). The conclusion from the presentation was that the benefits derived from inexpensive, well-tolerated bolus 5-FU/LV-based chemotherapy outweigh the inconvenience and cost for medically fit stage II patients [21].

More detailed analysis and longer follow-up will be available on full publication of the Quasar 1 results. However, it is not really conceivable that there will ever be another single data set as large as this, randomising stage II patients between adjuvant chemotherapy and surgery alone. The preliminary results do provide good evidence to support offering stage II patients adjuvant chemotherapy. However, the data should be presented in such a way that allows the patient to weigh up the relative risks and benefits on an individual basis before making any decision to proceed.

Other controversies in stage II colon cancer

Is lymph node retrieval important?

It has long been suspected that patients who are actually lymph node positive may be erroneously classified as stage II because of inadequate lymph node examination [22]. Further evidence to support this

came when Le Voyer and colleagues [23] assessed the relationship between survival and the number of lymph nodes retrieved from the surgical specimen using data from the INT-0089 study. Of 3411 assessable patients, 648 had no evidence of lymph node metastasis. Median number of nodes removed at colectomy was 11 (range 1–87). After controlling for the number of nodes containing cancer on histological examination, survival increased as more nodes were analysed ($P=0.0001$ for OS, DFS and cause-specific survival) irrespective of whether the patients were initially classified as stage II or stage III [23].

A similar, but smaller, study in 301 stage II patients demonstrated that the number of lymph nodes retrieved and examined had a greater impact on prognosis than grade of tumour; and that when less than 11 lymph nodes were examined the relative risk of death was 2.8 (95%CI: 1.6–5.2, $P=0.0008$) compared with patients with more than 11 lymph nodes examined [24].

There are a number of reasons why lymph node retrieval might impact upon survival. First and foremost a greater yield increases the resultant accuracy of our staging and increases the chance of correctly classifying the patient as stage III. In practical terms this means that if a patient has six nodes removed that are all negative he or she would be classified as stage II. In reality however, there is a reasonable chance, when so few nodes are examined, that lymph node metastases have been missed and therefore the natural history of the disease will mirror that seen with stage III patients, with the expected prognosis being adversely affected.

Alternatively, other authors have also suggested that a greater lymph node yield may correlate with superior technical skill of the surgeon (leading to improved outcome), favourable tumour biology and/or an exaggerated host–immune response.

Although no international guidelines exist about the number of lymph nodes that must be examined, these examples indicate that this may be critical for assessment of prognosis and for making stage-defined treatment decisions. Indeed, some proponents suggest that patients with fewer than 12 lymph nodes examined should be automatically upstaged to III and have adjuvant therapy based upon that supposition. However, if we accept that the delineation between stage II and stage III disease is now lessening with respect to our decisions about adjuvant treatment, then one might alternatively propose that examination of lymph nodes is becoming less important and that pathologists should instead concentrate upon other biological features that may be useful in prognostication or in terms of predicting response to therapy.

Should all stage II patients receive adjuvant chemotherapy?

The other controversy surrounding stage II colon cancer adjuvant therapy is which patients should we treat? If we accept that adjuvant chemotherapy can benefit stage II patients (3–4% OS benefit) should all patients be treated or should selection occur? If we are selective, what criteria for treatment should we use? Quasar 1, which is the only single study that has statistically significantly demonstrated a survival advantage, was not prescriptive about the patients recruited. So treatment of all stage II patients could be justified by the data. However, in practical terms this means that in order to cure 3–4 patients, 100 patients would need to be treated, approximately 78 of whom would have been by surgery alone, and 18 of whom will die irrespective of any treatment given. In return, all would be exposed to side-effects and a negative impact on their quality of life. Thus it is natural to ask whether it is possible to use morphological or molecular features to select and individualise therapy for those who might most benefit and avoid treatment for those cured by surgery alone or who are inherently resistant to the therapies available.

A number of basic histopathological features are associated with a poor prognosis. These include T4 tumours, lymphovascular invasion and perineural invasion. In an effort to become ever more sophisticated in our prognostication an abundance of molecular markers has been postulated to affect outcome. These include microsatellite instability [25], tumour DNA-ploidy [26], chromosomal deletions [27], and mutated p53 [28]. However, most studies assessing the importance of such markers have failed to evaluate them in a prospective comprehensive fashion with adequate patient numbers and proper multi-variate analysis. It is extremely difficult to take one marker in isolation and draw sensible conclusions about its impact upon prognosis when many hundreds of other molecular features may also be playing a significant role. Instead of taking a single marker in isolation, new methodologies including gene expression profiling and proteomics may allow a more comprehensive assessment of contributory features or prognostic signatures.

One recent study utilised an Affymetrix U133a gene chip containing approximately 22,000 transcripts, to assess RNA samples from 74 patients with stage II colon cancer. Patients were divided into two groups;

relapse within 3 years of surgery ($n=31$) and disease-free for more than 3 years ($n=43$). Using a multivariate Cox model, gene expression profiling identified a 23-gene signature that predicted recurrence in stage II patients. This signature was then validated in a new set of 36 independent patients, again retrospectively. The overall performance in the second group was 78%, with 13 of 18 relapsed patients and 15 of 18 disease-free patients predicted correctly, giving an odds ratio of recurrence of 13 ($P=0.003$). The authors suggested that the patients with the predicted high risk of relapse (13-fold) could be molecularly upstaged and treatments regarding adjuvant therapy based upon the finding [29].

In order to apply this test in the routine clinical setting, many hundreds or thousands of patients would need to be evaluated prospectively. Furthermore, comparisons with the predictive value of combinations of standard histopathological markers such as those described above would need to be made, in order to fully assess the added value of this complex test. Lastly, cost would need to be considered.

Conclusion

Quasar 1 has added significantly to the data from pooled analyses to support the use of adjuvant chemotherapy in stage II colon cancer. Across all trials a consistent proportional reduction in the odds of recurrence has been demonstrated. However the size of the absolute benefit of adjuvant therapy for stage II patients is small, and therefore consideration should be given to simple, well-tolerated 5-FU/FA regimes. Importantly, none of the trial results to date provide any evidence to promote the use of more aggressive regimes, particularly combination therapies including oxaliplatin or irinotecan, in stage II disease (see Fig. 1). Certainly the low but significant risk of long-term neurotoxicity with oxaliplatin is of real concern in this population. Furthermore, it is important that we do not assume that the promising results with capectabine in stage III disease (X-ACT study) can be extrapolated directly into stage II disease, as again the toxicity profile may preclude acceptability in a setting where the absolute benefits are small.

It is recommended that adjuvant trials planned for the future should incorporate a prospective collection of both tumour tissue and germline DNA. This will allow not only evaluation of prognostic markers, but also assessment of markers predictive for chemotherapeutic response. The final goal should be effective individualised therapy for the least number of patients producing the greatest absolute benefit.

Conflict of interest statement

None declared.

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