



Systemic Treatment for Colorectal Cancer

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Colorectal cancer ranked number two in incidence in both men and women in the year 2004 in Hong Kong, adding up to 3,500 new patients¹. In the same year there were about 1,500 deaths attributable to colorectal cancer.

The age-standardised incidence rate of colorectal cancer in Hong Kong is equal to that of the West. For Hong Kong men the age-standardised incidence rate in 2004 was 46.1/10⁵, for women it was 32.0/10⁵. The same rates for men in North America were 44.4/10⁵ and 32.9/10⁵ respectively. We have reached the same level of incidence as in high risk regions.

The median age of diagnosis for Hong Kong men is 70 and women 71. The fact that these are geriatric patients is a concern. A good performance status and minimal co-morbidities are pre-requisite for both successful surgery and systemic treatment. Balancing the risks and benefits of treatment can be difficult.

Surgery remains the mainstay of treatment of colorectal cancer. Surgery clears the tumour burden, helps avoiding bowel complications (obstruction, perforation) and at the same time provides pathological information. The need for adjuvant chemotherapy is based on the pathological findings.

The risk of relapse is dependent on stage. The two most important factors are the depth of penetration to the bowel wall and the number of lymph nodes involved. Stage I denotes node-negative cancer involving at most the muscle layer. Stage II is node-negative cancer with the primary tumour involving subserosa (T3) or serosa and beyond (T4). Stage III is node-positive cancer. Stage IV denotes distant metastasis. The corresponding 5-year survival rates, without adjuvant treatment, are 90%, 80%, 50% and 10% respectively.

Systemic treatment is divided into two scenarios: adjuvant and metastatic settings. In the adjuvant setting one is using systemic treatment to reduce the risk of relapse and improve survival. In the metastatic setting one is improving quality of life and trying to improve survival. So far adjuvant systemic treatment involves chemotherapy only. Biological agents or targeted therapy remains a research option. In treating metastasis chemotherapy and/or targeted therapy is used.

There is no indication for adjuvant treatment for stage I colorectal cancer after resection. Survival is in the region of 90%.

Stage II

For stage II colorectal cancer there is no indication for adjuvant chemotherapy in general. Most of the time survival rate is in the region of 80%. Adjuvant chemotherapy trials failed to demonstrate a survival benefit.

There are however, categories of high-risk stage II colorectal cancers. The high-risk factors are: T4 tumour, presence of perforation, presence of obstruction, presence of lymphovascular permeation or less than 12 lymph nodes examined.

Of note, the number of lymph nodes identified in the surgical specimen correlates with the prognosis². It was demonstrated that in patients with T3N0 disease and only 1 to 2 nodes identified, the 5-year survival rate is 64%, but when more than 25 negative nodes were identified, the 5-year survival rate increases to 80%. It suggests that without adequate node sampling, patients may be under-staged. It was recommended that the minimum number of nodes for adequate staging is 13. Therefore, if a stage II patient has fewer than 13 negative nodes identified, the clinician is well justified in recommending adjuvant chemotherapy because such a case may be understaged. The AJCC TNM staging manual recommended at least 7-14 nodes be available for pathological examination.

A subset analysis of the MOSAIC trial⁴ demonstrated that high-risk stage II disease derived the same benefit from FOLFOX4 compared with LV5FU2 as unselected stage III patients (4-year DFS of 84.9% versus 79.8%, respectively; hazard ratio, 0.72).

In well-motivated high-risk stage II patients in good performance status, adjuvant chemotherapy should be seriously considered.

Stage III colorectal cancer

Without adjuvant treatment, patients with stage III colorectal cancer face a relapse rate of 50-60% in 5 years. Fluorouracil-based adjuvant chemotherapy reduces the risk by 30%, translating into an absolute reduction of 10%³. Update of the MOSAIC trial comparing FOLFOX4 (oxaliplatin, fluorouracil and folinic acid) to LV5FU2 (fluorouracil and folinic acid) showed that the 6 year survival for stage III was 72.9% vs 68.3%, with a hazard ratio of 0.85.



Choice of adjuvant chemotherapy.

Adjuvant chemotherapy for colorectal cancer evolved a long way (Table 1). It started with single agent fluorouracil. Treatment went on for one year. At some time the antihelminthic levamisole was added but later abandoned. The efficacy of fluorouracil was enhanced by folinic acid. The Mayo clinic regimen of 5 days of bolus injection of fluorouracil and folinic acid every 4 weeks for 6 months became standard for a while. It was associated with toxicities like stomatitis, diarrhoea and alopecia. This was further improved by chromomodulation. With chromomodulation the toxicity was much less.

It was only 10 years later that a new agent was added. Oxaliplatin, when added to chromomodulated fluorouracil and folinic acid, has been shown as the most effective combination chemotherapy in adjuvant treatment (MOSAIC trial⁷) than chromomodulated fluorouracil and folinic acid with an HR of 28%. The drawback is that FOLFOX4 needs to be administered in 3 days every 2 weeks for a total of 12 cycles in 6 months. The repeated hospital admission is inconvenient to both patient and healthcare team. Irinotecan failed to make the adjuvant scene so far.

Modulated fluorouracil-based chemotherapy confers a hazard reduction in relapse by 40% and cancer-specific death by 33%. Oxaliplatin-based treatment⁷ further reduces the relapse risk by about 28%.

The oral variant of fluorouracil, capecitabine, is a valid alternative. The X-ACT trial⁸ shows that single agent capecitabine is at least equivalent to the Mayo Clinic regimen of fluorouracil plus leucovorin in patients younger than 70 years and those 70 years of age or older. The safety advantage of capecitabine over fluorouracil plus leucovorin was also maintained in these subgroups. Capecitabine is taken orally, with a different toxicity profile than intravenous fluorouracil. There is less marrow toxicity, less diarrhoea, less stomatitis and less alopecia with. On the other hand the dose-limiting toxicity is often palmar-plantar erythrodysesthesia. Clinical trials are on-going to evaluate the combination of capecitabine and oxaliplatin, which can be given in a day-case setting.

Currently the practical choice of adjuvant chemotherapy would lie between oxaliplatin-based, which is more effective but more demanding physically and financially; and capecitabine. Oxaliplatin-based regimens include FOLFOX4⁷ and FLOX⁹. These are both combinations of oxaliplatin, fluorouracil and folinic acid in different schedules. Both have been shown to reduce relapse risk by a similar magnitude (HR 25-28%). Capecitabine alone can be given with relative ease, without hospitalisation, and can be better tolerated in those in less favourable performance status or with comorbidities.

| | |
|------|------------------------------------|
| 1990 | 5-FU/lev better than surgery alone |
| 1994 | 5-FU/LV better than surgery alone |
| 1998 | 5-FU/LV better than 5-FU/lev |
| 1998 | 6 months = 12 months |
| 1998 | Levamisole unnecessary |
| 1998 | HDLV = LDLV |
| 1998 | Weekly = monthly |
| 2002 | LV5FU2 = monthly bolus |

Metastatic Colorectal Cancer

Treatment of metastatic colorectal cancer is based on seven drugs (Table 2): fluorouracil, folinic acid, capecitabine, oxaliplatin, irinotecan on one hand, bevacizumab and cetuximab on the other. The optimal combination and sequence of utilisation remains to be defined.

The basic skeleton is fluorouracil plus folinic acid. Either oxaliplatin or irinotecan can be added to this skeleton (FOLFOX or FOLFIRI), with a response rate of around 40% and a response duration of around 8 months. When the cancer progresses one can cross to the other. Capecitabine can replace the fluorouracil - folinic acid infusion, reducing the treatment duration of each session (XELOX or XELIRI).

Bevacizumab and cetuximab, being targeted therapy agents, are now incorporated into the scenario of metastatic colorectal cancer.

Bevacizumab is a chimerised monoclonal antibody against the vascular endothelial growth factor (VEGF). In 2006, the U.S. Food and Drug Administration (FDA) approved bevacizumab administered in combination with FOLFOX4 for the second-line treatment of metastatic carcinoma of the colon or rectum. The most serious, and sometimes fatal, bevacizumab toxicities are gastrointestinal perforation, wound-healing complications, haemorrhage, arterial thromboembolic events, hypertensive crisis, nephrotic syndrome, and congestive heart failure.

Cetuximab is a chimeric mouse-human monoclonal antibody targeting the extracellular domain of the epidermal growth factor receptor (EGFR). Cetuximab in combination with irinotecan has been registered in the USA and Europe for the treatment of patients with metastatic colorectal cancer expressing the EGFR after failure of prior irinotecan-based cytotoxic therapy. Important toxicities of cetuximab include an acneiform skin rash and diarrhoea.

Various phase II studies showed efficacy of either bevacizumab or cetuximab added to the chemotherapy combinations containing oxaliplatin or irinotecan.

It has been demonstrated that with the advent of these new drugs, survival in metastatic colorectal cancer is now in the region of 2-3 years, compared to just one year in the fluorouracil era.

Joining the arena of targeted therapy is Panitumumab, is a fully human monoclonal antibody directed against the epidermal growth factor receptor (EGFR). It was recently approved by the FDA for the treatment of chemotherapy refractory, epidermal growth factor expressing colorectal cancer. It was based on a phase III trial¹⁰ comparing panitumumab plus best supportive care (BSC) to that of BSC. Panitumumab significantly prolonged PFS (HR, 0.54; , [P < .0001]). Median PFS time was 8 weeks for panitumumab and 7.3 weeks for BSC. Mean PFS time was 13.8 weeks for panitumumab and 8.5 weeks for BSC. After a 12-month minimum follow-up, response rates were 10% for panitumumab and 0% for BSC (P < .0001). No difference was observed in



overall survival which was confounded by crossing-over. Panitumumab was well tolerated. Skin toxicities, hypomagnesaemia, and diarrhoea were the most common toxicities observed. No patients had grade 3/4 infusion reactions.

Table 2. Significant phase III trials of chemotherapy for metastatic colorectal cancer.

| Regimen | RR (%) | Median PFS or TTP (mo) | Median OS (mo) |
|---------------------------------------|---------------------|--|--|
| 5-FU/LV IFL (Saltz trial) | 21 39 (P<0.001) | 4.3 7.0 (P=0.004) | 12.6 14.8 (P=0.04) |
| 5-FU/LV FOLFIRI (Douillard trial) | 22 35 (P<0.005) | 4.4 6.7 (P<0.001) | 14.1 17.4 (P=0.031) |
| 5-FU/LV FOLFOX4 (de Gramont trial) | 22 51 (P=0.0001) | 6.2 9.0 (P=0.0003) | 14.7 16.2 (P=0.12) |
| IFL IROX FOLFOX4 (N9741 trial) | 31 35 45 | 6.9 (P=0.0014) 6.5 (P=0.001) 8.7 | 15.0 (P=0.0001) 17.4 (P=0.09) 19.5 |

References

1. Hong Kong Cancer Registry. Incidence and Mortality of Cancer in Hong Kong 2004.
2. GLOBOCAN 2002, International Agency for Research on Cancer.
3. Swanson RS, Compton CC, Stewart AK, et al. The prognosis of T3N0 colorectal cancer is dependent on the number of lymph nodes examined. *Ann Surg Oncol.* 2003;10:65-71.
4. Moertel CG, Fleming TR, Macdonald JS, et al: Levamisole and fluorouracil for adjuvant therapy of resected colorectal carcinoma. *N Engl J Med.* 1990; 322:352-358.
5. Hickish T, Boni C, Navarro M, et al: Stage II patients in the "MOSAIC" trial evaluating oxaliplatin/5-FU/LV as adjuvant treatment of colorectal cancer: A subpopulation analysis. *Ann Oncol* 15:III76, 2004
6. A de Gramont, et al. Oxaliplatin/5FU/LV in adjuvant colorectal cancer: updated efficacy results of the MOSAIC trial, including survival, with a median follow-up of six years. *Proc ASCO* 2007.
7. Andre T, et al. Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colorectal cancer. *N Eng J Med* 2004; 350:2343-2351.
8. Chris Twelves, et al. Capecitabine as Adjuvant Treatment for Stage III Colorectal Cancer. *N Eng J Med* 2005. 352:2696-2704
9. J. Philip Kuebler, et al. Oxaliplatin Combined With Weekly Bolus Fluorouracil and Leucovorin As Surgical Adjuvant Chemotherapy for Stage II and III Colorectal Cancer: Results From NSABP C-07. *Journal of Clinical Oncology.* 2007; 25, (16): 2198-2204.
10. Eric Van Cutsem, et al. Open-Label Phase III Trial of Panitumumab Plus Best Supportive Care Compared With Best Supportive Care Alone in Patients With Chemotherapy-Refractory Metastatic Colorectal Cancer. *Journal of Clinical Oncology,* 2007; 25, (13): 1658-1664