Disease recurrence and survival in node-negative colorectal cancer

A systematic review and meta-analysis show that the molecular detection of tumour cells in regional lymph nodes is associated with an increased risk of disease recurrence and poor survival in patients with node-negative colorectal cancer.

**Overview:** Colorectal cancer is the second most common cause of cancer death in the UK, and the third most common cancer after breast and lung cancer, with approximately 40,000 new cases registered each year.

Occurrence of colorectal cancer is strongly related to age, with almost three-quarters of cases occurring in people aged 65 or over. Around half of people diagnosed with colorectal cancer survive for at least 5 years after diagnosis. However, up to 25% of patients with stages I and II colorectal cancer ultimately die as a result of recurrent disease (Weitz et al. 2005).

**Current advice:** Patients with localised colorectal cancer who present without lymph node or distant metastases (that is, at stages I and II) may be cured by surgical resection alone. Therefore, NICE guidance does not recommend short-course preoperative radiotherapy or chemoradiotherapy to patients with low-risk operable rectal cancer, unless as part of a clinical trial.

**New evidence:** A systematic review with meta-analysis, of 39 studies with a cumulative sample size of 4087 patients, examined whether molecular detection of isolated tumour cells or micrometastases in regional lymph nodes indicates high risk of disease recurrence and poor survival in node-negative colorectal cancer (Rahbari et al. 2012).

The results showed that the molecular detection of tumour cells in regional lymph nodes is associated with an increased risk of disease recurrence and poor survival in patients with node-negative colorectal cancer (hazard ratio 2.20; 95% CI, 1.43 to 3.40).

Pooled analyses of available data revealed a significant association between molecular tumour-cell detection and the long-term outcome of patients.

The prognostic value of molecular tumour-cell detection was shown to be independent of the applied detection method, molecular target, and number of retrieved lymph nodes. The researchers suggested that molecular or cellular biomarkers may be used to tailor adjuvant chemotherapy in patients with node-negative disease. However, more research is needed.

**Commentary:** "Evidence shows that adjuvant post-operative chemotherapy provides a survival advantage for patients that have had a node-positive colon cancer excised (Dukes’ C / stage III). It is also clear that the only proven options for these patients are either a combination of oxaliplatin and a fluoropyrimidine such as 5-fluorouracil or a single agent fluoropyrimidine such as capecitabine. However, the case is not as straightforward for patients with node negative cancers (Dukes B / Stage II). The final results of the MOSAIC trial comparing oxaliplatin and 5FU (FOLFOX4) and just 5FU (LV5FU2) did not show an overall survival at 6 years in the stage II population when oxaliplatin was added. However, this study included all stage II cancers whatever their risk factors."
“The NICE guidance from November 2011 (CG131) states that we should ‘consider adjuvant chemotherapy after surgery for patients with high-risk stage II colon cancer’. The ongoing SCOT trial comparing 3 and 6 months of oxaliplatin-based chemotherapy does allow entry of patients with high-risk stage II tumours and defines them as having 'T4 disease, tumour perforation, obstruction, <10 nodes examined, poorly differentiated histology or extramural venous/lymphatic invasion'. But do these stage II patients truly have negative lymph nodes?

“The meta-analysis by Rahbari et al. showed that occult tumour cells were found in 25–50% of such patients when immunohistochemistry (mainly for cytokeratins) or RT-PCR was used. These patients subsequently had an increased risk of disease recurrence and worse overall survival. Interestingly the prognostic value of ‘molecular detection’ was independent of lymph node count. This could be advantageous since less than 12 lymph nodes are often retrieved from surgical specimens. Both of these techniques are very feasible and reverse transcriptase polymerase chain reaction in particular would allow high-throughput screening at a reasonable cost. We are therefore a little closer to defining which patients are definitely at high-risk and all we need now is a better therapy to treat them with! This sort of question would have to be answered as part of a prospective randomised trial.” – Mark Saunders, Consultant Oncologist with specialty in gastro-intestinal malignancies, The Christie Hospital, Manchester