Reviewer's report

Title: Metachronous metastases- and survival-analysis show prognostic importance of lymphadenectomy for colon carcinomas

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Reviewer: Karl Sondenaa

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The major issue in this study is if lymph nodes make mets. That may seem a bit odd because mets kill patients, being the major disadvantage of cancer. If the statistics show a discrepancy between mets and survival variables the authors should offer an explanation under Discussion since the statistical models are fundamental in the explanation of the findings in this study. E.g. N-category and UICC stage were not significant for survival, only mets. Most other studies would report that TNM stage is a major prognostic factor for overall survival (OS). May the influence of age and sex point to other explanations for poor outcome? OS certainly has shortcomings when it comes to a proper understanding of factors that are important for survival. Relative survival and cancer specific survival may contribute to a better analysis.

The authors have found that N+ was important for mets (p. 12) but not survival (p13), and in the last paragraph they conclude they conclude that a standard dissection of lymph nodes can be defended until proven otherwise. Do they mean then that distant mets are not important for survival or that other factors than N+ are important to the metastastic process?

Several studies have considered if a radical lymph node dissection (high tie or D3) is of benefit in TNM II patients. However, in stage III not only increased survival is an aim but also reduction of local recurrence. At least in that respect it makes sense in stage III patients. Several centers now adhere to the policy of radical, complete mesocolic excision (dissection) (CME) and removal of apical lymph nodes and they have reported improved results. A discussion of this would therefore seem appropriate.

Rather than focus on number of lymph nodes that may depend on several factors, and may be seen only as a surrogate measure of radicality, an emphasis on the importance of CME is warranted.

Many things in medicine are hard to prove and there are believers and non-believers. The authors should explain why they think it is important to demonstrate that lymph nodes may be or not be the origin of distant mets. The main problem is rather if removal of lymph nodes without mets have an impact on the disease development. In this respect I think the discussion is a bit skewed. In my opinion mets occur early as an inherent capacity of the main tumour although most with distant mets also have lymph node mets. To prove a connection would perhaps need more indepth studies. What goes on in all stages
in the mesocolic lymph nodes in the draining area of tumours?

The so-called upstaging has not been proven as long as an adequate number of lymph nodes are removed. In fact, many reports include at most 45% TNM III in any cohort and on average 3-4 positive lymph nodes per specimen no matter how hard they search for mets.

T should be called category, not stage.

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.

**Declaration of competing interests:**

My own interest in the field of colon cancer is associated with a research project of the utility of CME and radical lymph node dissection, see below:


Sundlisæter E, Røsland GV, Sakariassen PØ, Almaas B, Dicko A, Søndenaa K. Elevated lymphatic vascular density is established prior to Stage II colorectal cancers, and FGF-2 is down-regulated in tumour tissue. APMIS 2009; 117; 212-221.

Storli K, Lindboe CF, Kristoffersen C, Kleiven K, Søndenaa K. Lymph node harvest in colon cancer specimens depend on tumour factors, patients and doctors but foremost on specimen handling. APMIS 2011; 119 (2): 127-134.


