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ScienceDirect

EJSO 40 (2014) 747–755

EJSO the Journal of Cancer Surgery

www.ejso.com

Excellent prognosis of node negative patients after sentinel node procedure in colon carcinoma: A 5-year follow-up study

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Accepted 5 October 2013
Available online 23 October 2013

Abstract

Aim: Investigate the prognostic impact and clinical relevance of the sentinel node (SN)-procedure in colon carcinoma.
Patients and methods: Between May 2002 and January 2004, the SN-procedure was performed in 55 patients that underwent elective resection for clinically non-advanced colon carcinoma. A control group of 110 patients was identified from a cohort between January 2000 and April 2002. All lymph nodes were analysed by conventional haematoxylin–eosin staining. All negative SNs underwent in-depth analysis using immunohistochemical-staining and automated microscopy with the Ariol-system. Patients with positive lymph nodes were offered adjuvant chemotherapy. All patients were routinely monitored at 6-month intervals and follow-up was more than 5 years.
Results: The SN was successfully identified in 98% of the patients, with 94% sensitivity. In-depth analysis with immunohistochemistry and automated microscopy (Ariol-system) upstaged 3 and 4 patients respectively. When only node-negative patients were analysed, overall 5-year-survival was significantly better in the SN group (91% vs. 76%, $p = 0.04$). Cancer-specific-mortality was even 0% (vs. 8%, $p = 0.08$). Disease-free-survival was significantly improved to 96% (vs. 77%, $p < 0.01$).
Conclusions: This study describes the prognostic impact of the SN-procedure in colon carcinoma after 5-year-follow-up. Only one patient had recurrent disease after a negative SN procedure (disease-free-survival 96%). These results indicate that the SN-procedure is of prognostic relevance and might be useful to select patients for adjuvant chemotherapy. Patients that are lymph node negative after an SN-procedure have an excellent prognosis and do not need adjuvant treatment.

Keywords: Colorectal neoplasms; Colonic neoplasms; Sentinel lymph node biopsy; Lymphatic metastasis; Neoplasm staging; Follow-up studies

Introduction

The presence of lymph node (LN) metastases in colon carcinoma is one of the most important prognostic factors for disease recurrence and survival. About 25% of patients with stage II colon carcinoma develop recurrent disease.[1,2] Even with current improved adjuvant treatment including oxaliplatin, 16% of patients have a relapse.[3] It is most likely that standard pathological examination misses clinically relevant occult (micro)metastases.

Accurate lymphatic staging is important since it has been shown that patients with evident LN metastases will benefit from adjuvant chemotherapy.[3,4] However, adjuvant chemotherapy in patients without evidence of LN metastases remains debatable, and has been shown less beneficial with high numbers-needed-to-treat.[2,3,5] This raises the question whether it would be possible to improve lymphatic staging to better

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http://dx.doi.org/10.1016/j.ejso.2013.10.003

identify which patients might benefit from adjuvant chemotherapy.

Various techniques have been investigated to improve LN-staging. Using fat clearance techniques it is possible to increase the number of identified LNs to 58 per specimen.[6] Others tried to improve pathological examination itself by using techniques for in-depth analysis of the LNs by multi-sectioning, immunohistochemical (IHC)-staining or RT-PCR.[7–12] Several groups showed improved prognosis of the node-negative-group, but these techniques are expensive and very labour intensive and therefore have not become widely accepted.

A technique for automated analysis (Ariol-system) of multiple sections was introduced in our institute, making in-depth analysis more applicable.[13] Digitally acquired images from multiple sections are automatically analysed for IHC-stained tissue, whereupon only few sections need to be confirmed by conventional microscopy.

The sentinel node (SN)-procedure may facilitate pathologic examination, while only one or few nodes need in-depth analysis. Many studies have shown its technical feasibility in colon carcinoma with upstaging by the detection of (micro)metastases.[14–19] However, there is a lack of follow-up studies to prove its clinical significance.[10,19–23]

Currently, there are only two follow-up studies about the SN-procedure in colorectal carcinoma.[11,24] Bilchik describes 25 months follow-up of 141 patients. Twelve patients had recurrent disease. Ten recurrences were in patients with micrometastasis in the SN, the other two were in patients without micrometastasis in the SN. These last two patients had rectal carcinoma in which the SN-technique is less accurate.[25,26] None of the patients with colon carcinoma and a negative SN had recurrent disease. A recent study by Sirop briefly refers to a cohort of 109 patients; 5-year-cancer-specific-survival of the 62 node-negative patients was 96.2%. However, there were no numbers on recurrent disease. Interestingly, all patients with micrometastasis in the SN received adjuvant chemotherapy. None of these 14 patients had recurrent disease.

In 2002 we introduced the SN-technique in patients with colorectal carcinoma. Interim analysis showed the feasibility of the technique in colon carcinoma,[17] but also showed it was not reliable in rectal carcinoma.[25] This is the first 5-year-follow-up study of the SN-procedure in colon carcinoma. By comparing the results with a control-group we show the potential clinical impact of the SN-procedure for patients with colon carcinoma.

Patients and methods

Patients and operation

Between May 2002 and January 2004, all patients who underwent elective resection for primary colon carcinoma were included in the study. Exclusion criteria were: distant metastases or gross invasion of other organs, clinically obvious LN metastases at operation (multiple large and/or firm nodes), and multiple synchronous colon carcinomas.

After thorough examination of patient charts and operative reports from all consecutive patients operated for colon carcinoma between January 2000 and April 2002, we identified a control-group using the same in- and exclusion criteria as applied for the SN-group.

All patients underwent an oncological resection, including en-bloc resection of the mesocolon of the corresponding vascular trunk.

Sentinel node procedure

In the first 20 patients we used an 'ex-vivo'-technique; after resection the colon was opened at the antimesenteric border and 1–2 ml of Patent Blue V (Guerbet laboratories, Aulnay-Sous-Bois, France) was injected peritumourally in the submucosal layer. In the latter 35 patients an 'in-vivo'-technique was used, this to identify potential aberrant lymphatic drainage[27–29]; Patent Blue V was injected peritumourally in the subserosal layer during operation. In both techniques lymphatics stained blue within few minutes and the first 1–4 blue LNs were categorized as SNs, and marked with a suture. The fresh specimen was sent for pathological examination.

Pathologic examination

In the SN-group, all LNs (non-SNs and SNs) were analysed by conventional haematoxylin–eosin (HE)-staining. LNs <0.5 cm were embedded whole, 0.5–1.0 cm were bisected, and >1.0 cm were cut at 0.3 cm intervals. One section of each level was analysed. If the SN was negative for metastases, serial sectioning was performed at 500 μm intervals. At each level one section was HE-stained and an adjacent section was IHC-stained against cytokeratin AE1/AE3 (Dako, Glostrup, Denmark) to reveal micrometastases. Metastases were described using the criteria applied in breast cancer[30]; tumour cell deposits 0.2–2.0 mm were referred to as micrometastases and <0.2 mm as isolated tumour cells (ITC).

All SNs negative by HE-staining were analysed using automated microscopy on the Ariol-SL50 (Applied Imaging, a Genetix Company). This procedure has been described previously.[13] In brief; all sections, previously analysed by IHC-staining against cytokeratin AE1/AE3, were automatically re-analysed with 50 slides at-the-time, using this Ariol-system. Based on our previous experiments with the Ariol-system, single IHC-stained cells were scored but counted as negative, whereas groups of two or more adjacent cells were regarded as positive for IHC.[13]

In the control-group, a standard pathological examination was performed with HE-staining at one level of all LNs.

Adjuvant chemotherapy

According to clinical guidelines at that time, all patients with LN metastases on conventional HE-staining, younger