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Prognostic implications of occult nodal tumour cells in stage I and II colon cancer: The correlation between micrometastasis and disease recurrence

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Abstract

Introduction: Occult nodal tumour cells should be categorised as micrometastasis (MMs) and isolated tumour cells (ITCs). A recent meta-analysis demonstrated that MMs, but not ITCs, are prognostic for disease recurrence in patients with stage I/II colon cancer.
Aims & methods: The objective of this retrospective multicenter study was to correlate MMs and ITCs to characteristics of the primary tumour, and to determine their prognostic value in patients with stage I/II colon cancer.
Results: One hundred ninety two patients were included in the study with a median follow up of 46 month (IQR 33–81 months). MMs were found in eight patients (4.2%), ITCs in 37 (19.3%) and occult tumour cells were absent in 147 patients (76.6%). Between these groups, tumour differentiation and venous or lymphatic invasion was equally distributed. Advanced stage (pT3/pT4) was found in 66.0% of patients without occult tumour cells (97/147), 72.9% of patients with ITCs (27/37), and 100% in patients with MMs (8/8), although this was a non-significant trend. Patients with MMs showed a significantly reduced 3 year-disease free survival compared to patients with ITCs or patients without occult tumour cells (75.0% versus 88.0% and 94.8%, respectively, $p = 0.005$). When adjusted for T-stage, MMs independently predicted recurrence of cancer (OR 7.6 95% CI 1.5–37.4, $p = 0.012$).
Conclusion: In this study, the incidence of MMs and ITCs in patients with stage I/II colon cancer was 4.2% and 19.3%, respectively. MMs were associated with an reduced 3 year disease free survival rate, but ITCs were not.
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Keywords: Coloncancer; Occult tumour cells; Micrometastasis; Lymph nodes

Introduction

Occult nodal tumour cells are associated with an increased risk of disease recurrence in patients with stage I/II colorectal cancer (CRC).[1,2] According to the guidelines for TNM staging, occult tumour cells should be categorised

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into micrometastasis (MMs) and isolated tumour cells (ITC's).[3] Reported detection rates for occult tumour cells vary between 17% and 62% but studies which discriminate between MMs and ITCs are scarce.[1] However, little is known about the clinical implications of occult nodal tumour cells in patients with stage I/II CRC.

A recent meta-analysis showed that the odds of disease recurrence in patients with stage I/II colon cancer was significantly increased in the presence of MMs.[1] The presence of ITCs did not result in an increase odds of disease recurrence.[1] It is unclear whether detection of MMs or ITCs is correlated to other conventional risk factors such as tumour stage, differentiation, lymphatic invasion or extramural venous invasion.[4] The aim of this retrospective multicentre study was to investigate the incidence of MMs and ITCs in the sentinel lymph nodes of patients with stage I/II colon cancer. In addition, we studied how occult nodal tumour cells correlate to conventional histopathological findings, and analysed the prognostic value of MMs and ITCs for disease recurrence.

Methods

Patient selection

Patients with stage I/II colon cancer were identified from two hospitals. Patients from the Jeroen Bosch Hospital (JBH), 's-Hertogenbosch, were identified from a non-consecutive prospective cohort with patient registration between September 2010 and April 2013. Patients from the Gelre Hospital (GH), Apeldoorn, were identified from a consecutive prospective database with patient registration from November 2006 up until April 2013. Patients after elective resection for colon cancer were included in the study. Patients with macroscopic nodal metastasis (stage III) or with distant metastasis (stage IV) were excluded.

Detection of occult tumour cells in lymph nodes

Sentinel lymph nodes were marked after injection of 0.5–2.0 ml patent blue in the freshly resected specimen. The first one to four lymph nodes that had absorbed the blue dye were defined as sentinel lymph nodes, and MMs and ITCs were classified according to the 6th TNM edition.[5,6]

In patients from the JBH, three sentinel nodes were identified by the pathologist during routine examination of the specimen as described by Vogelaar et al.[7] All harvested lymph nodes were examined and additional staining was performed on the sentinel nodes if micrometastasis were absent in the routine H&E staining. Sentinel nodes were stained with pan-cytokeratin after multilevel sectioning at four levels with a 250 μm interval.

In patients from the GH, the sentinel node was identified by the surgeon and either dissected or marked with a suture. Further examination of the specimen was performed at the pathology department. All harvested lymph nodes were examined and additional staining was performed on all sentinel nodes if micrometastasis were absent in routine H&E staining. Sentinel nodes were stained with monoclonal antibodies for Ber-EP4, anti-CK20, anti-Cam5.2 or CK8/18 after multilevel sectioning at three levels with a 500 μm interval.[5] For the purpose of this study, only the Cam5.2 staining (against cytokeratin 8) or CK8/18 were used to identify MMs and ITCs.

Slides were retrospectively reviewed by pathologists from the GH and the JBH without knowledge of the clinical data (HD and JCL). Final decision on classifying occult nodal tumour cells as MMs or ITCs was made in consensus between pathologists.

Histopathological features of the primary tumour

Pathological investigation of the resected specimens was performed according to the local protocol. Histopathological features of the primary tumour were retrospectively obtained from pathology reports. Data extraction was blinded for findings in the sentinel node or the oncological outcome of patients.

Adjuvant treatment

Adjuvant chemotherapy was considered in high risk stage II patients. According to the Dutch guidelines, staging was defined according to the fifth edition of the TNM classification (1997).[8] In this edition, metastatic lesions smaller than 2 mm were not considered relevant for nodal upstaging. High risk factors were defined as pathological (p)T4 stage, poor differentiation, perforation or obstruction, harvest of less than 10 lymph nodes and/or angioinvasive growth.[9]

Follow-up

Survival data were obtained from clinical charts. Disease recurrence was defined as locally recurrent or distant metastatic disease, based on computed tomography or biopsy. The follow up of patients was organised according to the Dutch guidelines for non-metastasised colon cancer; at 3–6-month-intervals for 2–3 years after surgery, and annually for up to five years after surgery.[9] Ultrasound of the liver or abdominal computed tomography were offered every 6 months the first two years after surgery, than annually up to five years after surgery. After 2–3 years, a colonoscopy was scheduled.

Statistical analysis

Data was analysed using IBM SPSS Software, PASW Statistics version 18.0. Categorical variables were analysed using Pearson χ^2 test and Fisher's exact test. Continuous data was analysed with Kruskal–Wallis non-parametric

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