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Review

The prognostic value of micrometastases and isolated tumour cells in histologically negative lymph nodes of patients with colorectal cancer: A systematic review and meta-analysis

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Abstract

Introduction: Detection of occult tumour cells in lymph nodes of patients with stage I/II colorectal cancer is associated with decreased survival. However, according to recent guidelines, occult tumour cells should be categorised in micrometastases (MMs) and isolated tumour cells (ITCs). This meta-analysis evaluates the prognostic value of MMs and of ITCs, separately.
Methods: PubMed, Embase, Biosis and the World Health Organization International Trials Registry Platform were searched for papers published until April 2013. Studies on the prognostic value of MMs and ITCs in lymph nodes of stage I/II colorectal cancer patients were included. Odds ratios (ORs) for the development of disease recurrence were calculated to analyse the predictive value of MMs and ITCs.
Results: From five papers, ORs for disease recurrence could be calculated for MMs and ITCs separately. In patients with colorectal cancer, disease recurrence was significantly increased in the presence of MMs in comparison with absent occult tumour cells (OR 5.63; 95%CI 2.4–13.13). This was even more pronounced in patients with colon cancer (OR 7.25 95%CI 1.82–28.97). In contrast, disease recurrence was not increased in the presence of ITCs (OR 1.00 95%CI 0.53–1.88).
Conclusion: Patients with stage I/II colorectal cancer and MMs have a worse prognosis than patients without occult tumour cells. However, ITCs do not have a predictive value. The distinction between ITCs and MMs should be made if the detection of occult tumour cells is incorporated in the clinical decision for adjuvant treatment.

Keywords: Colorectal neoplasm; Staging; Occult tumour cells; Lymph nodes

Introduction

For patients with colorectal cancer, Tumour Node Metastasis (TNM) staging is the most valuable provider of prognostic information. Guidelines for TNM staging are provided by the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC). These guidelines are continuously updated, based on ongoing expert review of existing data. The predictive accuracy of TNM staging continues to increase with incorporation of additional prognostic features. Identification of such prognostic features is especially critical for patients with stage II colorectal cancer, to identify patients that might not be cured by surgery alone.[1]

Ever since reports are being published about the molecular detection of occult tumour cells in lymph nodes of stage I/II colorectal cancer patients, the prognostic features of these cells are debated. It is estimated that only a very small percentage of circulating tumour cells (<0.05%)

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survives to initiate a metastatic focus.[2] Additionally, the formation of a metastasis is a complex process.[3,4] Micrometastases (MMs) can only develop if there has been arrest, implantation and proliferation of isolated tumour cells (ITCs) in the organ involved.[5] For these reasons, the AJCC and IUCC guidelines suggested since 2002 to distinguish MMs from ITCs. MMs were considered a reason for nodal upstaging, whereas ITCs were not. However, the cut of point for distinction was chosen fairly random, and there was no evidence to support the suggested difference in prognostic value. Moreover, the significance of nodal occult tumour cells as a group was still controversial at that time.[6]

Changes in TNM staging based on postulations have raised concerns because some of these unfounded changes have been withdrawn in subsequent revisions. Gastrointestinal pathologists currently debate whether the recommendations concerning occult tumour cells should be incorporated into the TNM classifications.[7] Rahbari et al. demonstrated in a recent meta-analysis that molecular detection of occult tumour cells in lymph nodes of stage I/II colorectal cancer patients is indeed associated with disease recurrence and poor survival.[8] Unfortunately, only a minority of the included studies distinguished MMs from ITCs and a subgroup analysis to validate the prognostic features of MMs and ITCs separately was not possible. Therefore, the evidence for the downstaging of ITCs and upstaging of MMs remained controversial.

We hypothesized that a systematic search for additional publications one year later could be decisive in the clinically relevant validation of the prognostic features of MMs and ITCs.

Patients and methods

Search strategy and selection criteria

A literature search was independently performed by two researchers (D.S and S.S) and a clinical librarian in April 2013. The following databases were searched: Medline, Embase, Biosis and the WHO International Trials Registry Platform (ICTRP). The following keywords were used in various forms and combinations: colorectal neoplasms (Mesh), occult tumour cell, isolated tumour cell, micrometastasis, lymph node, cancer, tumour, carcinoma, adenocarcinoma, colon, colonic, colorectal, rectal, mesorectal, rectoanal, anorectal, rectum, procto, sigmoid. An example of how the search criteria were applied is provided in Supplement I.

We included all studies that evaluated the prognostic significance of occult tumour cells (MMs/ITCs) in patients who underwent curative resection for stage I/II colorectal cancer. The detection technique of interest was immunohistochemistry (IHC), since this qualitative analysis allows histological confirmation and sub classification of small volume lesions. Studies that reported solely on RT-PCR technique or detection of occult tumour cells in tissue other than lymph nodes were excluded. Original articles were considered relevant if endpoints were described as event rates or hazard ratios (HRs) for disease free survival (DFS), disease specific survival (DSS) or overall survival (OS). Descriptive studies that did not report survival data, abstracts, studies that were not published in peer-reviewed journals, or studies that were published in a different language than English were excluded. In case of overlapping cohorts, the most informative manuscript was included. The reference list of retrieved papers was reviewed to identify additional relevant publications. Articles were considered relevant for meta-analysis if detection rates and endpoint were specified for MMs and ITCs.

Assessment of study quality

To assess the risk of bias and the concern of applicability of selected publications, we used the QUADAS-2 quality rating system for diagnostic studies. We complemented this established rating system with recommendations for the evaluation of prognostic studies by Hayden et al.[9] For each publication the following domains were independently evaluated by two reviewers: patient selection, use of the reference, detection of the prognostic, measurement of confounding, outcome measurement, and analysis. The risk of bias and concern of applicability was scored as: high, low or uncertain. A final judgement was made in consensus.

Data extraction

The following data were independently extracted from included studies by two reviewers: study characteristics (first author, publication date, study design, study period, size of the study group, detection techniques, antigen marker, classification of detected tumour cells), baseline characteristics of included patients (age, male/female ratio, tumour site, tumour stage, number of lymph nodes retrieved, use of adjuvant therapy, duration of follow up), occult tumour cell detection rate with subdivision in MMs and ITCs and corresponding outcomes (DFS, DSS, OS, event rate for disease recurrence, disease specific mortality and overall mortality). Disagreement was resolved by discussion between the reviewers.

Descriptive statistics and meta-analysis

Descriptive analyses were performed in SPSS version 19.0 (SPSS Inc., Chicago IL). The interquartile range (IQR) or the standard deviation (SD) was provided, when informative, for the interpretation of medians and means, respectively.

The meta-analysis was limited to a pooled analysis of the OR for disease recurrence. Calculations for ORs were independently performed by two reviewers. In case of discordance, a statistician was consulted to achieve consensus. Extracted ORs for disease recurrence were pooled using the generic inverse-variance method in Review Manager (version 5.0). A pooled OR greater than