Chapter 8

CLINICAL RELEVANCE OF TUMOR CELL DISSEMINATION IN COLORECTAL, GASTRIC AND PANCREATIC CARCINOMA

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Abstract

Metastatic spread is a major factor in the prognosis of cancer patients. Early detection and eradication of circulating tumor cells prior to the development of metastases could help to improve the outcome of patients after tumor resection. Disseminated tumor cells have been detected in different compartments of the body using cytological and immunostaining methods and, more recently, using different molecular biological techniques. However, the specificity and the sensitivity of the methods and their prognostic impact are still being debated. This chapter gives an overview over the published studies regarding the prognostic relevance of the detection of disseminated tumor cells in lymph nodes, bone marrow, blood and peritoneal cavity in colorectal, gastric and pancreatic carcinoma patients.

INTRODUCTION

Although the mortality of patients with gastrointestinal carcinoma has been reduced in recent years by (i) early tumor detection, (ii) improved local surgical treatment (1) and (iii) multimodal therapeutic concepts (2), the survival rates of patients are still very unsatisfactory. Haematogeneous dissemination of tumor cells with subsequent development of distant metastases are the main reasons for recurrence in colorectal carcinoma; local recurrence and peritoneal seeding play a more important role in gastric and pancreatic carcinomas.

After curative resection of the primary tumor, the further therapeutic steps are guided by the staging of the primary tumor. The spread in the lymph nodes remains the most important available prognostic indicator so far. But immunohistochemical and molecular-based analyses could demonstrate that micrometastases and often disseminated single tumor cells can be found in patients with histologically negative lymph nodes (Tables 1, 4, 8).

Disseminated tumor cells can also be detected in gastrointestinal carcinoma patients in other compartments like bone marrow, venous blood, the peritoneal

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cavity and other body fluids (urine or pancreatic juice) or in liver biopsies at times conventional staging could not detect residual disease. Therefore, detection of this minimal residual disease will improve the tumor staging and may help to predict prognosis and guide therapeutic decisions (Tables 1–12).

The UICC decided in 2002 that a finding of disseminated tumor cells should not be considered in the TNM-classification. For future evaluation of their prognostic significance it was recommended to document the findings to uniform criteria. As reasons for this restrictive position differences in methodology and non-standardized techniques have been stated (3). However, this criticism also holds true for many so-called conventional staging procedures.

In cases of morphologic examination for isolated tumor cells in lymphatic nodes, the UICC suggest adding the result of these examinations in parentheses, with 'i' as symbol and for non-morphologic examinations the symbol 'mol' (for molecular) accompanied by '+' or '−' for positive or negative results after the N-stage. Disseminated tumor cells in bone marrow, blood, peritoneal washings or other specimens should be added in the same form after the M-stage, including information about the specimen analyzed (3).

The detection of disseminated tumor cells depends on a number of steps, including collection and treatment of the sample, cell separation protocol, chosen antibodies, number of analyzed cells, and evaluation techniques. Although the sensitivity of all different assays varies between 1 tumor cell in 10^6 and 10^7 mononuclear cells (4–9), the detection rate in an individual patient depends on the amount of cells investigated. It has been demonstrated, that multiple samples taken from different sides (for example, bone marrow from the right and left iliac crest) result in higher detection rates compared to one sample (10).

All methods used relay on the recognition of antigens or gene transcripts that are specifically expressed by tumor cells and not by surrounding cells. The great variability in antigenic expression (heterogeneity) between the disseminated tumor cells derived from the primary tumor (11) can, therefore, result in a downregulation or loss of an antigen expression that can be observed in the primary tumor (12–14). For some of the used markers (PSA, mucins) a modulation by hormonal influences has been demonstrated (15, 16).

Irrespective of the methods (immunostaining or RT-PCR), false positive results could also occur due to contamination with skin cells or release of epithelial cells in benign proliferative diseases as far as epithelial markes have been used (6, 17–19; see Tables 1–12); false negative results may occur due to losses of tumor cells during isolation of mononuclear cells (20, 21). PCR-reactions with multiple markers may overcome tumor cell heterogeneity and false positive results. This strategy would also increase sensitivity and specificity of the test.

The enrichment of tumor cells, e.g., by magnetic beads, may improve the results by reducing the background (22–24). However, this procedure is hampered by the heterogeneity in antigen expression of disseminated tumor cells. Further studies will also focus on (semi)-quantitative RT-PCR which allows