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Clinical consequences of node negative being positive in breast cancer

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Axillary lymph node metastases of breast cancer of the same side are the most significant prognostic indicator for patients with operable disease, yet the clinical relevance of micrometastases in these lymph nodes is uncertain. Previous studies indicated that axillary lymph node metastases less than 2 mm in diameter are associated with a favorable outcome compared with the node-positive, and with similar outcome compared with node-negative disease. In contrast, some retrospective studies on patients primarily identified as having node-negative disease and subsequently found to have axillary micrometastases, showed an inreased recurrence rate in the latter compared with "true" node-negative status. The prognostic value of micrometastatic disease in sentinel lymph node mapping, of the size of micrometastases (isolated tumor cells or larger) and of the application of highly sensitive immunohistochemical staining, is presently unclear. We retrospectively evaluated adjuvant treatment recommendations on 4195 consecutive patients with first diagnosis of invasive breast cancer (any pT, pN0-N1 and M0), referred to the Division of Medical Oncology after performed surgery at the European Institute of Oncology from April 1997 to September 2002, to evaluate if treatment decision was influenced by the degree of nodal involvement. A total of 3076 patients were classified pN0 (or pNSent neg), 477 had pN1a, and 642 pN1≥bi (AJCC TNM 5th edition). Patients with pN1≥bi disease (compared with patients with micrometastatic and node-negative disease) were prescribed more anthracycline containing chemotherapy (52.6% vs 35.7% vs 7.2% respectively, p<.001) and were less likely to receive endocrine therapy alone (22.4% vs 39.5% vs 55% respectively, p <.001). Axillary lymph node micrometastasis in breast cancer remains a subject for research. Treatment recommendations for patient care should take into consideration estimation of the degree of risk together with assessment of endocrine responsiveness of the tumor and patient's preferences.

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Minimal tumour cell involvement in lymph nodes in GI-and NSCL cancer

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The incidence of local relapse after complete (R 0) resection of solid tumors is largely determined by the skill of the surgeon, whereas distant disease is due to tumor biology. The presence of individual disseminated tumor cells - e.g., in bone marrow and lymph nodes as indicator organs - can be detected by sensitive immunocytochemical and molecular methods and is increasingly considered as clinically relevant and independent prognostic factor. The intention of an adjuvant therapy is the elimination of such occult tumor cells before these cells can establish clinically overt metastases. Therefore an early detection of such micrometastatic cells could identify a group of patients with a high risk of tumor relapse, who might benefit from such therapeutic regimen. Compared to solid metastases, isolated micrometastatic tumor cells are appropriate targets for intravenously applied anti-cancer therapeutics because they are easily accessible for macromolecules and immunologic effector cells. The majority of these tumor cells appear to be nonproliferating, which might explain the extended latency period ("dormancy") between their primary diagnosis and the occurrence of a subsequent metastatic relapse in some tumor entities. Furthermore this "dormancy" might be an explanation for the failure of standard antiproliferative adjuvant chemotherapy. Adjuvant therapeutic strategies aimed at both quiescent and proliferative tumor cells are therefore of increasing interest. In this paper the current state of research in the field of minimal tumor cell dissemination in patients with solid epithelial tumors is discussed.

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Can we trust the sentinel lymph node in melanoma?

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Background: The aim of the study was to determine the reliability of sentinel node biopsy in melanoma.

Methods: Between December 1993 and October 2002, 250 patients with cutaneous melanoma were studied prospectively. Preoperative lymphoscintigraphy was performed after injection of a mean dose of 65.6MBq ^{99m}Tc-nanocolloid (Amersham Cygne, Eindhoven) intradermally around the primary lesion site in a volume of 0.3 ml. The sentinel node was surgically identified with the aid of 1.0ml patent blue dye (Patent Blue, Laboratoire Guerbet, Aulnay-sous-Bois) and a gamma-ray detection probe (Neoprobe 2000, Hamburg).

Results: Lymphoscintigraphic visualization and surgical identification were 100%. In 60 patients (24%), one or more sentinel nodes were tumour-positive. The patients were followed for recurrent disease for a median duration of 72 months (range 13 – 104 months). A total of 105 recurrences were seen in 59 patients (24%). In seven patients, the first recurrence was seen in the lymph node basin from which a tumour-free sentinel node had been removed earlier. The false negative rate was thus 10%. In-transit metastases in sentinel node negative and sentinel node positive patients were seen in thirteen (7%) and fourteen (23%) patients respectively. The five-year overall survival rates for patients with a tumour-negative or tumour-positive sentinel node were 89% and 64% respectively (p<0.001).

Conclusions: The reliability of lymphatic mapping in determining the tumour-status of the basin concerned is limited (sensitivity 90%). The incidence of in transit metastases in sentinel node positive patients is high (23%). These unfavourable factors have to be weighed against the reliable prognostic information and potential survival benefit of the early removal of nodal metastases.

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Micrometastases in lymph nodes in urological tumours

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Using monoclonal antibodies to epithelial cytokeratins (CK) or tumour-associated cell membrane glycoproteins, individual carcinoma cells derived from various types of solid tumours (including urological tumours) can be detected on cytologic preparations at frequencies of 10^{-4} to 10^{-6}. These assays may be used to improve tumour staging with potential consequences for adjuvant therapy. Some clinical studies have suggested that the presence of these immunostained cells in bone marrow and lymph nodes of patients without clinical or histopathological signs of metastases might be prognostically relevant, while other studies failed to do so (for review, see Pantel et al, J. Natl. Cancer Inst. 91: 1113-24, 1999; Mueller & Pantel, Am. J. Cancer 2:77-86, 2003). In addition to immunocytochemistry, new molecular detection methods based on the amplification of a marker mRNA species by the polymerase chain reaction (PCR) technique have been developed. Although this technique is in principle more sensitive than immunocytochemistry, their specificity is lower due the illegitimate low level expression of the marker transcript in the surrounding leukocytes. This can lead to false-positive findings, as shown by the analysis of normal lymphoid and hematopoietic tissue from noncarcinoma control patients. In our hands, only PSA mRNA showed a sufficient specificity as RT-PCR marker (Zippelius et al, J. Clin. Oncol. 15:2701-08, 1997). However, the suitability of PSA as marker is limited by downregulation of PSA expression in prostate tumour cells, which can lead to false-negative findings. Besides tumour biology, variations in the PCR assays may lead to substantial differences in the reported rates of micrometastases in lymph nodes and other organs such as blood or bone marrow (Zippelius et al., Clin. Cancer Res. 6: 2741-50, 2000). This may explain at least in part the discrepant results on the clinical significance of micrometastasis in urological tumours (and other tumour entities as well). The low number of micrometastatic tumor cells hampers approaches to obtain information on their biological properties, which might help to identify new therapeutic targets. The tools established in our laboratory (e.g., micrometastatic cell lines, single cell (RT)PCR, multiple labeling, and FISH) allow to obtain further insights into the phenotype and genotype of micrometastases at the single cell level (e.g., Solagoklu et al., PNAS 99: 2246-51, 2002). In conclusion, there is an urgent need for the development of standardized protocols that can then be used in large scale clinical trials to determine whether nodal micrometastases really matters in urological tumours. Moreover, the identification of the molecular determinants of micrometastasis may help to design new strategies to detect and eliminate minimal residual cancer.

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The importance and validation of molecular imaging

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Molecular imaging has its roots in molecular biology and cell biology as well