



# University of Texas

Health Science Center at Houston

## Pathology Diagnostic Laboratory

Newsletter

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### Metastases Without Primary Tumor (the CUP Syndrome)

#### Introduction

As *Cancer of Unknown Primary Site* (CUP syndrome) are summarized neoplastic diseases, in which after a primary diagnostic approach only metastases were identified but no primary tumor. Consequently, the CUP syndrome consists of a clinically and pathologically heterogeneous group of tumors which still possess some biological characteristics in common and thus require a specific diagnostic and therapeutic approach. CUP is observed in 3-5% of all neoplastic diseases being somewhat more frequent in males than in females. The mortality rate is reported for Germany in 1997 as 4.5/100,000 for women and 7.1/100,000 for men. Etiology and pathogenesis in CUP usually remains obscure, yet it is generally assumed that metastases possess a growth advantage over its occult primary tumor. Califano & colleagues (1999) assumed in CUP of head & neck tumors, the primary may have been immunologically suppressed, for instance, while metastases grew progressively. Even systematic use of advanced radiologic and endoscopic techniques allows to identify only in 10-20% the initially occult primaries during the further course of the disease. This also includes current immunohistochemical classification of tumor cells. In contrast, **postmortem investigation allows to identify the initially occult primary in 50-75% of the cases** (Neben K et al., 2008). According to one autopsy study, more than half of CUP primaries were later located in the lung or in the pancreas (Abbruzzese JL et al., 1995). Two more recent studies show following distribution of primaries in CUP at autopsy: lung 5-35%, pancreas 15-20%, liver & gall bladder 10-15%, colon & rectum 3-8%, and kidney 3-5%.

#### Basic diagnostic approach

The task of basic diagnostic techniques is not only to identify the unknown primary, yet even more so to differentiate between potentially treatable diseases and resistant ones, and to determine the optimal therapeutic approach (Bugat R et al., 2002). Basic studies include: detailed case history and physical examination including male & female gonads, biopsy histology & cytology, CT (neck, thorax, abdomen, pelvis), routine lab (incl. PSA, AFP,  $\beta$ -hCG), case-related additional diagnostics according to working diagnosis and for therapeutic planning. **Histopathologic and immunophenotypic studies in this context are of special relevance for upcoming procedure planning.** Determination of tumor markers, of endocrine activities and selected modern molecular techniques add to the usefulness of pathologic investigations.

#### Microscopy and immunohistochemistry

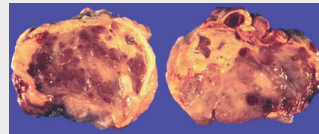
Tumor biopsies and/or cytology of malignant effusions are standard diagnostic measures in CUP. Considering the commonly poor prognosis of CUP patients, the least invasive technique should be used that permits to provide sufficient material for the required investigations (discussion with pathologist advised). Fairly easily identified are adenocarcinomas (50-70%), undifferentiated carcinomas (20-30%), squamous cell carcinomas (5-8%), and undifferentiated tumors (2-3%). Tumors with neuroendocrine features including small cell carcinomas should be differentiated because of their usually good chemosensitivity. **A panel of selected immunohistochemical techniques serves the further classification of the tumors including lymphomas, sarcomas and malignant melanomas.**

## Genomic analyses and gene expression studies

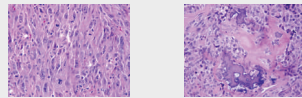
There are only very limited studies available on CUP-specific mutational and gene expression markers using small and heterogeneous patients groups with CUP. The usual task of such analyses is to identify a site of origin of the metastases by comparing known RNA expression profiles of identified primaries with those of metastases in CUP. Tothill & colleagues (2005) used gene expression profiles of **known primary tumors for comparison with metastatic tumors of CUP by cDNA microarrays**. They developed a classifier which permitted the correlation in 89% of 229 tumor specimens with 13 tumor entities. When the same classifier was applied to tumor probes from 13 CUP cases, they were able to identify the site of the primary in 11 cases. Several similar studies suggest that this technique may be promising in the future for the identification of primary tumors in CUP patients.

Patient 1: unknown primary tumor site

Patient 2: known primary tumor site

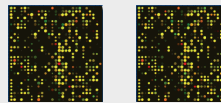


Tumor biopsy & microscopy

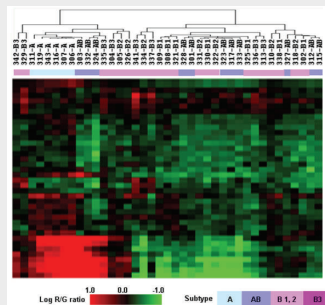


RNA extraction

Gene expression analysis with microarrays



Statistical evaluation and comparison of expression profiles



**Further reading:** *Califano J et al.*: Unknown primary head and neck squamous cell carcinoma: molecular identification of the site of origin. *J Nat Cancer Inst* 91: 599-604, 1999

*Varadhachary GR et al.*: Diagnostic strategies for unknown primary cancer. *Cancer* 100: 1776-1785, 2004

*Abbruzzese JL et al.*: Analysis of a diagnostic strategy for patients with suspected tumors of unknown origin. *J Clin Oncol* 13: 2094-2103, 1995

*Bugat R et al.*: Summary of the standards, options and recommendations for the management of patients with carcinoma of unknown primary site. *Br J Cancer* 89 (suppl 1): 59-66, 2003

*Tothill RW et al.*: An expression-based site of origin diagnostic method for clinical application to cancer of unknown origin. *Cancer Res* 65: 4031-4040, 2005

*Motzer RJ et al.*: Molecular and cytogenetic studies in the diagnosis of patients with poorly differentiated carcinomas of unknown primary site. *J Clin Oncol* 13: 274-282, 1995

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