# CORRESPONDENCE

## Metastases in the Absence of a Primary Tumor: Advances in the Diagnosis and Treatment of CUP Syndrome

by PD Dr. med. Kai Neben, Dr. med. Gerdt Hübner,
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### Cervical Lymph Node Metastases of Unknown Primaries

The statements made in the review article concerning treatment of metastases of unknown primaries are basically correct, especially the request to identify subgroups of patients that have a relatively good prognosis and chance of cure thanks to specific therapies. However, the authors do not give any more details about these subgroups, except for a table summary and a cursory remark about some treatment options. A more interdisciplinary constituted group of authors might have set this out better.

One example is the treatment of cervical lymph node metastases in the absence of a known primary tumor. The prognosis of these patients hardly differs from the prognosis that has been discussed in the above mentioned article by using a combination of surgery and radiotherapy. This equals the prognosis of known primary tumors in the epipharynx, oropharynx, and hypopharynx (laryngopharynx). We reported this as early as 1997 (1). In 64 patients with partly very extensive cervical lymph node metastases and an unidentified primary tumor, we found a tumor specific survival rate after 5 years of 51 ± 7% and an overall survival of 38.8 ± 7%. Survival of patients who did not develop distant metastases was 70 ± 7%. Patients whose cervical lymph node metastases were macroscopically removed by means of lymphadenectomy and who received homogenous radiotherapy to the entire pharynx had the best 5 year survival rate, at 67%.

These data deserve mention in connection with the depressing results of other patient groups with unidentified primary tumors, in whom even a 1 year survival rate of 25-50% in a selected patient cohort counts as progress.

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### Additional Points From the Perspective of Ear, Nose, and Throat Medicine

The review article shows the problem of CUP (carcinoma unknown primary) syndrome from the perspective of internistic oncology. From the perspective of otolaryngology, head and neck surgery, a few additional points deserve mention. The readers are not provided with information that is crucial for the appropriate diagnosis and treatment of cervical CUP syndrome.

In 70–80% of such cases, the primary tumors are located in the mucosa of the upper aerodigestive tract and take the shape of squamous cell carcinomas (3). In up to 10% of the cervical lymph node metastases, the primary tumors are initially unknown. In imaging studies of CUP, primary tumors of the oropharynx and nasopharynx are described in second place, after lung cancer.

The necessary diagnostic measures described as necessary in the literature were reflected only incompletely. Further to panendoscopy and bilateral tonsillectomy, "blind" biopsies should be taken from the base of the tongue and the nasopharynx. In total, the detection rate of primary tumors then can reach 30% (1, 2).

For the treatment of CUP, the literature clearly points out the benefit of modified radical neck dissection of the side of the neck that is affected and subsequent radiotherapy or radiochemotherapy. The radiation area should reach from the nasopharynx to the upper mediastinum and include both sides of the neck if required. By using this technique, 5 year survival rates in prospective studies have been improved from less than 20% to as high as 50% (2, 3).

In looking at all the available facts we think it is important to point out that oncological diagnosis and treatment are by necessity always influenced by the respective specialist groups and cannot be determined by generalists alone. Only in this way can a complete overview of the current state of diagnostics and therapy be achieved. This forms the basis for the development of unified standards for the benefit of our patients.

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## In Reply:

All correspondents discuss the therapy of prognostically favorable cervical lymph node metastases with squamous cell differentiation and an unknown primary tumor. Undoubtedly, the relatively rare subgroups of the CUP syndrome—which are mostly prognostically more favorable and suitable for specific therapies—deserve separate attention and detailed description. As we noted in our article, however, a detailed explanation of the therapeutic approaches in the numerous subgroups of CUP syndrome—as listed in a table of our article—would have exceeded not only the remit of the article but also the editorial rules in terms of word counts. For this reason, we restricted ourselves to delivering a detailed explanation of the standard procedures for disseminated, undifferentiated and adeno-CUP syndromes which account for 80% of cases. Further, we added pointers about the particular importance of the identification of patients who can be categorized in certain subgroups; we listed in a table the subgroups and recommended additional diagnostic tests and therapeutic strategies; and we mentioned diagnostioc and therapeutic guidelines of German Society for Hematology and Oncology (http://www.dgho.de), the European Society of Medical Oncology (http://www.esmo.org), and the National Comprehensive Cancer Network (http://www.nccn.org).

We agree with the correspondents that especially patients with CUP syndrome particularly benefit from interdisciplinary cooperation of almost all medical specialties in the form of regular, interdisciplinary tumor conferences.

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