The term cancer of unknown primary site (CUP) syndrome is used to describe malignancies in which a complete diagnostic work-up detects metastases in the absence of an identifiable primary tumor.

Methods: Based on a selective literature review, national and international guidelines, and the experience of the “Arbeitskreis CUP-Syndrom der Arbeitsgemeinschaft Internistische Onkologie der Deutschen Krebgesellschaft” (CUP Syndrome Committee of the Medical Oncology Joint Working Group of the German Cancer Society), developments in the diagnosis and treatment of CUP syndrome are reported.

Results: Most patients diagnosed with CUP have an unfavorable prognosis, with a life expectancy of less than 12 months. Nevertheless, it is important to identify subsets of patients in whom specific treatment offers the chance of long-term survival or even full recovery.

Discussion: Only rigorous further development of diagnostic tools and treatment protocols will enable an improvement of the poor prognosis of patients with CUP syndrome. Specific molecular treatment strategies have shown promising results.

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Key words: CUP syndrome, diagnosis, treatment success, molecular medicine, metastasis
under 20% (e2–e4). On the other hand, some more recent prospective studies with selected patients have found a median survival of 6 to 13 months, with a one year survival rate of between 25% and 53% (4–7).

The authors would like to report on progress in the diagnosis and treatment of patients with the CUP syndrome. They would like to emphasize that, even though the prognosis is still very poor, it is very important to identify patients with specific subgroups of the CUP syndrome, who can be given specific treatment, with the option of long-term survival or even cure. This review article is based on a selection of scientific articles identified with Medline, using the terms “cancer of unknown primary,” “CUP,” and “occult primary cancer.” We have concentrated on studies with modern diagnostic procedures and on randomized clinical trials. Single case reports have been excluded.

**Basic diagnosis**

The basic diagnostic strategy in CUP syndrome does not have the objective of identifying the primary tumor by using all available methods. It is more important to distinguish localized from disseminated disease and thus to identify potentially curable and therapy-sensitive tumor entities. This must be achieved as rapidly as possible and with a minimum of stress to the patient (2, 3, 8, 9). Routine diagnostic procedures include a detailed medical history, a thorough medical examination, basic laboratory diagnosis, CT investigation of the neck, chest, abdomen and pelvis, a gynecological investigation for women, and a tumor biopsy, which is primarily used to confirm the tumor diagnosis (box). The further diagnostic and therapeutic procedure is greatly influenced by the histopathological and immunohistological findings, together with the anatomical localization of the tumors (9). Aside from basic laboratory parameters, some selected tumor markers should be determined. These should be markers which are known to be useful for deciding treatment strategies. The following tumor markers may directly indicate the primary tumor: AFP (hepatocellular carcinoma, germ cell tumors), beta-hCG (germ cell tumors) and PSA (prostate carcinoma). If the histological diagnosis is a differentiated neuroendocrine tumor, calcitonin can indicate a medullar thyroid gland carcinoma. Other tumor markers, such as CEA, CA 125, CA 19-9, or CA 15-3, are of low specificity and can only be used to follow the course of the illness.

**Histology and immunohistology**

Tumor biopsy or cytology of malignant effusions is part of the essential diagnostic workup of CUP syndrome, to confirm the diagnosis of malignancy and to guide further diagnostic steps. As the overall prognosis of these patients is poor, the procedure for taking the biopsy should expose the patients to as little stress as possible and be as noninvasive as possible. It must nevertheless provide enough material to allow extensive immunohistological investigation.

Adenocarcinoma (50% to 70%), undifferentiated carcinomas (20% to 30%), squamous cell carcinomas (5% to 8%) and undifferentiated tumors (2% to 3%) may be distinguished histologically (e1–e3, 8). If cervical lymph node metastases are not considered, the proportion of squamous cell carcinomas sinks to under 5%. Tumors with neuroendocrine differentiation, including small cell carcinomas, may be relatively rare (2% to 4%), but deserve special attention, as they are sensitive to chemotherapy (10).

Immunohistology is of special importance for the classification of metastases when the primary tumor is unknown (9, 11, 12). This can restrict the number of possible primary tumors, as well as exclude tumor entities with well defined histology, such as lymphomas, sarcomas, or melanomas. To avoid excessive diagnostic work, a panel of immunohistological stains should be worked

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**MEDICINE**

**BOX**

**Basic diagnostic strategy for patients with CUP syndrome**

- Medical history, physical examination, including testicular palpation for men and breast examination for women
- Histology and cytology with immunohistology
- CT neck, chest, abdomen and pelvis
- Women: gynecological investigation
- Routine laboratory, PSA (men >40 years), AFP, beta-hCG
- Additional diagnostic procedures depending on working diagnosis, if this is of therapeutic consequence

AFP, alpha-fetoprotein; beta-hCG, beta–human choriongonadotropin; CT, computed tomography; PSA, prostate-specific antigen
through which permits the identification of defined tumor entities (figure 2). The initial positive stains can suggest possible diagnoses, which can be followed up with other stains. Even though the primary tumor can often not be identified with epithelial tumors, it is often feasible to reduce the number of possible primary tumors.

**PET and PET/CT diagnosis**

Positron emission tomography (PET) is a nuclear medical procedure which can be used for patients with the CUP syndrome to localize the primary tumor or previously unrecognized metastases. There is also an indication to use this method if there is localized manifestation of the tumor and if additional metastatic colonization must be excluded before potentially curative treatment strategies are started.

The role of PET in the CUP syndrome depends on whether the patient has cervical metastasis (predominantly squamous cell carcinoma) or extracervical metastases (predominantly adenocarcinoma). Although PET is established in head and neck CUP, its use in extracervical CUP is still controversial.

The use of PET in the extracervical CUP syndrome has recently been subject to a meta-analysis, including 221 patients from 10 studies (13). Most of these studies had small numbers of patients. Many patients had only one metastasis localization, the preceding basic diagnostic procedure was not standardized and often consisted of only a medical history, a physical examination, a chest X-ray, and abdominal ultrasound. In 41% of patients, a primary tumor was identified which had not been found in the basic diagnostic procedures. In 59% of patients, the primary tumor was in the lung. In 37% of patients, previously unidentified metastases were found. The sensitivity of PET in these studies was 91.9%; the specificity was 81.9%. One problem was the high rate of false positive findings in the lower digestive tract (58%) and this limits the usefulness of PET diagnosis below the diaphragm.

Combined PET/CT systems have been available for some years. These combine the high spatial resolution and detailed anatomical images of CT with the highly sensitive metabolic information of PET (figure 3). Another advantage of the PET/CT hybrid technique is that it takes less time than using PET and CT separately. In three published case series with a total of 91 patients, the primary tumor was identified in 40% of cases with the hybrid technique (e5–e7). If PET/CT is compared with PET alone, it is concluded that there are any more correct positive results, but that the proportion of false positives is reduced (e5, e7).

Although there have been some encouraging results with PET and PET/CT investigations in small series of patients with the CUP syndrome, it must be clearly stated that there is currently no consensus on the use of these methods in extracervical CUP syndrome and that these methods require further validation in clinical studies.

**Genomic analyses and gene expression studies with microarrays**

In contrast to most other malignancies, there are only few data on the expression and mutation status of tumor suppressor genes and oncogenes in CUP syndrome. The reason for this is that most studies have been performed on small and highly heterogenous groups of patients.

Early data from Hedley et al. showed that cell populations with aberrant DNA content can be detected by flow cytometry in about 70% of patients with adenocarcinomas with an unknown primary tumor. The probable diagnosis is gradually approached using the immunohistological profile. There are additional marker profiles for the subgroups of specific tumors, but these will not be discussed in this review. The diagnoses are given in regular typeface, the immunohistological markers are given in bold (e18).
 marker for response to platinum chemotherapy. In a study on 40 poorly differentiated CUP tumors (14), (12p) could be detected in 30% of cases; this correlated with response to platinum chemotherapy (75% versus 18%, p = 0.002).

The frequency of p53 mutations is apparently lower in the CUP syndrome (26%) than in other malignancies, in which the frequency is mostly >50% (e11). This is however with the reservation that only a few CUP tumors have been examined and that mutation analysis was restricted to exons 5–9 of the p53 gene—those most affected by mutations.

The main objective of gene expression analysis in the CUP syndrome is to identify the site of the primary tumor. With this aim in mind, the RNA expression profile of CUP tumors has been compared with the profiles for tumors with known primaries. Thus Tothill et al. investigated whether tumors with known primaries can be classified with gene expression analysis using cDNA microarrays (15) (figure 4). They developed a classifier which allowed the correct classification of 229 tumor samples to 13 tumor entities with a precision of 89%. The classifier was then used to classify tumors in CUP patients to the organ of the primary tumor; this was successful in 11 of 13 cases. Several additional studies have also been recently published which indicate that primary tumor identification is possible with gene expression analysis (e12–e14).

The authors would nevertheless like to point out that both genomic investigations and gene expression analyses should be restricted to clinical studies, as they are highly expensive, take a great deal of time, and the current data is rather limited.

**Treatment**

There is no drug specifically approved for the treatment of the CUP syndrome. Identification of subgroups with favorable prognosis is of decisive importance for the therapy of patients with CUP syndrome (table 1). The first step is always to test whether a patient has one of these well characterized disease entities and then to plan the treatment accordingly. These CUP subgroups with favorable prognosis are mostly rare and a detailed description of the therapeutic procedure would go beyond the scope of this review article. For additional information, please refer to the guidelines of the 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).

About 70% of all patients with CUP syndrome cannot be classified to one of the subgroups with a favorable prognosis. This large group exhibits the following characteristics: in histology, either adenocarcinoma or undifferentiated carcinoma, disseminated tumor growth, negative hormone receptor status, no exclusive peritoneal carcinosis. Local therapy (resection followed by radiation) is used for CUP with only one recognized metastasis, but is not applicable for this larger group. For study purposes, CUP patients in this larger group were taken together and given chemotherapy, which was usually palliative.

Table 2 summarizes all nine prospective randomized studies published on this subject (5–7, 16–20). The groups of patients and study designs are markedly heterogeneous, so that it is difficult to compare the individual studies. The number of recruited patients was between 34 and 101, so that there is really no comparison with the much larger randomized clinical trials with other tumor entities, which included much larger groups of patients. In three studies, the efficacy of cisplatin regimens was compared with regimens not containing cisplatin (17–19). The response rate with cisplatin regimens was somewhat better (27% to 50%) than with regimens without cisplatin (14% to 42%). On the other hand, the toxicity of the cisplatin regimens was higher. Thus chemotherapy with combinations containing cisplatin is apparently superior to combinations not containing cisplatin in randomized studies on the CUP syndrome, even though this has not yet been formally proved.

Phase II studies in recent years confirm the therapeutic value of platinum derivatives and of the newer substances, such as taxanes, gemcitabine, and irinotecan (5–7, 21). These regimens led to median survival times of up to 13.6 months (7). In spite of the difficulties in interpreting these results, the consequence has been that
most oncology centers now regard regimens containing platinum as standard therapy for the treatment of CUP patients. Most research groups prefer combinations of two substances over threefold combinations, as the tolerability of the former is better and it has not been shown that the threefold combinations are superior. Dose escalation, including high-dose therapy with autologous blood stem cell transplantation, and dose-dense chemotherapy protocols supported by hematopoietic growth factors have not led to any improvement in the therapeutic results either (e15, e16).

Both the CUP Syndrome Committee of the Medical Oncology Joint Working Group (CUP-AIO) of the German Cancer Society and the American Minnie Pearl Cancer Research Network prefer carboplatin to cisplatin, as the tolerability is better. In several phase II studies in recent years, paclitaxel has turned out to be a suitable combination partner for carboplatin (4, 6, 22, 23). On the other hand, there have been no randomized comparisons which have demonstrated that paclitaxel is superior to other substances in combination with carboplatin. Combination therapy with carboplatin and paclitaxel gives a response rate of 30% to 40% and 2-year survival rates of 20% to 25% in the primary treatment of patients with CUP syndrome.

In summary, the dual combination of a platinum and a taxane derivative can now be regarded as standard first line therapy for the treatment of patients in good general condition suffering from CUP syndrome (histology: adenocarcinoma or undifferentiated carcinoma). As an alternative for patients in poor general condition, monotherapy with gemcitabine can be considered.

**Attempts at specific molecular therapy**

Immunohistochemical studies (24, e17) have shown that, just as with other tumor entities, various oncogenes and growth factor receptors are overexpressed in tumor cells from CUP patients. For example, Massard et al. (24) have recently demonstrated by immunohistochemistry that the epidermal growth factor receptor (EGFR) is expressed in 66% of all CUP tumors, whereas Her2/neu was only expressed in 4% of tumors. Only 10% of the biopsies were positive for c-kit.

The data from a phase II study have recently been published, in which patients with the CUP syndrome (most of whom had been previously treated) were treated with a combination of the EGFR inhibitor erlotinib and the antiangiogenic VEGF antibody bevacizumab (25). According to the RECIST criteria (response evaluation criteria in solid tumors), 5 of 48 patients (10%) achieved partial remission. In addition, 29 of 48 patients (61%) exhibited temporary stabilization of their illness, corresponding to lack of progression within 8 weeks of therapy. The therapy was comparatively well tolerated and led to an overall survival of 7.4 months. This result is superior to many frequently used second-line chemotherapies for the CUP syndrome, so that it appears that the combination of erlotinib and bevacizumab is active.
TABLE 1

<table>
<thead>
<tr>
<th>Tumor constellation</th>
<th>Clinical presentation and recommended additional diagnostic procedures</th>
<th>Recommended therapy</th>
</tr>
</thead>
</table>
| Axillary lymph node metastases of an adenocarcinoma in women | • Mammography, MRI and sonography of the breasts, possibly PET if available  
• Immunohistology, including hormone receptor status and c-erbB2 expression | • ESMO Minimal Clinical Recommendations: Therapy identical to the treatment of patients with mammary carcinoma and corresponding lymph node involvement (stage II) |
| Peritoneal carcinosis of a serous papillary adenocarcinoma in women | • Tumor marker Ca 125 often increased  
• Frequent in patients with BRCA1 mutations | • ESMO Minimal Clinical Recommendations: Therapy identical to that of metastatic ovarian carcinoma in stage FIGO III |
| Cervical lymph node metastases of squamous cell carcinoma | • CT and/or MRI of the neck; PET recommended  
• ENT investigation with panendoscopy and biopsies of lesions  
• If no suspicious lesions, ipsilateral tonsillectomy | • General recommendation: Therapy as with metastatic ENT tumors with known primary tumors |
| Inguinal lymph node metastases of squamous cell carcinoma | • Digital rectal investigation, proctoscopy  
• Women: gynecological investigation with sample biopsies from lesions in the vulva, vagina and cervix | • General recommendation: Lymph node dissection and/or local radiation lead to protracted remission in specific patients; possibly consider multimodal treatment concepts in analogy to anal, cervical or bladder carcinoma with combined radio-CHT |
| Undifferentiated neuroendocrine carcinoma | • Determine degrees of differentiation and proliferation by histology  
• Somatostatin receptor scintigraphy | • General recommendation: a) Well differentiated, positive for somatostatin receptor: somatostatin  
b) Poorly differentiated; combination CHT with carboplatin/etoposide (level of evidence C) |
| Poorly differentiated carcinoma with germ cell characteristics | • Young men (<50 years) with retroperitoneal and mediastinal lymph node metastases  
• Beta-hCG and/or AFP often raised  
• Cytogenetics: i(12p) aberration | • General recommendation: In analogy to germ cell tumors, with combination CHT containing cisplatin, e.g. cisplatin/etoposide/bleomycin |
| Solitary metastasis | • PET or PET-CT investigation  
• Additional metastases are often diagnosed in hospital, so that curative therapy is rarely successful | • General recommendation: Tumor resection and/or local radiation |

In summary, we can say that the prognosis for the CUP syndrome is still poor and that we will only be able to improve it by consistently developing both diagnostic and therapeutic strategies. This necessitates that patients with CUP syndrome, exactly like patients with other malignancies, are treated within controlled clinical studies. These must be accompanied by a supporting scientific program to supply the urgently needed data to improve our understanding of the pathophysiology of this neglected disease at a molecular level.

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Conflict of interest statement
Dr. Folprecht has received fees and financial support for research from Merck, Sanofi-Aventis and Pfizer and fees from Lilly and Takeda. The other authors declare that no conflict of interest exists according to the guidelines of the International Committee of Medical Journal Editors.

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Translated from the original German by Rodney A. Yeates, M.A., Ph.D.
### TABLE 2

**Prospective randomized studies on the treatment of patients with CUP syndrome**

<table>
<thead>
<tr>
<th>Study (reference)</th>
<th>Number of patients</th>
<th>Chemotherapy</th>
<th>Response rate (%)</th>
<th>Median PFS (months)</th>
<th>Median OS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palmeri et al., 2006 (7)</td>
<td>66</td>
<td>Cisplatin + gemcitabine + paclitaxel vs cisplatin + gemcitabine + vinorelbine</td>
<td>48.5</td>
<td>7.4</td>
<td>9.6</td>
</tr>
<tr>
<td>Hübner et al., 2005 (6)</td>
<td>92</td>
<td>Carboplatin + paclitaxel vs gemcitabine + vinorelbine</td>
<td>23.8</td>
<td>7.0</td>
<td>11.0</td>
</tr>
<tr>
<td>Culin et al., 2003 (5)</td>
<td>80</td>
<td>cisplatin + gemcitabine vs cisplatin + irinotecan</td>
<td>55</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>Assersohn et al., 2003 (20)</td>
<td>88</td>
<td>5-FU vs 5-FU + mitomycin C</td>
<td>11.6</td>
<td>4.1</td>
<td>6.6</td>
</tr>
<tr>
<td>Dowell et al., 2001 (21)</td>
<td>34</td>
<td>Carboplatin + etoposide vs paclitaxel + 5-FU + folic acid</td>
<td>19</td>
<td>NA</td>
<td>6.5</td>
</tr>
<tr>
<td>Falkson et al., 1998 (19)</td>
<td>84</td>
<td>Cisplatin + epirubicin + mitomycin C vs mitomycin C</td>
<td>50</td>
<td>4.5</td>
<td>9.4</td>
</tr>
<tr>
<td>Eagan et al., 1987 (18)</td>
<td>55</td>
<td>Cisplatin + doxorubicin + mitomycin C vs doxorubicin + mitomycin C</td>
<td>27</td>
<td>5.4</td>
<td>9.4</td>
</tr>
<tr>
<td>Milliken et al., 1987 (17)</td>
<td>101</td>
<td>Cisplatin + vinblastin + bleomycin vs doxorubicin + mitomycin C</td>
<td>32</td>
<td>NA</td>
<td>6.2</td>
</tr>
<tr>
<td>Woods et al., 1980 (16)</td>
<td>47</td>
<td>cyclophosphamide + methotrexate + 5-FU vs doxorubicin + mitomycin C</td>
<td>5</td>
<td>NA</td>
<td>1.7</td>
</tr>
</tbody>
</table>

CUP: carcinoma of unknown primary site; 5-FU, 5-fluorouracil; NA, not available; NS, not statistically significant; PFS, progression free survival; OS, overall survival

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