Cancers of unknown primary site: ESMO Clinical Recommendation for diagnosis, treatment and follow-up

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incidence
Cancers of unknown primary site (CUPs) represent a heterogeneous group of tumors first presenting with metastases for which a work-up, as listed below, fails to identify the site of origin at the time of diagnosis. CUP accounts for 3–5% of all malignancies.

diagnosis
CUPs require pathologic evaluation and are categorized by pathology into:

- well and moderately differentiated adenocarcinomas
- poorly differentiated carcinomas
- squamous cell carcinomas
- undifferentiated neoplasms
- carcinomas with neuroendocrine differentiation.

Immunohistochemistry should be applied in poorly differentiated cases to exclude chemosensitive and potentially curable tumors (i.e. lymphomas and germ-cell tumors).

If diagnosis is adenocarcinoma, immunostaining for prostate-specific antigen (PSA) in male patients and for estrogen and progesterone receptors in females with axillary node metastases is advisable to rule out hormone-sensitive tumors amenable to specific therapy. Staining for keratins CK7 and CK20 may provide indications towards a possible primary site.

staging and risk assessment
CUPs are by definition metastatic tumors. Therefore, in patients who present with CUP the diagnostic evaluation aims to define the extent of tumor dissemination and help identify a minority of CUP patients who can expect to benefit from directed therapy. The following recommendations epitomize standard and optional assessments suggested.

- Thorough physical examination (including head and neck, rectal, pelvic and breast examination), basic blood and biochemistry survey, urinalysis, fecal occult blood test and CT scan of thorax, abdomen and pelvis constitute a minimal basic work-up.
- Endoscopies should be sign- or symptom-guided. Serum assessment of α-fetoprotein (αFP), β-human chorionic gonadotropin (bHCG) and PSA is suggested in male patients to exclude potentially curable extragonadal germ-cell tumor and those amenable to hormone treatment for prostate cancer.
- Whole-body CT/[2-deoxy-2-[F-18]fluoro-D-glucose positron emission tomography] (FDG-PET) may contribute to the management of patients with CUP tumors, especially those with cervical adenopathies and single metastasis.
- Subsets of chemosensitive and potentially curable tumors, such as young and middle-aged adults with predominantly nodal metastases of poorly differentiated carcinomas and females with peritoneal carcinomatosis of a serous histologic type adenocarcinoma must not be missed.

Diagnostic and staging guidelines for patients with an anticipatory CUP diagnosis are summarized in Table 1.

treatment
Therapy should be tailored on an individual basis by recognition of well-defined clinical–pathologic subsets that differ in prognosis as described in Table 2 [III, D].

response evaluation
Response evaluation is recommended after two or three chemotherapy cycles by individually adequate tests.

follow-up
There is no evidence that follow-up of asymptomatic patients is needed. Specific examinations as clinically indicated.

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Conflict of interest: the authors have reported no conflicts of interest.

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Levels of evidence [I–III] and grades of recommendation [A–D] as used by the American Society of Clinical Oncology are given in square brackets. Statements without grading were considered justified standard clinical practice by the expert authors and the ESMO faculty.

**literature**
