ESMO Minimum Clinical Recommendations for diagnosis, treatment and follow-up of cancers of unknown primary site (CUP)

**Definition and incidence**

- CUP represents 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 a 3–5% of all malignancies.

**Diagnosis**

- Carcinomas of unknown primary site require histologic 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 routinely applied especially in poorly differentiated cases to exclude chemosensitive and potentially curable tumors (i.e. lymphomas and germ cell tumors).

- If diagnosis is adenocarcinoma, immunostaining for 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.

**Staging and risk assessment**

- Thorough physical examination (including head and neck, rectal, pelvic and breast examination), basic blood and biochemistry survey, urinalysis, fecal occult blood test, chest X-ray, CT-scan of the abdomen and pelvis [III, B].

- Further evaluation and endoscopies should be sign- or symptom-guided [III, B]. Assessment of serum α-fetoprotein (αFP), β-human chorionic gonadotropin (βHCG) and PSA is suggested in male patients to exclude potentially curable extragonadal germ cell tumor, prostate cancer or breast cancer amenable to hormone treatment [III, B].

- Subsets of chemosensitive and potentially curable tumors, such as middle-aged adults with predominately nodal metastases of poorly differentiated carcinomas and females with peritoneal carcinomatosis must not be missed.

**Treatment**

- Therapy should be tailored on an individual basis by recognition of well-defined clinicopathologic subsets that differ in prognosis [III, B] as described in Table 1.

**Response evaluation**

- Response evaluation is recommended at least after 2–3 chemotherapy cycles by the individually adequate tests [V, D].

**Follow-up**

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

**Note**

Levels of Evidence [I–V] 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**


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