clinical practice guidelines

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

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definition, incidence and biology

Cancers of unknown primary site (CUPs) represent a heterogeneous group of metastatic tumors for which a standardized diagnostic work-up fails to identify the site of origin at the time of diagnosis. CUPs account for 3–5% of all malignancies. The unique biology of these tumors remains unknown. Nonetheless, current data suggest that metastatic dissemination can occur in the absence of growth of a primary tumor by virtue of inherent metastatic aggressiveness of cancer cells or through site-specific transformation of circulating cells, by oncogene induction at metastatic stroma.

diagnosis

Diagnosis of CUP requires pathology evaluation. These tumors are categorized by pathology into:

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

Immunohistochemistry should be applied meticulously in order to identify the tissue of origin and to exclude chemosensitive and potentially curable tumors (i.e. lymphomas and germ cell tumors) (Table 1). If diagnosis is carcinoma or 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 of a possible primary site, and staining for chromogranin A and synaptophysin is needed to profile neuroendocrine differentiation (Figure 1). Currently gene expression profiling assays have become commercially available, aiming to identify the tissue of origin in patients with CUP. These assays may aid in the diagnosis of the putative primary tumor site in some patients. However, their impact on patient outcome via administration of primary site-specific therapy remains questionable and unproven in prospective trials [IV, D].

staging and risk assessment

CUPs are by definition metastatic cancers, and the prognosis for patients with CUP is poor. However, appropriate diagnostic work-up can help to 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, and computed tomography (CT) scans of thorax, abdomen and pelvis constitute a minimal basic work-up [IV, B].

Endoscopies should be sign-, symptom- or laboratory abnormality-guided. Serum assessment of α-fetoprotein (AFP), human chorionic gonadotropin (hCG), plasma chromogranin A and PSA is suggested in male patients to exclude potentially curable extragonadal germ cell tumors, neuroendocrine tumors and prostate cancers amenable to hormonal treatment.

Distinct subsets of patients with CUP have been defined based on clinical and pathological criteria [2] (Table 2). A minority of patients (15–20%) belong to clinicopathological subsets with more favorable prognosis. These favorable risk CUP patients harbor chemosensitive and potentially curable tumors and may experience long-term disease control with appropriate multidisciplinary management.

The majority of patients (80–85%) do not belong to specific subsets. Sensitivity to therapy is only modest and median overall survival is generally <1 year (6–10 months). Two prognostic groups can be identified within patients with CUP: those with a good performance status (0–1) and a normal lactate dehydrogenase (LDH) value, with a median life expectancy of 1 year, and those with either one or both these prognostic factors, with a median overall survival of only ∼4 months [10].

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Table 1. Basic immunohistochemical work-up of bioptic material from patientw with cancers of unknown primary site (CUPs)

	Cytokeratins	ER, PgR	Thyroglobulin, calcitonin	LCA	S100, HMB45	NSE, chromogranin, synaptophysin	PSA	AFP, OCT 4, hCG, PLAP	Vimentin, desmin
Undifferentiuated carcinoma	+	+/–	–	–	–	+/–	–	–	–
Breast cancer	+	+/–	–	–	–	–	–	–	–
Prostate cancer	+	–	–	–	–	–	+	–	–
Germ cell cancer	+	–	–	–	–	–	–	+	–
Lymphoma	–	–	–	+	–	–	–	–	–
Melanoma	–	–	–	–	+	+	–	–	+
Sarcoma	–	–	–	–	–	–	–	–	+
Neuroendocrine	+	–	–	–	–	+	–	–	–
Thyroid cancer	+	–	+	–	–	–	–	–	–

AFP, α-fetoprotein; ER, estrogen receptor; hCG, human chorionic gonadotropin; LCA, leukocyte common antigen; NSE, neuron-specific enolase; OCT 4, octamer-binding transcription factor 4; PgR, progesterone receptor; PLAP, placental alkaline phosphatase; PSA, prostate-specific antigen.

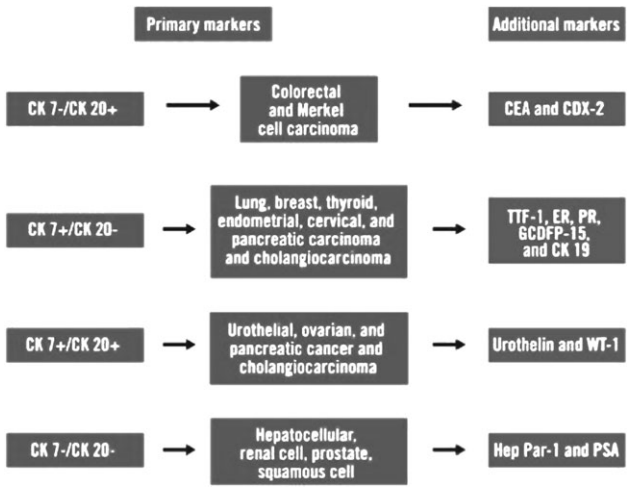

Figure 1. Basic immunohistochemical work-up of carcinomas of unknown primary. Reproduced with permission: Varadhachary GR. Carcinoma of unknown primary origin, Gastrointest Cancer Res 2007; 1: 229–235.

A proposal for the practical management of patients with CUP, including recognition of specific subsets, exclusion of non-CUP neoplasms and use of prognostic parameters in the clinical practice, is summarized in Figure 2.

Diagnostic and staging guidelines for patients with an anticipatory CUP diagnosis are summarized in Table 2. Whole-body 2-deoxy-2-[^{18}F]fluoro-D-glucose-positron emission tomography (CT/FDG-PET) may contribute to the management of patients with CUP tumors and especially those with cervical adenopathies and single metastasis [IV, B].

treatment

Therapy should be tailored on an individual basis according to the clinicopathological subset of distinct prognosis in which the patient belongs [III, B]. The 10–15% of CUP patients of the favorable risk subsets should be treated similarly to patients with equivalent known primary tumors with metastatic dissemination [IV, B]. These patients experience long-term disease control in 30–60% of cases, and optimal management is pivotal for long-term survival (Table 3). Retrospective analyses support that the clinical behavior, biology, response to treatment and outcome of patients with favorable risk CUP are no different from those with metastatic tumors of known primary [15–17].

Patients with poor-risk CUP have a dismal prognosis despite management with a variety of chemotherapeutic combinations in small clinical studies [9, 13]. A recent meta-analysis showed no evidence of superior efficacy of any of the administered regimens incorporating platinum salts, taxanes or new-generation cytotoxic compounds (gemcitabine, vinca alkaloids or irinotecan) [18]. Recently a randomized prospective phase III study of 198 patients compared gemcitabine/irinotecan with paclitaxel/carboplatin/oral etoposide in fit poor-risk patients and reported significantly less toxicity with the two-drug

Table 2. Diagnostic and staging guidelines for cancers of unknown primary site (CUPs)

Assessment suggested	Target patient population
Thorough medical history and physical examination	All patients
Basic blood and biochemistry survey	All patients
CT scans of thorax, abdomen and pelvis	All patients
Mammography	Female patients
Work-up for CUP subsets	
Breast MRI	Female with axillary adenocarcinoma
Serum α-fetoprotein and human chorionic gonadotropin	Patients with midline metastastatic disease
Serum prostate-specific antigen	Male with adenocarcinomatous bony metastases
Head and neck CT/PET scan (optional)	Cervical squamous carcinoma
Endoscopies	Sign/symptom/lab-oriented
Octreoscan and plasma chromogranin A	Patients with neuroendocrine tumor CUP

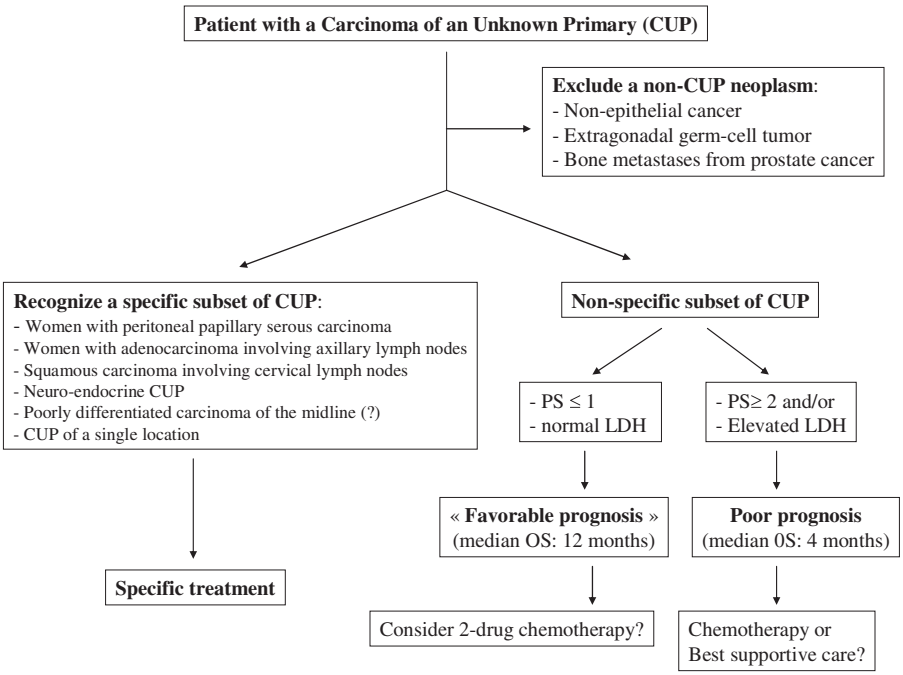

Figure 2. Clinical management of patients presenting with CUPs.

Table 3. Therapy of patients with favorable risk cancers of unknown primary site (CUPs)

CUP subtype	Proposed treatment	Potential equivalent tumor
Poorly differentiated neuroendocrine carcinomas of an unknown primary	Platinum + etoposide combination chemotherapy	Poorly differentiated NET with a known primary
Well differentiated NET of unknown primary	Somatostatin analogs, streptozocin + 5-FU, sunitinib, everolimus	
Peritoneal adenocarcinomatosis of a serous papillary histological type in female	Optimal surgical debulking followed by platinum–taxane-based chemotherapy	Ovarian cancer
Isolated axillary nodal metastases in female	Axillary nodal dissection, mastectomy or breast irradiation and adjuvant chemohormonotherapy	Breast cancer (found in 50–70% when breast MRI is performed)
Squamous carcinoma involving non-supraclavicular cervical lymph nodes	Neck dissection and/or irradiation of bilateral neck and head–neck axis. For advanced stages induction chemotherapy with platinum-based combination or chemoradiation	Head and neck squamous cancer
Single metastatic deposit from unknown primary	Resection and/or RT ± systemic therapy	Single metastasis
Men with blastic bone metastases and IHC/serum PSA expression	Androgen deprivation therapy ± RT	Prostate cancer
Midline Cup	Platinum-based chemotherapy	Extragonadal germ cell tumor

5-FU, 5-fluorouracil; IHC, immunohistochemistry; MRI, magnetic resonance imaging; NET, neuroendocrine tumor; PSA, prostate-specific antigen; RT, radiotherapy.

Table 4. Commonly used low-toxicity palliative chemotherapy regimens for poor-risk patients with cancers of unknown primary site (CUPs)

Chemotherapy (mg/m^2)	Time	Interval	Comments
Cisplatin 60–75 Gemcitabine 1000	Day 1 Day 1 + 8	Q 3 weeks	Fit patients, adequate hydration
Cisplatin 75 Etoposide 100	Day 1 Days 1–3	Q 3 weeks	Fit patients with neuroendocrine feature-CUP, adequate hydration
Paclitaxel 175 Carboplatin AUC 5	Day 1	Q 3 weeks	Convenient outpatient regimen, monitor neurotoxicity
Docetaxel 75 Carboplatin AUC 5	Day 1	Q 3 weeks	Convenient outpatient regimen, monitor neurotoxicity
Irinotecan 160 Oxaliplatin 80	Day 1	Q 3 weeks	Outpatient regimen, monitor for neurotoxicity and diarrhoea
Oral Capecitabine 2000 ± Oxaliplatin 85–130	Days 1–14 Day 1	Q 3 weeks	Outpatient regimen, risk for diarrhea and neurotoxicity
Gemcitabine 1000/Irinotecan 100	Day 1+8	Q 3 weeks	Convenient outpatient regimen, monitor diarrhoea

regimen and equal survival rates [I, A] [19]. On the other hand, the efficacy/toxicity ratio of the cisplatin–gemcitabine combination was found to be better than that of the cisplatin–irinotecan regimen in a randomized phase II trial [I, A] [20]. Modest survival prolongation and symptom palliation with preservation of quality of life are currently the only realistic aims of therapy for these patients [I, A]. Consequently, low-toxicity patient-convenient chemotherapy regimens should be administered to reasonably fit poor-risk CUP patients.

Whether targeted agents should be used or not in patients with CUPs is still unknown [21]. Preliminary retrospective data suggest that CUP patients with immunohistochemical and/or molecular profile assay diagnoses of 'colorectal' carcinomas have response rates and survival after colorectal site-specific therapies (i.e. FOLFOX or FOLFIRI) similar to known advanced colorectal carcinomas [IV, B] [22]. These data are from small numbers of patients, and additional prospective validation is necessary to substantiate these preliminary findings.

Participation in clinical trials evaluating combinations of cytotoxic compounds with targeted agents or site-specific therapy in patients with putative primary tumor sites highly suspected from immunohistochemical or microarray studies should be strongly encouraged [22–25].

Commonly used chemotherapy regimens for patients with poor-risk CUP are summarized in Table 4.

response evaluation

Response evaluation is recommended after two or three chemotherapy cycles by individually adequate tests. Quality of life issues are particularly relevant for patients with poor-risk CUP for whom excessive treatment-related toxicity is not justified [IV, B].

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.

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