Treatment of patients with specific subsets of carcinoma of an unknown primary site

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introduction
The management of patients with carcinoma of an unknown primary site (CUP) is a notoriously difficult task. The prognosis of these patients is overall poor, with median survival rates still being in the 8 months range. Much progress has been made in recent years, including extensive studies of evidence-based data [1–4], the publication of results from randomized trials [5], which where not available for a long time in this setting, and better biological phenotyping of the tumor sample, which is mostly based on immunohistochemistry (see related chapter in this Educational book).

CUP are an heterogeneous group of neoplasms, and one of the major advances in their clinical management has been the recognition of a number of clinico-pathological subsets with a favorable prognosis and a specific recommended treatment. Patients who fit into these subgroups represent a minority (about 15%) of the population of patients with CUP and they are traditionally (and adequately) excluded from prospective clinical trials testing new approaches in the entire group of CUP. The present article will describe these subsets and review the current evidence-based recommended treatments. For each subset, therapeutic guidelines provided in the ‘Minimum Clinical Recommendations’ produced by the European Society for Medical Oncology (ESMO) [3] and those provided in the Standard, Options, and Recommendations (SOR) [2] are mentioned. The methodology to generate these guidelines was quite different:

The Minimum Clinical Recommendations produced by the ESMO was one of the first initiatives to undertake the development of European-wide cancer guidelines. The ESMO guidelines task force was established in 1998 and decided to set Minimum Clinical Recommendations on CUP based on already existing clinical practice guidelines (without generating completely new guidelines from original data). Using these guidelines, a coordinator wrote a draft of Minimum Clinical Recommendations that was subsequently modified and validated by the task force and the ESMO faculty. The Minimum Clinical Recommendations on CUP were originally published in Annals of Oncology in 2001 and updated in 2005 [3].

Standard, Options, and Recommendations: In 2001, a multidisciplinary working group was set up by the French National Federation of Cancer Centres (FNCLCC) to review the literature on CUP in order to generate evidence-based guidelines from original data. After selection and critical appraisal of the literature (search on Medline from 1980–2001), the working group defined the ‘Standards’, ‘Options’ and ‘Recommendations’ for the management of patients with CUP, based on a synthesis of the best available evidence and expert agreement. These guidelines were then reviewed by a group of independent experts and finalized after taking into consideration their comments. When all the members of the working group agree, based on the best available evidence, that a procedure or intervention is beneficial, inappropriate, or harmful, it is classified as a ‘Standard’; when the majority agree, the procedure is classified as an ‘Option’. ‘Recommendations’ provide additional information that enables the available options to be ranked using explicit criteria (e.g. survival, toxicity) with an indication of the level of evidence. The English version of the Standard, options, and recommendations on CUP was originally published in the British Journal of Cancer in 2003 [2].

patients with a favorable subset of CUP
women with isolated adenocarcinoma involving the axillary lymph nodes
A lymph node dissemination from an occult breast cancer should be suspected in all women who are found to have metastatic adenocarcinoma involving axillary lymph nodes [6]. Therefore, the initial pathologic evaluation should include measurement of estrogen and progesterone receptors and HER2 status, with elevated levels providing strong evidence for the diagnosis of breast cancer. In patients with normal breast examination and mammography, magnetic resonance imaging (MRI) should be performed since this technique has greatly aided in the identification of occult primary breast tumors (in up to 75% of cases). PET scanning may also be considered. The prognosis of this entity is similar to that of stage II breast cancer. Like in breast cancer, the number of the positive lymph nodes correlates with the outcome: the 5-year overall survival is 87% and 42% in patients with 1–3 and >3 positive nodes, respectively [7].

In the rare subset of patients who have no demonstrable breast primary after MRI, clinical management may follow

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guidelines for stage II breast cancer, although the evidence is limited, with only very few cases published in the literature.

**ESMO Minimal Clinical Recommendations.** 'Identical (treatment) to breast cancer with similar nodal involvement.'

**Standard, Options, and Recommendations.** 'Locoregional treatment (breast): If the results from the breast MRI is negative, surgery and breast radiotherapy should not be offered (standard, expert agreement).

Locoregional treatment (axilla): Axillary dissection should be offered (standard, expert agreement). Axillary and/or supraclavicular irradiation may be undertaken (option, expert agreement).

Systemic treatment: The management of these patients should be identical to that for patients with breast cancer with lymph node metastases (recommendation)'

### women with papillary serous adenocarcinoma of an unknown primary

The syndrome of peritoneal carcinomatosis with papillary serous histology (and pathologically non-involved ovaries) resembles ovarian carcinoma: serum levels of CA125 are usually elevated, this entity may occur in women with BRCA-1 mutations or in those from families at high-risk for ovarian cancer even after prophylactic oophorectomy. This neoplasm is chemo-sensitive, and long-term remissions may be obtained in about 15% of patients [8]. Chemotherapy regimens containing cisplatin and cyclophosphamide have been used most frequently; however, since taxane/platinum combinations have proven superior in advanced ovarian cancer, these regimens are currently mostly used in this setting. As in ovarian cancer, most long-term remissions have been observed in patients who had successful surgical cytoreduction prior to chemotherapy.

**ESMO Minimal Clinical Recommendations.** ‘(Treatment) similar to FIGO III ovarian cancer: platinum-based chemotherapy.’

**Standard, Options, and Recommendations.** ‘By analogy with ovarian cancer, the standard treatment is tumor reduction by surgery (level of evidence: D) followed by polychemotherapy containing a platinum salt (standard, expert agreement). About six cycles of treatment should be administered (recommendation).’

### squamous carcinoma of the cervical lymph nodes

Cervical lymph node metastasis of a squamous cell carcinoma of an unknown primary tumor is a rare situation. The patient work-up should include a physical examination, a panendoscopy (oropharynx, hypopharynx, nasopharynx, larynx, and upper esophagus) with biopsies of all suspicious sites, computer tomography and/or MRI. In the absence of detectable lesions, ipsilateral tonsillectomy may identify a primary tumor in about 25% of the patients. Positron emission tomography (PET) can identify primary tumors in 25% of the patients and results in a change in treatment strategy in 24 to 53% of the patients. These results still require a confirmation.

The treatment options include surgery, alone or followed by radiotherapy, and radiotherapy alone. Combined modality treatment may result in a better outcome. The extent of radiation fields remains debatable. In high-risk patients the addition of chemotherapy may improve anti-tumor efficacy.

The prognosis of patients with cervical lymph node metastasis is much more favorable than that of patients with a CUP at other localizations: 5-year survival rates range from 20% to 60% [9].

**ESMO Minimal Clinical Recommendations.** ‘Irradiation for N1-N2 disease. For higher stages, induction chemotherapy with platinum-based combination is suggested.’

**Standard, Options, and Recommendations.** ‘Patients with cervical lymph node metastasis from squamous cell carcinoma should be offered lymph node dissection and complementary radiotherapy (standard, level of evidence: C).

If surgery is not possible, radiotherapy should be performed (standard). Chemotherapy may be proposed to patients with tumors that are not suitable for resection or surgery (option).’

### undifferentiated neuro-endocrine carcinoma of unknown origin

In 10–15% of poorly differentiated carcinomas of unknown primary site, immunoperoxidase staining or electron microscopy identifies neuro-endocrine features [8]. These neoplasms are rarely associated with clinical signs and symptoms produced by tumor secretion of bioactive substances. Recognition of this patient subset is important, since poorly differentiated neuro-endocrine carcinomas are often highly sensitive to combination chemotherapy. In a series of 43 such patients treated within a larger group of patients with unknown primary cancer, Hainsworth and Greco documented objective responses in 33 of 43 evaluable patients (77%) when treated with platinum/etoposide-based regimens and 8 patients remained continuously disease-free more than two years after completion of therapy. These data have been since confirmed by other groups [8].

Although the nature of these tumors remains undefined, patients with poorly differentiated neuro-endocrine carcinoma often respond well to chemotherapy, and all patients in this group should be considered for an empiric trial of a platinum/etoposide-based regimen. In patients with a single tumor site, local treatment (either surgical resection or radiation therapy) should be considered in addition to combination chemotherapy.

**ESMO Minimal Clinical Recommendations.** No specific recommendation.

**Standard, Options, and Recommendations.** ‘The treatment of metastases from a neuro-endocrine carcinoma is not modified by the identification of the primary site (expert agreement). The management of patients with neuro-endocrine carcinoma of unknown primary site should take into consideration the cellular differentiation (standard, expert agreement).

Poorly differentiated forms are considered to be chemo-sensitive (level of evidence: C). The usual treatment is based on a combination of a platinum compound and an etoposide salt.
Although the results from clinical trials do not provide evidence for efficacy in terms of increased survival, clinicians should prescribe this treatment (standard, expert agreement).

There is no standard for the forms that are well differentiated.

**poorly differentiated carcinoma of the midline**

In the 1980s, an ‘extragonadal germ cell cancer syndrome’ was recognized in young patients with undifferentiated carcinoma of an unknown primary, a predominance of mediastinal and retroperitoneal cancer site, and in some of them, an elevated serum human chorionic gonadotrophin (hCG) and/or alpha-fetoprotein (AFP) [8]. In the initial reports, this subgroup of patients had a high probability (62%) of response to cisplatin-based chemotherapy. However, follow-up indicated that their cure expectancy was not as high as originally expected, with only 14% of patients being alive and disease-free at 8 years. Moreover, elevation of serum hCG and AFP has not been predictive of chemotherapy responsiveness in a subsequent experience [10]. Finally, the group at M. D. Anderson could not identify a subset of patients with poorly differentiated carcinoma who experienced long-term survival following chemotherapy in their large prognostic study [11] and the group of Institut Gustave Roussy found no obvious survival difference between the two groups of a prospective study in which patients with a CUP were treated differently according to pathological differentiation [12].

It is quite likely that germ cell tumors (and lymphomas) are much better identified among these patients compared to the 1970–1980s due to progress in pathology, especially immunohistochemistry. Therefore, it is not certain that patients with a poorly differentiated carcinoma of the midline should be currently identified as a specific subset of CUP. A cisplatin-based regimen should probably be recommended, although recent studies did not show clear evidence of an increased chemo-sensitivity.

**ESMO Minimal Clinical Recommendations.** ‘Subsets of chemosensitive and potentially curable tumors, such as middle-aged adults with predominantly nodal metastases of poorly differentiated carcinomas must not be missed.’

**Standard, Options, and Recommendations.** No specific recommendation.

**CUP presenting as a single metastatic lesion**

Single lesions have been described in a variety of sites, including lymph nodes, brain, adrenal gland, lung, liver, and bone [8, 13]. The possibility of an unusual primary site mimicking a metastatic lesion should always be considered, but this possibility can usually be excluded based on clinical or pathologic features. Prior to planning treatment, a PET scan is probably helpful in this patient group, primarily for the purposes of excluding other occult metastatic sites. In most patients who present with a single metastatic lesion, other metastatic sites become evident within a relatively short time. However, definitive local treatment sometimes produces long disease-free intervals, and occasionally patients have prolonged survival. Therefore, the resection of the solitary lesion should be undertaken, if clinically feasible. In some instances, local radiation therapy may also be appropriate to maximize the chance of local control. Following successful local treatment, ‘adjuvant’ systemic chemotherapy may be considered. In isolated case reports, such patients have had long-term survival. However, there has been no systematic study of this issue,

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**Figure 1.** A proposal of practical management of patients with CUP. BSC, best supportive care; OS, overall survival; PS, performance status; LDH, lactate dehydrogenase.
and proof of its superiority versus local treatment alone is lacking.

**ESMO Minimal Clinical Recommendations.** No specific recommendation.

**Standard, Options, and Recommendations.** ‘Patients with a single metastatic site can be offered specific treatment (option, expert agreement).’

**integrating prognostic factors in decision-making of patients with CUP**

Besides the recognition of specific subset of CUP with a specific treatment and a better outcome, progress has recently been made to identify prognostic factors among the vast majority (about 80–90%) of patients with CUP who do not fall into one of these favorable subsets. A number of studies with multivariate analyses identified poor performance status, an elevated serum lactate dehydrogenase (LDH) level, and, in some studies, liver metastases, as the main independent adverse prognostic factors [11, 14, 15]. Specifically, the combined use of performance status and serum LDH allows to identify and to validate two prognostic subgroups with median overall survival rates of 4 months and 12 months, respectively [14]. The knowledge of these prognostic factors may help the oncologist to refine the daily management of patients, to assess the results of and to better design clinical trials. A proposal of 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 1.

Whether we should integrate new biological/pathological features (such as micro-array profiling or cytokeratine profiling in decision-making and hopefully also new anticancer drugs in this decision tree), is a challenge for further research.

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**references**


