

12a

The clinical problem of Cancer of Unknown Origin

E. Bombardieri (Milano)

Cancer of Unknown Origin (CUO) or Unknown Primary (CUP) is defined as the presence of a metastatic cancer without a known primary site of origin. This entity is a real diagnostic problem and a therapeutic challenge. CUP comprises 2-4 % of all malignancies and with few exceptions has a grave prognosis (mean survival 5-6 months). The overall 5-year survival is less than 10 % . Treatment of CUP depends on many factors, including the site and the extension of metastases, the microscopic features of the cancer cells, and the patient's age.

Patients with an unidentified primary cancer are an heterogeneous group including poorly differentiated carcinoma, adenocarcinoma, neuroendocrine tumours, squamous cell carcinoma, melanoma. When the cancer cells are poorly differentiated the tumour may be either a lymphoma or a germ cell tumour. It is crucial to identify those treatment-responsive presentations in order to obtain a better survival. Some types of secondary cancers from unknown primaries are responsive to treatment based on chemotherapy, hormone therapy or radiotherapy, alone or in combination. Recent advances in diagnostic techniques have improved the possibility to detect the primary site and in this case the management of the patient can be carried out tailoring the therapy according to the specific tumour type.

The reasons why the primary tumour cannot be found are different: a) the primary tumour has disappeared because the immune system may have destroyed the primary origin; b) the secondaries may have grown very quickly and the primary is too small to be detected with imaging modalities; c) the primary tumour is hidden by the secondaries or several anatomical conditions; d) some tumours of the lining of the digestive system may have been eliminated through the bowel.

The diagnostic options are based on signs and symptoms (not always present), clinical examination, biopsies (fine needle, core needle, excisional, incisional, bone marrow biopsy), blood test (blood cell counts and examinations, serum tumour markers), pathology (immunohistochemistry, electromicroscopy, flow cytometry, cytogenetics, molecular testing),

imaging studies (chest X-ray, computed tomography, magnetic resonance imaging, ultrasound, X-rays of the G.I. tract, endoscopy).

In particular PET and PET/CT imaging has been validated for localization and staging of many tumours. Sixteen studies (involving a total of 302 patients with cervical lymph node metastases) published over 10 years evaluated the role of PET in the detection of unknown primary tumours after conventional workup. In all studies the conventional workup included endoscopy and CT or MRI. The overall sensitivity, specificity and accuracy rates of PET in detecting unknown tumours were 88.3 % , 74.5 % and 78.8 % respectively. Furthermore PET detected 24.5 % of tumors not depicted by the conventional workup. In addition PET imaging also led to detection of previously unrecognized metastases in 27.1 % of patients. In the same way, many other investigations support that PET imaging is very effective in imaging unknown primary tumours in different series of patients with metastases in other sites.

It is not still clear if PET scan should be adopted in the clinical management of all unknown primary patients or only in a selected series of patients. However there is no doubt that the use of PET can strongly contribute to decline the frequency of unknown primary cancers, mainly in association with the increased specificity of the pathologic diagnostics (immunologic and molecular genetic).

References

- 1) Hainsworth JD, Greco FA Management of patients with cancer of unknown primary site *Oncology* 2000; 14:563-574
- 2) Mintzer D.M., Warhol M., Martin A.M., Greene G. Cancer of Unknown primary: changing approaches *The Oncologist* 2004;9:330-338
- 3) Pantou D, Tsarouha E, Papadopoulou A cytogenetic profile of unknown primary tumours: clues for their pathogenesis and clinical management *Neoplasia* 2003, 5:23-31



- 4) Kole AC, Nieweg OE, Pruim Detection of unknown occult primary tumours using positron emission tomography *Cancer* 1998;82:1160-1166
- 5) Rades D, Huhnel G, Wildfang I Localised disease in cancer of unknown primary: the value of PET for individual therapeutic management *Ann Oncol* 2001;12:1605-1609
- 6) Rusthoven KE, Koshy M, Paulino AC The role of fluorodeoxyglucose PET in cervical cancer lymph node metastases from unknown primary tumour *Cancer* 2004;101:2641-2649