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## Does PET/CT change the approaches and decline the frequency of CUP?

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The Cancer of Unknown Primary (CUP), i.e. the presence of a metastatic tissue without a known primary site of origin represents a difficult diagnostic and therapeutic challenge, and it accounts for 2-4 % of all malignancies. Although in an unknown proportion of cases the metastatic site may represent the only presence of malignancy (because of involution, destruction or elimination of the primary site), the remaining majority of cases represent the failure of diagnostic procedures in identifying the primitive localization. This may prevent a tailored therapeutic approach, which explains the poor prognosis of CUP syndrome. Therefore a big effort should be accomplished in order to reduce the number of "CUP syndromes", thus providing a more rational and tailored approach to therapy, with the hope of improving prognosis and survival of these patients.

Previous reports describe that in CUP syndrome only 10-35 % of the primary sites are detected by conventional imaging modalities (1); on the other hand, several studies have indicated that Positron Emission Tomography (PET) with <sup>18</sup>F-fluorodeoxyglucose (FDG) is useful to locate primaries both in patients with tumor metastases within the head and neck region, and in patients with extracervical metastases, with detection rate ranging between 24 and 53 % (2).

In 2001 these data led the German Consensus Conference to recognize the whole body FDG-PET study as a class I-a diagnostic technique (i.e. scientifically proved benefit and established clinical use) in patient with CUP syndrome (2).

Subsequently, the clinical introduction of combined PET/CT tomographs, by allowing the simultaneous acquisition of accurately aligned whole body anatomical and functional images, resulted to be more accurate than PET alone in assessing presence and location of tumor foci and therefore in tumor staging; similar benefits could be expected in metastatic cancer of unknown primary origin.

Recently, three different papers (3-5) studying heterogeneous populations with CUP syndrome, including patients with cervical lymph node metastases and extracervical metastases, agreed on the concept that dual-modality PET/CT is "a promising alternative to separate acquisition of morphologic and functional data when assessing patients with cancer of an unknown primary tumor", showing that whole body FDG-PET/CT technique has an interesting sensitivity associated with a high positive predictive value..

Furthermore, because FDG-PET scan today is strongly indicated in the disease staging of most oncological patients, this indication should be considered in patients with CUP syndrome to plan an adequate oncological treatment (as instance, in our experience, in 48.5 % of patients, the disease management was influenced by PET scan findings).

These results support the idea that, in CUP syndrome, whole body PET/CT scan with FDG has a high clinical impact and should be performed early in the workup of these patients.

However, because of the limits in the available scientific studies and in particular of the limited number of the cases included in each single study, compared to the extremely heterogeneous cohort of patients presenting with CUP syndrome, until now FDG-PET/TC has often been considered only at the end of an unsuccessful conventional diagnostic approach, and not in the early phases of diagnostic workup, with considerable losses of time and money.

Considering recently published studies, whole body FDG-PET/CT has to be considered a useful tool in CUP syndrome, allowing an identification of primary tumors in 1 out of 3 cases (thus reducing of about 1/3 the number of CUP syndromes), and modifying the stage of the disease and oncological treatment in about 50 % of cases. These results suggest the use of PET/CT with FDG in an early phase of the diagnostic workup to optimize management in these patients.



### References

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