Carcinoma of unknown primary (CUP); some considerations about pathogenesis and diagnostic strategy, particularly focusing on CUP$_S$ pertaining to the Urology

C. ALBERTI

SUMMARY: **Carcinoma of unknown primary (CUP); some considerations about pathogenesis and diagnostic strategy, particularly focusing on CUP$_S$ pertaining to the Urology.**

C. ALBERTI

The term "carcinoma of unknown primary" (CUP) defines a malignant condition in which a metastatic cancer is documented in absence of a detectable primary site. It occurs in about 2÷6 % of cancer patients, according to various literature reports. The primary tumor site results indefinable because of several either single or associated factors, even remaining occult at autopsy in 15÷25% of CUP patients. The metastatic spread pattern of CUP is quite unlike that expected for analogous known primary malignancy. For instance, the unknown prostate cancer often metastasizes to the lungs and liver while the its known analogous usually spreads to the bone. Whether certain genetic abnormalities might play a role in determining a CUP condition, it remains undefined. Most CUP are adenocarcinoma, squamous cell carcinoma, either undifferentiated or differentiated carcinoma, whereas less frequently may be sarcoma, melanoma or neuroendocrine tumor. As CUP diagnostic management is concerned, two opposite approach modalities may be adopted, one, named "shotgun modality", consisting in a multiplicity of examinations aimed at achieving the identification of the primary tumor and the other, a nihilistic modality, by adopting tout court a palliative therapy of the metastatic disease. A reasonable intermediate diagnostic strategy consists in undertaking some procedures with a specific target and low cost/benefit ratio. Selected imaging studies, serum tumor markers, immunohistochemical analyses and genetic-molecular examinations on biopsy material allow sometimes to reach the detection of primary malignancies that might be responsive to a potential treatments. Nevertheless, in spite of recent sophisticated -laboratory and imaging progress, CUP remains a strong challenge in clinical oncology.

RIASSUNTO: **Carcinoma a sede primitiva occulta (CUP); alcune considerazioni su patogenesi e strategia diagnostica, soprattutto circa i CUP$_S$ concernenti l'Urologia.**

C. ALBERTI

Il termine "carcinoma a sede primitiva sconosciuta" (carcinoma of unknown primary, CUP) configura una condizione neoplastica in cui è documentata la presenza di metastasi in assenza di dimostrabile tumore primitivo. Secondo i dati della letteratura, tale condizione incide per il 2÷6 % dei pazienti affetti da cancro. La sede neoplastica primitiva risulta indefinibile a causa di diversi fattori, rimanendo addirittura occulta all'autopsia nel 15÷25 % dei pazienti con CUP. Il pattern di metastatizzazione del CUP è affatto dissimile da quello tipico di analoghi tumori primitivi "noti". Ad esempio, il CUP della prostata sovente metastatizza al polmone ed al fegato mentre il cancro prostatico "noto" comunemente metastatizza alle ossa. I CUP, per la maggior parte dei casi, sono adenocarcinoma, cancro a cellule squamose, carcinoma differenziato o indifferenziato, mentre meno frequentemente figurano sarcoma, melanoma o tumore neuroendocrino. Circa la gestione diagnostica dei CUP, due modalità diverse di approccio possono essere adottate, una, a mo' di "sparo con fucile da caccia", consistente in una molteplicità di esami intesi ad individuare il tumore primitivo ed un'altra, relativamente astensionista, volta ad attuare tout court una terapia palliativa della malattia metastatica. Una ragionevole strategia, intermedia tra le due sopra accennate, consiste nell'intraprendere alcune procedure diagnostiche mirate su determinati bersagli e con basso rapporto costo/beneficio. Esami di imaging ben selezionati, marcatori tumorali serici, analisi immunoistochimiche e studi genetico-molecolari su materiale bioptico consentono talvolta di scoprire tumori primitivi che possano essere responsivi a potenziali cure. Malgrado ciò, a fronte dei recenti progressi di sofisticate tecniche di laboratorio e d'imaging, il CUP costituisce ancora una grossa sfida in oncologia clinica.

KEY WORDS: Occult carcinoma - Distant metastasis - Urology - Surgery - Radiology.
Carcinoma occulto - Metastatizzazione - Urologia - Chirurgia - Radiologia.

---

* L.D. of Surgical Semeiotics, Italy

«Ὁκόσοισι κρυπτοὶ καρκίνοι γίνονται,
μὴ θεραπεύειν βέλτιον»

(*Hippocrates*, Aphorism 38)

Carcinoma of unknown primary (CUP) – also named occult carcinoma, recalling the occurrence of metastases from unknown primary tumor site – is an uncommon malignant condition in which metastases are documented without the identification of the primary tumor site (tumor-orphan metastases), even after an intensive search. Indeed, in spite of modern sophisticated diagnostic procedures, also detailed analyses are unsuccessful in detecting the primary site of tumor origin for a subset of patients with metastatic disease. It occurs approximately in 2-6% of cancer patients, whose 15-25%, according to various literature reports, remain undefined even at post-mortem examinations, making CUP seventh in order of frequency after lung, breast, prostate, colon, cervix uteri and stomach tumors (1-5).

Pathogenetic conditions and pathological features

The primary tumor may not be detected because of different either single or associated factors such as its extremely small size or possible local regression due to antitumor immune defences as well as its protracted clinical latency compared with early metastatic spread via atypical pathways or even its previous unaware removal during radical organ surgery because of nonmalignant pathology (e.g., hysterectomy to treat a fibromatous uterus also affected by an unidentified small malignancy) (4-6).

The *metastatic pattern* of tumor presenting as CUP is sometimes absolutely unlike that peculiar to usual appearance. For instance, the bone spread prevailing over that hepatic has been often shown for pancreatic cancers presenting as CUP. Just recently, an intracardiac metastasis has been oddly found as the first sign of an initially unknown esophageal squamous cell carcinoma (7, 8).

Whether certain genetic factors might play a role in to inducing a CUP condition, it remains undefined. However Met oncogene activating mutations appears to be often implicated in the premature metastatic dissemination as such gene encodes for c-Met tyrosine kinase receptor for HGF (hepatocyte growth factor) that promotes early cancer invasion by increasing cell motility (9, 10).

Most CUP are adenocarcinoma (34.8%), squamous cell carcinoma (24.6%), undifferentiated carcinoma (20.4%), carcinoma (20.2%), whereas less commonly may be melanoma, sarcoma and, in very small percentage (2%), neuroendocrine tumor (10-12). Pancreas and

lung are the most frequent site of cancers initially presented as CUP, while other organs, such as bowel, prostate, breast, infrequently resulting the primary site of tumors at first thought as CUP$_S$ (3, 13).

Clinical and laboratory diagnostic approaches

CUP is a heterogeneous neoplastic entity with a variety of clinical features (1, 5, 6, 12). Different symptoms and signs of CUP – pain, cough, bleeding, changes in bowel or urinary bladder habits – depend on where the metastatic spreading has took place, although some CUP may be subjectively asymptomatic. Possible thickening and lump everywhere in the body, weight loss, skin changes must be properly evaluated. There are rare instances of CUP systemic *ouverture,* in the form of cryptogenic fever, thrombophlebitis migrans, fasciitis-panniculitis, hypercalcemia, Cushing's syndrome from ectopic ACTH, what resulting included in so-called *CUP syndrome*, that «reflects a clinical state of advanced cancer due to metastatic deposit more symptomatic that its unknown primary» (14). Some *paraneoplastic syndromes* – either endocrine such as ectopic ACTH syndrome and paraneoplastic hyperparathyroidism or immunoreactive –, rather than indicating the distant metastasis, may at times point out the presence of a deep visceral tumor (15).

As CUP diagnostic procedures are concerning, apart from those routine performed – case history, clinical evaluation including digital rectal examination in men and breast-pelvic examination in women, complete blood cell count, blood chemistry with liver-renal function analysis, serum lactate dehydrogenase levels, fecal occult blood test, chest x-ray – two opposite approaches have been adopted: a «shotgun modality » by resorting to a wide range of examinations aimed at reaching the detection of the primary malignancy and, on the other hand, an nihilistic approach in which a *tout court* sheerly palliative therapy of CUP is prefered to thorough investigations (1, 4, 8, 16). A reasonable intermediate choice consists in undertaking some procedures with a specific diagnostic target and low cost/benefit ratio. In this regard, the diagnostic tests to detect the site of primary tumor depend on where the metastatic spread has taken place, although the CUP metastatic pattern might be really different from that usually appearing for a known primary tumor (17-19).

Selected imaging studies – CT, RMI, PET, hybrid either PET/CT or PET/RMI – of the head/neck, chest, abdomen and pelvis may be performed to identify the primary site and show the extent of malignancy together with allowing a targeted biopsy. *Mammography* should be carried out in women with bone/lung metastases, particularly if associated with an axillary adenopathy, MRI

of the breast resulting useful when x-ray and ultrasound findings are negative in spite of suspected breast tumor.

Endoscopic examinations, such as laryngo-broncho-scopy, esophago-gastro-duodenoscopy, colonoscopy and cystoscopy, must be reserved for symptomatic patients or when the resort to them might be suggested by laboratory or/and imaging pathological findings (5, 20, 27).

Most serum tumor markers – CA 19-9, CEA, CA-125, CA 15-3 – are non peculiar to locate the primary malignancy site, whereas high levels of β-hCG (β-human chorionic gonadotropin) and α-FP (α-fetoprotein) might suggest the presence of extragonadal germ cell tumors (EGCT). Osteoblastic metastases in men require PSA (prostate specific antigen) test to attribute them to primary prostate carcinoma (1, 4, 8, 20, 27). Serum chromogranin and urinary 5-HIAA (5-hydroxy-indoleacetic acid) levels are reliable markers of both neuroendocrine tumors and neuroendocrine differentiation in carcinomas (11, 21). When the aforesaid examinations allow to show where predictably might be the primary site of tumor, the either excisional/incisional biopsy or large-needle core/fine-needle aspiration biopsy is done and if the histo-cytopathology is not consistent with that expected to be found, a final diagnosis of CUP may be assumed. In the field of biopsy-specimen examinations, the immunohistochemistry, electron microscopy and molecular-genetic studies must be today included to reach a more thorough insight into the diagnostic puzzle of CUP. Particularly *immunohistochemical analyses* are extremely reliable to define the neoplastic lineages. The use of specific monoclonal antibodies to 20 subtypes of cytokeratin (CK) intermediate filaments can allow to locate the site of CUP origin. Indeed, CK20 is expressed in the urothelium, gastro-intestinal epithelium and Merkel's cell tumors while CK7 stains are positive in lung, endometrium, breast, ovary, pancreatico-biliary malignancies. Similarly, thyroglobulin tissue marker and thyroid transcription factor-1 (TTF-1) nuclear stain are typically positive in thyroid cancers as well as URO-III cytokeratin-thrombomodulin-CK20 and PSA immunohistochemical tests are used to respectively diagnose tumors of either urothelial or prostatic origin. Cytokeratin/vimentin co-expression is distinctive of renal clear-cell carcinoma (20-24). Particularly, thyroid occult cancer, as well as that latent, because of their insidiously malignant features, must be thoroughly assessed and aggressively treated (24).

Positive stains for Glut-1 (glucose transporter-1), HIF-1α (hypoxia-induced factor-1) and COX-2 (cyclo-oxygenase-2) in squamous cell carcinoma are associated with a poor prognosis (12). Chromogranins, synaptophysin, neuron specific enolase are immunohistochemically significant for neuroendocrine pattern tumors whereas S-100 and HMB-45 positive stains suggest the diagnosis of melanoma (1, 4, 8, 10, 20, 25, 27).

Genome-wide expression profiling technologies allow to characterize today the molecular state of both CUP cell types and microenvironmental epithelial/stromal cells surrounding the tumor. Gene profile has been frequently studies in different CUP samples by commonly using DNA microarray or quantitative RT-PCR (reverse transcriptase-polymerase chain reaction). Overexpression of several genes – such as bcl-2, Ras, p53, Her-2 – has been shown in different CUP specimens, nevertheless without significantly indicative results (4, 25). Met oncogene activating mutations, instead, may sustain an early metastatic process of occult carcinoma, thus resulting a validated genetic marker associated with CUP (9). However, given the both availability and diagnostic reliability of immunohistochemical examinations, the cytogenetic studies should be reserved for undifferentiated tumors with undefined immunohistochemistry findings. Indeed, intriguing prospective gene signature studies, using microRNA-based assay, have been performed to identify the tissue of primary tumor site in CUP patients with non-diagnostic metastasis immunohistochemistry profile (4, 20, 25-29).

Uro-genital system implications in the CUP problems

The urological scenario in the field of CUP may be examined by considering the uro-genital system as either primary (**a**) or metastatic (**b**) site of CUP (Table 1). As for **a**), the frequency, at autopsy, of kidney, prostate, adrenal gland and testis clinically non-identified tumors is absolutely lower than those of pancreas, lung, large bowel, liver-biliary tract and stomach. Their metastasis pattern is quite different from that expected for analogous known primary malignancies. Indeed, whereas the known *prostate carcinoma* usually spreads to the bone, the unknown equivalent, instead, mainly metastasizes to the lung and liver. As a matter of such discrepancy, the usual vertebral spread is due to low spine-epidural venous flow rate together with its to and fro blood stream because of the absence of valves while the metastasis to the liver implies prostato-rectal neoangiogenesis-induced venous by-pass, hence a preferential portal drainage (19). Still regarding the prostate CUP, the patient's clinical history should always be examined for past endoscopic BPH (benign prostate hyperplasia) treatments – such as electrovaporization and holmium- or thulium laser-induced adenoma ablation – since it is clear that coagulation/vaporization do not allow the detection of an incidental carcinoma and, therefore, its casual link with subsequent appearance of metastases (19). The discrepancy of metastatic spread between an occult and a known form is, instead, not relevant for *kidney tumors* given the anyhow capricious dissemination even of the

TABLE 1 - UROLOGICAL SCENARIO OF THE OCCULT CARCINOMA.

a) Uro-genital system as primary site of tumors remaining occult	b) Uro-genital system as site of metastasis from unknown primary tumors
CUP$_S$ of kidney, prostate, adrenal gland and testis, as compared with those of pancreas, lung, biliary tract and large bowel, are placed down in the frequency of primary tumor site, at necropsy.	Frequency-scale of metastatic spread sites from occult primary tumor: • Lung • Liver • Bone • **Kidney**, adrenal gland The incidence of metastasization to the adrenal gland is on a par with that to the kidney. Such gland, if account is taken of its small weight and size, is the prevalent metastatic target, often bilaterally, from lung, breast, large bowel, prostate, kidney tumors as well as melanomas and neuroendocrine malignancies

Primary site	Frequency %
• Pancreas	21
• Lung	21
• Large bowel	11.5
• Liver, biliary tract	10.5
• Stomach	10
• **Kidney**	6.5
• Ovary	6
• **Prostate**	4
• Breast	3
• Thyroid	2
• Adrenal gland	1.5
• **Testis**	1
• Other	2

(means from the literature review)

known renal cell carcinoma. As far as *testis tumors* are concerned, several studies suggest that most so-defined primary retroperitoneal germ-cell tumors are actually metastases from testicular malignancies undetected by physical examination and ultrasounds. On the contrary, the true extragonadal germ-cell tumors may arise either from abnormal migration of yolk sac ectoderm-derived germ-cells to the gonadal region or from the blastula totipotent stem cells, such tumors mainly usually lying in midline body structures such as mainly mediastinum and retroperitoneum, sometimes central nervous system and occasionally prostate gland, bladder, liver. The presence of little testicular tumors runs the risk of remaining, for a long lime, unsuspected because the attention may be directed elsewhere by metastasis-dependent lumbar-abdominal pain, cough, respiratory distress, supraclavicular swellings. Leydig-cell testicular tumors, as well as adrenal gland functioning malignancies, do no present similar problematic conditions since their hormonal products can easily direct to the identification of the primary tumor site. As for b) both *renal* and *adrenal* metastatic dissemination from CUP is fourth, in decreasing order of frequency, after lung, liver and bone, while the most common primary sites, in increasing order of frequency, are pancreas, stomach, breast and lung. A solitary renal metastasis, without evidence of a tumor in another organ, is often preoperatively classed as a primary tumor. Exfoliative pyelocalyceal cytology is of little assistance since parenchymal metastases seldom come to

surface sheding tumor cells from the calices and pelvis together with, for the same reason, exceptionally causing hematuria. Adrenal glands, given their small size and weight, are an important target for metastatic spread – nearly always bilateral – from lung, breast, colon, prostate and kidney malignancies, particularly when they show neuroendocrine features such as pulmonary oat cell carcinoma or neuroendocrine-differentiated prostate carcinoma as well as they are neuroectoderma-derived tumors like melanoma (11, 20, 21, 22, 27).

Conclusive remarks

The unability to detect a primary site of a subset of patients with metastatic tumor arouses intriguing challenges (1, 5, 6, 8, 20, 27). Clinical and pathological examinations to find the primary malignancies which might be responsive to a potential treatment – such as breast, ovarian, prostate, germ-cell tumors and lymphomas – must be undertaken.

Recent lab advances allow great selectivity in reaching a diagnosis from biopsy of the metastatic material, particularly in characterizing poorly differentiated tumors as of epithelial, neuroendocrine or neuroectodermal, hematopoietic origin. In this regard, an indication on the typology of an occult epithelial tumor is offered by the ultrastructural appearance in *electron microscopy*, since microacinic spaces and surface microvilli are associated with

adenocarcinomas whereas tonofilaments are typical of squamous cell carcinomas. Moreover, electron dense core granules are diagnostic of neuroendocrine tumors (11, 21-23). As far as *immunohistochemistry* is concerned, monoclonal antibodies to cell-specific tumor-associated antigens can characterize the nature of CUP. About that, indeed, specific anti-cytokeratin, anti-epithelial membrane and anti-leucocyte antibodies play an important role to identify undifferentiated malignancies (1, 5, 16, 20, 21, 27, 31). Positivity of either β-HCG and α-FP or PSA immunohistochemical markers is respectively indicative of germ-cell tumors or prostate carcinoma (27, 31, 33). Moreover, the status of androgen/estrogen receptors may allow the pathological assessment of metastases from hormone-dependent neoplasms (20, 27, 32).

Chromosome and molecular-genetic studies may help to identify the tumor cytotype: e.g., isochromosome of the short arm of chromosoma 12 is typically associated with both gonadal and extragonadal germ-cell tumors (25, 26, 29). Intriguingly, the cytotype emerging from *in vivo* cloning of undifferentiated tumor tissue to obtain a certain cell re-differentiation through specific "differentiation inducers", could provide a clue to the primary malignancy (33).

Modern imaging techniques – CT, MRI and PET – and tissue characterization by magnetic resonance spectroscopy, have reduced the resort to many invasive examinations such as hemo- or lymphangiography and, particularly, to open-exploratory surgical procedures (17, 18, 27, 34).

Nevertheless, in spite of noteworthy laboratory and imaging advances, CUP remains a great problem in clinical oncology, as representing a mortifying diagnostic stumbling-block in the current cultural phase in that one is increasingly less inclined to accept any diagnostic, hence therapeutic defeat (4, 5, 18, 25, 27, 34-37). The physician's both diagnostic talent and cultural synchretism skill prove to be excellent in such obscure clinical conditions by brightly lifting the veil from the occult so as to adopt a suitable treatment, about that outclassing, albeit...with due respect, the ancient Hippocratic aphorism «those who suffer from occult tumors must not be treated» (38).

References

1. Hess KR, Abbruzzese MC, Lenzi R et al. Classification and regression tree analyse of 1000 consecutive patients with unknown primary carcinoma. Clin Cancer Res 1999; 5: 3403-3410.

2. Briasoulis E, Pavlidis N. Cancer of unknown primary origin. Oncologist 1997; 2: 142-152.

3. Cristoforo MG, Giudice A, Colangeli W, Giudice M. Unique and rare bone metastases from occult primary cancer. Ann Ital Chir 2011; 82: 289-296.

4. Varadhachary GR, Spector Y, Abbruzzese JL et al. Prospective gene signature study using microRNA to identify the tissue of origin in patients with carcinoma of unknown primary. Clin Cancer Res 2011; 7: 4063-4070.

5. Dennis JL, Oien KA. Hunting the primary: novel strategies for defining the origin of tumours. J Pathol 2005; 205: 236-243.

6. Shu X, Liu H, Ji J et al. Subsequent cancers in patients diagnosed with cancer of unknown primary: etiological insights? Ann Oncol 2012; 23:269-275.

7. Tayama K, Enomoto N, Kohno M et al. Intracardiac metastasis of esophageal squamous cell carcinoma: report of a case. Ann Thorac Cardiovasc Surg 2011; 17: 166-169.

8. Hainsworth JD, Greco FA. Treatment of patients with cancer of an unknown primary site. N Engl J Med 1993; 329: 257-263.

9. Stella GM, Benvenuti S, Gramaglia D et al. Met mutations in cancers of unknown primary origin. Hum Mutat 2011; 32: 44-50.

10. Pavlidis N, Briasoulis E, Hainsworth J et al. Diagnostic and therapeutic management of cancer of an unknown primary. Eur J Cancer 2003; 39: 1990-2005.

11. Stoyianni A, Pentheroudakis G, Pavlidis N. Neuroendocrine carcinoma of unknown primary: a systematic review of the literature and a comparative study with other neuroendocrine tumors. Cancer Treat Rev 2011; 37: 358-365.

12. Koo JS, Kim H. Hypoxia-related protein expression and its clinicopathologic implication in carcinoma of unknown primary. Tumour Biol 2011; 32: 893-904.

13. Altman E, Cadman E. An analysis of 1539 patients with cancer of unknown primary site. Cancer 1986; 57: 120-124.

14. Nissenblatt MJ. The CUP syndrome (carcinoma of unknown primary). Cancer Treat Rev 1981; 8: 211-224.

15. Alberti C. Sindromi paraneoplastiche correlate a tumori dell'apparato uro-genitale: rassegna d'aggiornamento. G. Chir 2008; 29: 437-448.

16. Mayordomo JL, Guerra JM, Guijarro C et al. Neoplasms of unknown primary site: a clinicopathological study of autopsied patients. Tumori 1993; 79: 321-324.

17. Hu M, Zhao W, Zhang PL at al. Clinical applications of 18F-fluorodeoxyglucose positron emission tomography computed tomography in carcinoma of unknown primary. Chin Med J 2011; 124: 1010-1014.

18. Park JS, Yim JJ, Kang WJ et al. Detection of primary sites of unknown primary tumors using FDG-PET or FDG-PET/TC. BMC Res Notes 2011; 4: 56.

19. Alberti C. Unknown primary carcinoma in Urology. Acta Urol Ital 1995; 1: 35-38.

20. Abbruzzese JL, Abbruzzese MC, Lenzi R et al. Analysis of a diagnostic strategy for patients with suspected tumors of unknown origin. J Clin Oncol 1995; 13: 2094-2103.

21. Garrow GC, Greco FA, Hainsworth JD. Poorly differentiated neuroendocrine carcinoma of unknown primary site. Semin Oncol 1993; 20: 287-291.

22. Tasdemir C, Turkmen Samdauci E, Dogan M et al. Primary malignant melanoma of kidney. Eur Rev Pharmacol Sci 2011; 15: 971-972.

23. Lobins R, Floyd J. Small cell carcinoma of unknown primary. Semin Oncol 2007; 34: 39-45.

24. Di Matteo G, Lucci S. Thyroid occult cancer: correct approach and treatment. G Chir 1983; 4: 121-124.

25. Varadhachary GR, Talantov D, Raber MN et al. Molecular profiling of carcinoma of unknown primary and correlations with clinical evaluation. J Clin Oncol 2008; 26: 4442-4448.

26. Horling HM, van Laar RK, Kerst JM et al. Gene expression profiling to identify the histogenetic origin of metastatic adenocarcinoma of unknown primary. J Clin Oncol 2008; 26: 4435-4441.

27. Greco FA, Hainsworth JD. Cancer of unknown primary site. In: De Vita VT Jr, Hellman S, Rosenberg SA, eds. Cancer, principles and practice of Oncology. 8th ed. Philadelphia, USA. Lippincott Williams & Wilkins, 2008, pp. 2363-2387.

28. Christensen JG, Burrows J, Salgia R. c-Met as a target for human cancer and characterization of inhibitors for therapeutic intervention. Cancer Lett 2005; 225: 1-26.

29. Bosl GJ, Ilson DH, Rodriguez E et al. Clinical relevance of the i (12p) marker chromosome in germ-cell tumors. J Natl Cancer Inst 1994; 86: 349-355.

30. Goss PE, Schewertfeger L, Blackstein ME et al. Extragonadal germ-cell tumors. Cancer 1994; 73: 1971-1979.

31. Fujimoto J, Hata JI, Ishii E et al. Differentiation antigens defined by mouse monoclonal antibodies against human germ-cell tumours. Lab Invest 1987; 57: 350-355.

32. Ruddon W. Tumor markers in the recognition and management of poorly differentiated neoplasms and cancers of unknown origin. Semin Oncol 1982; 9: 416-426.

33. Robert NJ, Garnick MB, Frei E. Cancer of unknown origin: current approaches and future perspectives. Semin Oncol 1982; 9: 526-531.

34. Pejcić I, Vrbić S, Filipović S et al. Significance of serum tumor markers monitoring metastases in carcinoma of unknown primary site. Vojnosanit Pregl 2010; 67: 223-231.

35. Rades D, Kühnel G, Widfang I et al. Localised disease in cancer of unknown primary: the value of positron emission tomography for individual therapeutic management. Ann Oncol 2001; 12: 1605-1609.

36. Wang SH, Lee JC, Liu TC. Occult prostate cancer detected by hyoid bone metastasis after resection of thyroglossal duct cyst. Int J Oral Maxillofac Surg 2011; 40:1326-1328.

37. Knee TC, Basu S, Alavi A. PET and PET/CT for unknown primary tumors. Methods Mol Biol 2011; 727: 317-333.

38. Hippocrates. Aphorismes, 38. In: Oeuvres complètes d'Hippocrate. Traduction par E. Littre, tome IV. A.M. Hakkert Editeur, Amsterdam, 1978, p. 572.