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MINI REVIEW

A mini review on cancer of unknown primary site: A clinical puzzle for the oncologists

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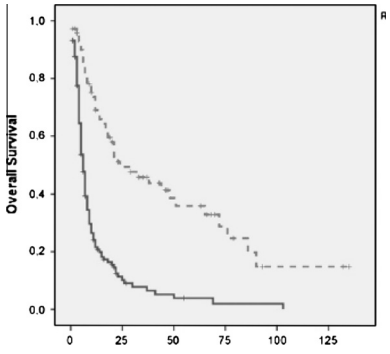
GRAPHICAL ABSTRACT



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ABSTRACT

Cancer of unknown primary (CUP) is a well recognized clinical syndrome, accounting for 3–5% of all malignancies. It is characterized as a disease with an early dissemination of metastases without a primary detected site after extensive laboratory and clinical investigations. CUP is divided into the favorable and unfavorable groups based on histopathological and clinical manifestations. Adenocarcinoma of various differentiations is the commonest histopathological subtype. Favorable groups are treated with local or systemic treatment and some of them are enjoying long-term survival. On the contrary, unfavorable groups are treated with empirical

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chemotherapy having usually a dismal prognosis. Gene-profiling microarray diagnosis has a high diagnostic sensitivity, but its predictive or prognostic value remains uncertain.

Keywords:
Cancer
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Introduction

CUP is a common disease with an incidence of 3–5% among other epithelial tumors. Worldwide the overall age-standardized incidence per 100.000 people per year is ranging between 4–19 cases. It is characterized as a metastatic cancer diagnosed without the primary site, despite histopathological and radiological laboratory investigations. The median age at diagnosis is 60 years with a male predilection [1].

Today, the definition of CUP includes patients who present with histologically-confirmed metastatic cancer in whom a detailed medical history, complete physical examination including pelvic and rectal examination, full blood count and biochemistry, urinalysis and stool occult blood testing, histopathological review of biopsy material with the use of immunohistochemistry, chest radiography, computed tomography (CT) of the abdomen and pelvis and, in certain cases, mammography and PET scan fail to identify the primary site [1].

Biology of CUP

CUP's biology is poorly understood although several molecular or translational research studies are available. One hypothesis postulates that CUP does not undergo type 1 progression (from a premalignant lesion to malignant) but instead it follows a type 2 progression without forming a primary site. A second hypothesis supports that CUP follows the parallel progression model, where metastases can arise early in the development of a malignant process [2,3].

Several research data have shown that CUP rarely harbors activating point mutations in either oncogenes or tumor suppressor genes, has active angiogenesis in 50–80%, overexpress various oncogenes in 10–30%, hypoxia-related proteins in 25%, epithelial–mesenchymal transition markers in 16% and have activated intracellular signaling axes such as AKT or MAPK in 20–35% [4–6] (Table 1). Very recently global microRNA profiling showed no significant expression differences with metastases of matched known primary tumors failing to identify any specific "CUP signature" [7,8].

Clinicopathological subsets

CUP is associated with a short history of symptoms and signs, has an early dissemination with an aggressive behavior in most

Table 1 Molecular events in CUP patients.

N patients	Molecules	Method	Results	Prognostic/predictive value
Oncogenes				
420	HER-2	IHC	Overexpression 10–35%	None
50	HER-2	PCR	No mutations	–
201	EGFR	IHC	Overexpression 12–61%	Superior survival/correlated with response to cisplatin
126	c-Kit	IHC	Overexpression 3–13%	None
50	c-Kit	PCR	No mutations	–
173	PDGFR	IHC	Expression 3%	None
			Overexpression 10–25%	None
Tumor suppressor genes				
157	p53	IHC	Overexpression 48–53%	None
46	p53	PCR	Mutations 26%	None
Angiogenesis/hypoxia				
253	VEGF	IHC	Overexpression 26–83%	None
197	CD34	IHC	Density 56–59%	None
80	TSP-1	IHC	Overexpression 20%	None
125	HIF 1α	IHC	Expression 20%	Adverse prognostic factor
Tumor stroma				
76	MMP-2	IHC	Overexpression 49%	None
76	MMP-9	IHC	Overexpression 36%	None
76	TIMP-1	IHC	Overexpression 44%	Adverse prognostic factor
100	E-Cadherin	IHC	Expression 79%	
100	EMT-phenotype	IHC	Expression 8%	Adverse prognostic factor
Molecular pathways				
100	cMet	IHC	Expression 42%	Adverse prognostic factor
100	pMAPK	IHC	Expression 54%	Predictive for chemotherapy
100	Notch 3	IHC	Expression 73%	None
100	PTEN	IHC	Expression 50%	None
	pAKT	IHC	Expression 76%	Prognostic for survival
	pRPS6	IHC	Expression 59%	Prognostic for survival
	p21	IHC	Expression 60%	Prognostic for survival

IHC: immunohistochemistry, MMP = metalloproteinase, TIMP-1: tissue inhibitor of metalloproteinase 1, EMT: epithelial mesenchymal transition, HIF: hypoxia – inducible factors.

Table 2 Required investigations for searching the primary site.

Clinicopathological data
- Histologically confirmed metastatic cancer
- Detailed medical history
- Complete physical (including pelvic and rectal) examination
- Histopathology review with specific immunohistochemical study

Work-up for all patients
- Full blood count
- Biochemistry
- Urinalysis
- Testing for occult blood in stools
- Chest radiography
- CT scan of thorax, abdomen, and pelvis

Work-up for selected patients only
- Mammography (for all women)
- Breast MRI
- Testicular ultrasonography
- PET or CT scan
- Concentrations of serum α-fetoprotein and β human chorionic gonadotropin
- Concentrations of serum prostate-specific antigen (for all men)
- Concentrations of serum cancer antigen 125 and carcinoma antigen 15–3
- Endoscopy

Table 3 CUP subsets.

Favorable subsets
1. Women with adenocarcinoma involving axillary lymph nodes
2. Women with papillary adenocarcinoma of peritoneal cavity
3. Squamous cell carcinoma involving cervical lymph nodes
4. Poorly differentiated neuroendocrine carcinomas. Merkel cell carcinoma of unknown primary (localized disease)
5. Adenocarcinoma with a colon-profile ($CK20^+$, $CK7^-$, $CDX2^+$)
6. Men with blastic bone metastases and elevated PSA (adenocarcinoma)
7. Isolated inguinal adenopathy (squamous carcinoma)
8. Patients with a single, small, potentially respectable tumor
Unfavorable subsets
1. Adenocarcinoma metastatic to the liver or other organs
2. Poorly differentiated carcinoma
3. Non-papillary malignant ascites (adenocarcinoma)
4. Multiple cerebral metastases (adeno or squamous Ca)
5. Multiple lung/pleural metastases (adenocarcinoma)
6. Multiple metastatic bone disease (adenocarcinoma)
7. Squamous-cell carcinoma of the abdominal cavity

of the times (three or more organs are involved) and often carries unpredictable metastatic patterns. Unpredictable metastatic pattern at diagnosis refers to the differences in the incidence of metastatic sites between known and unknown primary carcinomas i.e. pancreatic cancer presenting as CUP has 4-fold higher incidence to affect bones, and 30% incidence to appear with lung metastases in contrast to the known natural history of known primary pancreatic cancer.

To search the primary site a number of investigations are required including clinical data, immunohistochemistry studies, blood tests, radiological techniques and endoscopic procedures [1]. Table 2 indicates the necessary investigations that should be performed in suspected CUP cases.

Since 2003 CUP is divided into two separated groups the favorable (20%) and the unfavorable (80%) group [9]. Favorable subsets are those entities that respond to local and/or systemic treatments and have a longer survival. Table 3 demonstrates the classification of CUP patients into various clinicopathological subsets.

Woman with adenocarcinoma involving axillary nodes

This is a CUP subset in which the primary site is most often hidden in the breasts. It has a presentation similar to breast cancer of stage II (N_2 or N_3 disease), and it affects exclusively women of a mean age of 52 years. The most frequent histology is ductal adenocarcinoma. Forty percent have positive estrogen receptors. After undergoing mastectomy, almost 70% of the patients have an occult breast primary identified [10].

Women with papillary adenocarcinoma of peritoneal cavity

This entity has also been called primary peritoneal carcinoma. Clinical presentation includes pain, ascites, abdominal masses or intestinal obstruction. Median age is 60 years. Histopathology is always compatible with serous papillary adenocarcinoma with or without psammoma bodies. Immunohistochemical expression of MUC10, estrogen receptors, mesothelin, WT1 and KRT7 can be found. Serum CA 125 is very often raised.

In comparison with primary ovarian cancer, primary peritoneal carcinoma affects older women, has more bulky disease and has more overexpression of HER 2 oncogene and Ki67 [11].

Squamous cell carcinoma involving cervical nodes

It is more frequent in men (80%) with a median age of 60 years and it constitutes 5% of all head and neck cancers. Clinical presentation includes a painless and unilateral cervical mass, most commonly affecting Level II lymph nodes (jugulodigastric or upper nodes). Fine needle aspiration has a diagnostic

Table 4 Immunohistochemistry tests for investigating CUP.

	Diagnosis
Step one	
AE1 or AE3 pan-cytokeratin	Carcinoma
Common leukocyte antigen	Lymphoma
S100; HMB-45	Melanoma
S100; vimentin	Sarcoma
Step two	
CK7 or CK20;PSA	Adenocarcinoma
PLAP; OCT4; AFP; human chorionic gonadotropin	Germ-cell tumor
Hepatocyte paraffin 1; canalicular pCEA, CD10, or CD13	Hepatocellular carcinoma
RCC; CD10	Renal cell carcinoma
TTF1; thyroglobulin	Thyroid carcinoma
Chromogranin; synaptophysin; PGP9.5; CD56	Neuroendocrine carcinoma
CK5 or CK6; p63	Squamous cell carcinoma
Step three	
PSA; PAP	Prostate
TTF1	Lung
GCDFP-15; mammaglobin; ER	Breast
CDX2; CK20	Colon
CDX2 (intestinal epithelium); CK20; CK7	Pancreas or biliary
ER; CA-125; mesothelin, WT1	Ovary

Table 5 Cytokeratins used in CUP.

	Cytokeratins
Colon	CK7−/CK20+
Stomach	CK7−/CK20+; CK7+/CK20+
Biliary	CK7+/CK20−; CK7+/CK20+
Pancreas	CK7+/CK20−; CK7+/CK20+
Lung	CK7+/CK20−
Ovarian, non-mucinous	CK7+/CK20−
Ovarian, mucinous	CK7−/CK20+; CK7+/CK20+
Breast	CK7+/CK20−
Urothelial	CK7+/CK20+
Endometrium	CK7+/CK20−
Prostate	CK7−/CK20−
Renal	CK7−/CK20−
Liver	CK7−/CK20−

accuracy of almost 95%. A panendoscopy with biopsy should follow. Radiology is very helpful with a sensitivity of CT-scan in 22%, MRI in 36% and PET-scan up to 60% [12].

Poorly differentiated neuroendocrine carcinoma

It represents the 90% of CUP neuroendocrine tumors, the rest being of well differentiated low grade histology. It affects males (65%) of a median age of 65 years. Retroperitoneal, mediastinal or peripheral lymph nodes are the most common dominant sites (40%) following by liver (25%) and bones (10–15%) [13].

Recently, neuroendocrine Merkel cell nodal carcinoma of stage IIIB has been recognized as having also a long-term survival [14].

Adenocarcinoma with a colon-profile ($CK20^+$, $CK7^-$, $CDX2^+$)

Up to now less than 100 cases have been reported mostly in women, with a median age of 57 years. Disease is extended in the abdomen involving abdominal nodes in 51%, peritoneal surfaces in 50%, liver in 30% and ascites in 27% [15,16].

Unfavorable subsets metastatic visceral or skeletal CUP

These are the most frequent subsets of CUP. They have a poor prognosis with a short survival. The most common histological types are adenocarcinomas of moderate to poorly differentiated (64%), the rest been undifferentiated tumors. It involves mainly the liver in 40–50% of the cases, followed by lymph nodes (35%), lungs (31%), bones (28%) and the brain (15%) [1,9].

Searching for the primary

Pathology and immunohistochemistry

Histopathology is one the most important avenue in the elaboration of CUP diagnosis. Immunohistochemistry with a wide battery of staining (including cytokeratins), is of a great value since it could differentiate between: (a) carcinoma, sarcoma or lymphoma, (b) adenocarcinoma, germ-cell tumor, hepatocellular, renal, thyroid, neuroendocrine or squamous carcinomas as well as (c) the primary site of an adenocarcinoma (lung, breast, ovarian, prostate, colon, pancreas or biliary cancer) (Tables 4 and 5) [17].

Molecular diagnosis

During the last decade commercial tests of gene profiling microarrays became available for the diagnosis of CUP. Assays on cDNA or miRNA platforms gave accuracy rates up to 93% in detecting the primary site and could probably allow particular and specific therapeutic management in CUP patients [18,19]. Whether this promising technology will lead us to better patients' outcome, it remains uncertain. A number of clinical trials are still ongoing.

Radiology

Over the past 30 years CT scan, MRI and PET-scan added substantially to the detection of primary site. CT scans provided a diagnostic accuracy of 55% (36–74%) mainly in pancreatic, colorectal and lung cancer, while MRI was found to be very sensitive in detecting primary breast cancers in 70% of cases [1].

Fluorodeoxyglucose (FDG) PET accuracy in CUP ranges between 25% and 43%. The most common primary sites detected by PET are lung cancer (33%), head and neck cancers (27%), followed by pancreatic, breast and colon cancers (4–5%). ^{68}Ga-DOTA-NOC receptor PET/CT is also very accurate in identifying primary neuroendocrine tumors or their metastatic lesions [20,21].

Endoscopy

Endoscopies in general, carry low accuracy rates and low sensitivity and specificity. Endoscopies should not be used in all CUP patients for the detection of primary site, unless they are clinically presenting with relevant symptoms and signs or in patients with specific histopathological findings. A colonoscopy should be requested in $CK7^+$, $CK20^+$ and $CDX2^+$ cases or bronchoscopy in $CK7^+$ and $TTF1^+$ patients [1].

Serum tumor markers

Elevated epithelial serum tumor markers can be overexpressed in CUP patients. In almost 70% of them two or three markers can be concomitantly increased in a non-specific way. CA-125, CA-15-3, CA19-9, CEA can be raised without any diagnostic, prognostic or predictive value. Therefore, routine request of these tumor markers is not recommended. However, in specific cases it might offer diagnostic aid such as serum prostate-specific antigen in men with osteoblastic bone metastases, CA125 in females with primary serous papillary peritoneal adenocarcinoma, or CA 15-3 in women with isolated axillary adenocarcinoma [22].

Molecular diagnosis

During the last ten years gene-expression profiling in the classification and detection of primary tumor sites has led to the development of commercially available tests. The accuracy

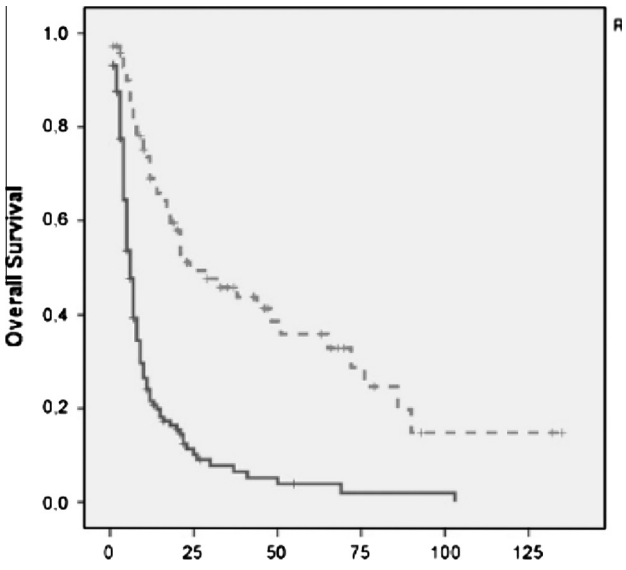


Fig. 1 Overall survival between CUP favorable and unfavorable patients treated at Ioannina University Hospital from 1995 to 2011. Favorable (- - - - -) and unfavorable (——).

rates of these tests are up to 90% but its validity in daily practice remains uncertain. Randomized prospective studies are needed to establish whether patients' outcomes are improved by its clinical use.

It should be added here, that the frequency of detecting the primary site by all conventional investigations antemortem is around 30% (excluding gene profiling techniques) whereas from the postmortem studies the detection could be up to 70% [9].

Therapeutic management (Table 6)

Women with adenocarcinoma involving axillary nodes

These patients should be treated with complete axillary dissection, ipsilateral breast radiotherapy followed by adjuvant chemotherapy and/or hormonotherapy depending on the risk factors. Patients without local treatment are associated with high locoregional relapse rates (40–55%). Survival is longer in patients who received primary breast radiotherapy as well as in patients with adjuvant systemic treatment [1,10].

Women with papillary adenocarcinoma of peritoneal cavity

Patients with primary peritoneal adenocarcinoma should be treated similarly to stage III and IV ovarian cancer. Surgical cytoreduction followed by platinum and paclitaxel chemotherapy is the treatment of choice. Median response rate is 80% with 30–40% complete responders and a median survival of 36 months. Some reports have demonstrated poorer survival of patients with primary peritoneal carcinoma as compared to primary ovarian cancer due to reasons depicted in the section of clinicopathological entities [1,11].

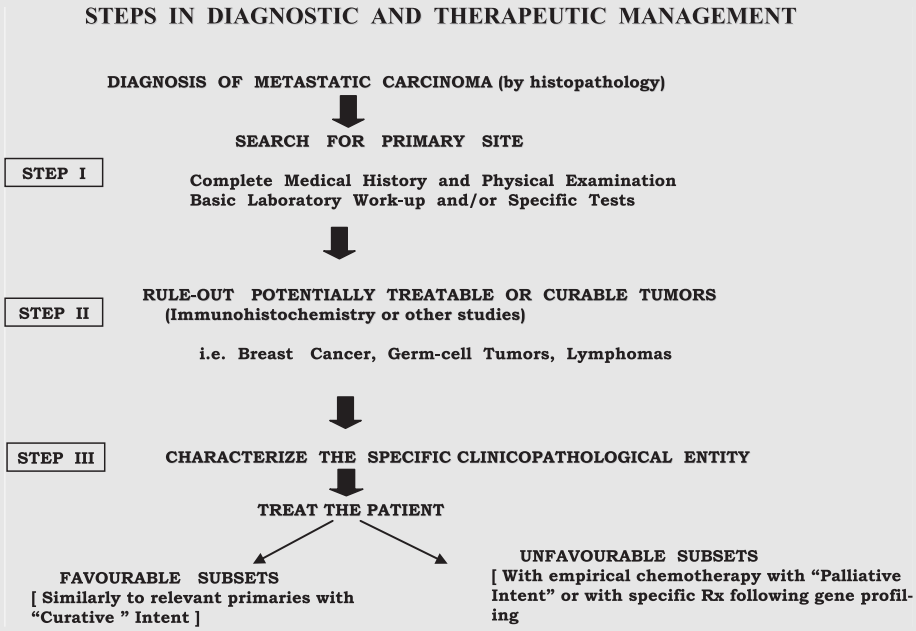
Table 6 Therapy of patients with CUP according to ESMO guidelines.

CUP subsets	Recommended treatment
Poorly differentiated neuroendocrine carcinoma	Platinum + etoposide combination chemotherapy
Serous papillary peritoneal adenocarcinoma	Optimal surgical debulking followed by platinum–taxane-based chemotherapy
Isolated axillary nodal metastases	Axillary nodal dissection, mastectomy or breast irradiation and adjuvant chemohormonotherapy
Squamous carcinoma involving 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
Adenocarcinoma with a colon-profile	Chemotherapy regimens for colorectal cancer
Men with blastic bone metastases and IHC/serum PSA expression	Androgen deprivation therapy ± RT
Single metastatic deposit from unknown primary	Resection and/or RT ± systemic therapy
Unfavorable subsets	Platinum-based empirical chemotherapy

Table 7 Prognosis of favorable CUP patients.

CUP subset	Survival
Women with adenocarcinoma involving axillary nodes	Mean 5-year overall survival: 72%
Women with papillary adenocarcinoma of peritoneal cavity	Mean overall survival : 36 months (2–6 months less than primary ovarian cancer)
Squamous cell carcinoma involving cervical nodes	5-year survival: 60–65%
Poorly differentiated neuroendocrine carcinoma	Median survival: 15.5 months with 2-yr survival: 33–50%. Long-term survivors : 10–15%
Adenocarcinoma with a colon cancer profile	Median overall survival: 20–36 months

Table 8 Algorithm in searching and treating the primary site.



Squamous cell carcinoma involving cervical nodes

Patients with N_1 or N_{2a} disease without extra capsular extension could be treated with surgery alone including excisional biopsy, radical or modified radical neck dissection, and/or bilateral tonsillectomy. Locoregional control is around 80–90% and 5-year overall survival up to 65%. Postoperative radiotherapy is indicated in excisional or incisional biopsy, extracapsular extension, stage N_{2b} or higher, in fixed nodes to the adjacent structure or in patients with low performance status and comorbidities. The irradiation fields include the involved nodal stations (65–70 Gy), the uninvolved sites (50 Gy) and the mucosal sites (50–60 Gy).

Chemoradiation could be indicated in N2 or N3 cases with cisplatin based chemotherapy. Chemoradiation could be associated with significant grade 3 toxicities [1,12].

Poorly differentiated neuroendocrine carcinomas

This group of patients should be treated with platinum-based or platinum–taxane combination chemotherapy. Response rates are up to 55% with 20% complete responders and overall survival of 15 months and almost 10–15% long-term survivors [1,13].

Adenocarcinoma with a colon-profile ($CK20^+$, $CK7^-$, $CDX2^+$)

This subset of patients should be treated as advanced colorectal cancer cases. Overall response rate is 50% with 15% complete and 35% partial responses and median survival of 21–37 months [1,15,16].

Other favorable subsets

Patients with metastatic bone metastases and elevated serum PSA should be managed as advanced prostate cancer [1]. Patients with isolated inguinal nodal metastases or a single metastatic lesion should undergo local dissection with or without local radiotherapy [1].

Treatment of unfavorable subsets

Unfortunately, this group of CUP patients represents the 80% of the cases. They are usually treated with empirical chemotherapy mostly with platinum or taxane combinations. Response rates are around 20% and median survival of six months (Fig. 1). A recent meta-analysis has shown that no type of chemotherapy has demonstrated any survival benefit in these subsets [23,24]. Specific targeted treatment in CUP patients following gene profiling microarray tests has not yet been proven. Since there are no prospective randomized studies available, we have to wait until some already ongoing trials appear. Table 6 summarizes therapeutic options according to the ESMO guidelines [25] and Table 7 the prognostic features of favorable subsets. Finally, Table 8 provides an algorithm of searching the primary site and treating CUP patients accordingly.

Conclusions

CUP is a well recognized clinical syndrome and may be defined as a disease with early disease dissemination without a primary detected site. It could have a favorable or unfavorable out-

come. Adenocarcinoma is the commonest histopathological subtype. While favorable groups are treated with local or systemic treatment, unfavorable groups are treated with empirical chemotherapy having usually a dismal prognosis. The value of gene-profiling microarray diagnosis though sensitive, its predictive or prognostic impact remains elusive.

Conflict of interest

The authors have declared no conflict of interest.

Compliance with Ethics Requirements

This article does not contain any studies with human or animal subjects.

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