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Review

Diagnostic and therapeutic management of cancer of an unknown primary

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Abstract

Metastatic Cancer of Unknown Primary Site (CUP) accounts for approximately 3% of all malignant neoplasms and is therefore one of the 10 most frequent cancer diagnoses in man. Patients with CUP present with metastatic disease for which the site of origin cannot be identified at the time of diagnosis. It is now accepted that CUP represents a heterogeneous group of malignancies that share a unique clinical behaviour and, presumably, unique biology. The following clinicopathological entities have been recognised: (i) metastatic CUP primarily to the liver or to multiple sites, (ii) metastatic CUP to lymph nodes including the sub-sets involving primarily the mediastinal–retroperitoneal, the axillary, the cervical or the inguinal nodes, (iii) metastatic CUP of peritoneal cavity including the peritoneal papillary serous carcinomatosis in females and the peritoneal non-papillary carcinomatosis in males or females, (iv) metastatic CUP to the lungs with parenchymal metastases or isolated malignant pleural effusion, (v) metastatic CUP to the bones, (vi) metastatic CUP to the brain, (vii) metastatic neuroendocrine carcinomas and (viii) metastatic melanoma of an unknown primary. Extensive work-up with specific pathology investigations (immunohistochemistry, electron microscopy, molecular diagnosis) and modern imaging technology (computed tomography (CT), mammography, Positron Emission Tomography (PET) scan) have resulted in some improvements in diagnosis; however, the primary site remains unknown in most patients, even on autopsy. The most frequently detected primaries are carcinomas hidden in the lung or pancreas. Several favourable sub-sets of CUP have been identified, which are responsive to systemic chemotherapy and/or locoregional treatment. Identification and treatment of these patients is of paramount importance. The considered responsive sub-sets to platinum-based chemotherapy are the poorly differentiated carcinomas involving the mediastinal-retroperitoneal nodes, the peritoneal papillary serous adenocarcinomatosis in females and the poorly differentiated neuroendocrine carcinomas. Other tumours successfully managed by locoregional treatment with surgery and/or irradiation are the metastatic adenocarcinoma of isolated axillary nodes, metastatic squamous cell carcinoma of cervical nodes, or any other single metastatic site. Empirical chemotherapy benefits some of the patients who do not fit into any favourable sub-set, and should be considered in patients with a good performance status.

Keywords: Cancer; Unknown primary; Unknown origin; Metastasis; Diagnosis; Treatment

1. Introduction

In a general medical oncology service, metastatic carcinoma of an unknown primary site may constitute as much as 3–5% of the referred solid tumour patients [1–3]. These are patients who are assigned the diagnosis of Metastatic Cancer of Unknown Primary Site (CUP). CUP represents a heterogeneous group of metastatic tumours for which no primary site can be detected following a thorough medical history, careful clinical examination and extensive diagnostic work-up. The primary site may either have a slow growth rate or it may possibly involute; therefore, the primary site rarely becomes manifest during the clinical course [4,5].

Several terms have been used as synonyms of CUP such as Unknown or Occult Primary Tumour, Carcinoma or Adenocarcinoma of Unknown Primary, Metastases of Unknown Origin, Metastases from Unknown Primary Tumours and Tumour of Unknown or Unidentified Origin. Currently, the most widely accepted comprehensive term in use is 'Cancer of Unknown Primary'. Historically, the definition of CUP

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has varied over time according to the inclusion criteria used and to the evolution of diagnostic tools.

In the early 1970s, some researchers argued that the diagnosis of CUP could be made only if the primary tumour was not found at autopsy [6]. 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 fail to identify the primary site [7,8] (Table 1).

Despite the recent advances in molecular immunohistochemistry and imaging technology, the diagnosis and therapy of these patients remains a real dilemma for practising oncologists. Whereas the majority of CUP patients are relatively resistant to systemic therapy and have short survival times, certain clinicopathological sub-sets defined by either clinical or pathological features have been identified which respond to treatment and have a better prognosis.

2. Pathology

Cancers of the unknown primary are categorised into four major sub-types by routine light microscopy criteria: (a) adenocarcinomas well–moderately differentiated, (b) undifferentiated or poorly differentiated adenocarcinomas, (c) squamous cell carcinomas and (d) undifferentiated neoplasms.

Approximately half the patients will be diagnosed with metastatic adenocarcinoma, 30% will have undifferentiated or poorly differentiated carcinomas, 15% squamous cell carcinomas and the remaining 5% will have undifferentiated neoplasms. With modern immunohistopathology, most of the tumours in the latter group can be better characterised, and can include poorly differentiated carcinomas, neuroendocrine tumours, lymphomas, germ cell tumours, melanomas, sarcomas and embryonal malignancies [9] (Table 2). In childhood, embryonal malignancies make up the majority of the rare cases of disseminated malignancies without an identified primary tumour.

Table 1
Clinical and laboratory data required to define a patient as having a carcinoma of unknown primary

✓	Histologically-confirmed metastatic cancer
✓	Detailed medical history
✓	Complete physical examination (plus pelvic and rectal exam)
✓	Full blood count
✓	Biochemistry
✓	Urinalysis
✓	Stool occult blood testing
✓	Histopathology review and use of immunohistochemistry
✓	Chest radiography
✓	Computed tomography (CT) of the abdomen and pelvis
✓	Mammography (in certain cases)

3. Epidemiology—demographics

Data from epidemiology surveys and large registries indicate that CUP constitutes 2.3–4.2% of all human cancers (Table 3). Among overall solid-tumour incidence in the United States (US), CUP represents approximately 40 000 of the 950 000 new cases per year [10]. The annual age-adjusted incidence is 7–12 cases per 100 000 population per year in USA and 18–19 cases per 100 000 population per year in Australia [11,12]. In The Netherlands, almost 2500 new patients are diagnosed annually giving an age-standardised incidence rate of 6.7 per 100 000 for males and 5.3 per 100 000 for females [13]. CUP therefore represents the seventh to eighth most frequent type of cancer and the fourth commonest cause of cancer death in both males and females. It is considered to be more common than non-Hodgkin's lymphoma. Table 3 lists epidemiological data from different countries [2,11–17].

Median age at presentation is approximately 60 years with a marginally higher frequency in males. In children, CUP represents less than 1% of diagnosed solid tumours.

4. The clinical presentation

4.1. Natural history

CUP represents a unique entity in which it is presumed a primary tumour is able to metastasise before the primary site becomes large enough to be identified. The natural history of these patients differs considerably

Table 2
Histological classification

Histology	Incidence (%)
Adenocarcinoma	
Well to moderately differentiated	50
Poorly or undifferentiated	30
Squamous cell carcinoma	15
Undifferentiated neoplasms	5
Not specified carcinoma	
Neuroendocrine tumours	
Lymphomas	
Germ cell tumours	
Melanomas	
Sarcomas	
Embryonal malignancies	

Table 3
Epidemiology of carcinoma of unknown primary

Geographical area [Ref.]	Source	Frequency (%)	Period
USA [11]	SEER	2.3	1973–1987
Australia [12]	New South Wales Registry	4.2	1970–1990
Netherlands (Southeast) [13]	Eindhoven Cancer Registry	4.0	1984–1992
Finland [14]	IARC	2.5	–
Germany [15]	–	7.8	1968–1984
Russia (Dniepropetrovsk region) [16]	–	3.6	–
Switzerland (Vaud and Neuchâtel Cantons) [2]	Local registries	2.3	1984–1993
Japan [17]	IARC	3.0	–

SEER, Surveillance, Epidemiology, End-Results; IARC, International Agency for Research into Cancer.

from that of patients with known primary tumours. Early dissemination, clinical absence of the primary tumour, unpredictability of metastatic pattern and aggressiveness constitute the fundamental characteristics of these tumours. Early dissemination is reflected in the clinical absence of symptoms related to a primary tumour.

The unpredictable metastatic pattern refers to the differences in the incidence of metastatic sites at diagnosis between known and unknown primary carcinomas. For example, lung cancer presenting as CUP involves the bones in 4%, while presenting as a known primary the osseous involvement is 30–50%. Similarly pancreatic cancer presenting as CUP has 4-fold higher incidence to affect bones, whereas prostatic cancer has a 3-fold less incidence compared with the known primaries. Similar unpredictable patterns can be seen in splanchnic metastatic sites [18].

It seems that these tumours do not undergo type 1 progression (from a premalignant lesion to malignant), but are malignant at the onset of the disease (type 2 progression). The main difference, however, from other type 2 progressors is that they do not form a primary site and do not follow any predictable pattern of metastatic spread [7].

More than 50% of CUP patients present with multiple sites of involvement, while the rest have a single site most commonly in the liver, bones, lungs or lymph nodes [19].

4.2. Clinicopathological entities

4.2.1. Metastatic CUP primarily to the liver or to multiple sites

Patients with mainly liver metastases represent one of the most frequent subgroup accounting for approximately 25% of all the CUP population. Metastatic lesions to other organs can also be seen at the time of diagnosis. Adenocarcinoma of moderately to poorly differentiated or undifferentiated type are the commonest histologies. The prognosis of this sub-set is poor with a median survival of 6–9 months. However, cases with hepatic metastases carrying neuroendocrine features have a better response to treatment and longer survival [9,19–21] (Table 4).

4.2.2. Metastatic CUP to lymph nodes

4.2.2.1. Mediastinal–retroperitoneal nodal involvement. Patients who present with CUP affecting predominantly mediastinal or retroperitoneal areas are sometimes referred to as having the 'extragonadal germ cell syndrome'. This group was first described in 1979 [22,23] and later characterised in detail by Greco and associates [24]. It affects mainly males who are less than 50 years old and is clinically characterised by metastatic disease of a midline distribution, usually involving mediastinal and retroperitoneal lymph nodes and/or pulmonary lesions. Histopathologically, these patients carry the diagnosis of undifferentiated or poorly differentiated carcinoma [24–28]. These tumours are rapidly progressive; however, some respond dramatically to chemotherapy and patients often enjoy a durable remission. Serum human chorionic gonadotropin (β-HCG) or alpha-fetoprotein (AFP) are elevated in some patients. Few patients have all the elements of this syndrome. However, the presence of any one of the above features suggests the diagnosis of this entity.

4.2.2.2. Isolated axillary nodal involvement. Most patients presenting with lymph node metastases isolated to one axillary area are female, and should be suspected of having stage II breast cancer. Only a small percentage (0.3%) of women with subsequently confirmed breast cancer present in this manner. Median age is 52 years (range 21–80 years). Histopathological examination usually reveals an invasive ductal adenocarcinoma of grade III, while oestrogen or progesterone receptors are positive in 20–30% of the cases. 70% of patients have N1 disease; only 5% of the cases present with disseminated disease at diagnosis. Mammography and/or sonography are highly recommended. Recently, magnetic resonance imaging (MRI) of the breast has been useful in identifying a primary site in some of these patients. Suspicious areas should be always biopsied. These patients should be managed according to guidelines for stage II breast carcinoma, and many have a

prolonged disease-free survival. Male patients have a worse prognosis [29–32].

4.2.2.3. Cervical nodal involvement. Cervical nodal metastases from clinically undetectable primary squamous cell carcinoma accounts for 1–2% of head–neck malignancies. With locoregional treatment, these patients can achieve a considerable prolongation of survival. Patients with supraclavicular lymphadenopathy which histologically are either of squamous cell or undifferentiated carcinoma origin, have a worse prognosis. 18-F-Fluorodeoxyglucose (FDG)-Positron Emission Tomography (PET) is sometimes useful in localising a primary tumour in the head–neck area [33,34].

4.2.2.4. Inguinal nodal involvement. This is an uncommon sub-set, and the most common histology is that of undifferentiated (anaplastic) carcinoma. Squamous carcinoma or mixed squamous/adenocarcinoma can also be found. Examination of the anorectal region, a meticulous gynaecological examination and probably cystoscopy are necessary investigations for these patients. Lymphomas and metastatic or amelanotic melanomas of unknown primary site should also be ruled out [35,36].

4.2.3. Metastatic CUP of the peritoneal cavity

4.2.3.1. Peritoneal carcinomatosis in females. These are usually female patients with a median age of 60 years old, who present with ascites and peritoneal masses and no evidence of a primary tumour in the ovaries. This syndrome has also been termed '*multifocal extraovarian serous carcinoma*' or '*peritoneal papillary serous carcinoma*'. Diagnosis is usually made by exploratory laparotomy. Biopsies from peritoneal deposits frequently show papillary serous adenocarcinoma, with or without psammoma bodies. Serum CA 125 levels are usually elevated. Response to chemotherapy and survival rates are similar to stage III ovarian cancer. Differential diagnosis includes peritoneal mesothelioma, pseudomyxoma peritonii and malignant ascites arising from tumours of gastrointestinal origin or elsewhere [37–39].

4.2.3.2. Malignant ascites of other unknown origin (non-papillary serous adenocarcinoma). Some patients have non-papillary tumours, and are as likely to be male as female. In those with mucin-producing adenocarcinoma often with signet ring cells, a gastrointestinal origin should be suspected. The tumours in these patients are generally not as responsive to chemotherapy as the papillary serous adenocarcinomas [40].

4.2.4. Metastatic CUP to the lungs

4.2.4.1. Parenchymal metastases (pulmonary nodules). These patients present with multiple bilateral lung lesions and with a histological diagnosis of adenocarcinoma of various differentiations. The prognosis is poor for most patients. Young male patients with possible extragonadal germ-cell should be carefully distinguished from this group of patients [9,19,20].

4.2.4.2. Isolated malignant pleural effusion. Malignant pleural effusion is not uncommon in patients with CUP; however, in a small group it can be the only area of demonstrable involvement. The primary cancer remains unknown in approximately 7% of all cases of metastatic carcinomatous pleurisy. Adenocarcinoma is the main histopathological type; primary sites in the lung, breast, or ovary should be excluded. Mesothelioma should also be included in the differential diagnosis. In general, the outcome of this sub-set carries a poor prognosis [9,19].

Table 4
Clinicopathological entities of CUP

Organ	Histology
Liver (mainly) and/ or other organs	Adenocarcinoma moderately or poorly differentiated
Lymph nodes	
Mediastinal-retroperitoneal (midline distribution)	Undifferentiated or poorly differentiated carcinoma
Axillary	Adenocarcinoma well to poorly differentiated
Cervical	Squamous cell carcinoma
Inguinal	Undifferentiated carcinoma, squamous, mixed squamous/adenocarcinoma
Peritoneal cavity	
Peritoneal adenocarcinomatosis in females	Papillary or serous adenocarcinoma (±psammoma bodies)
Malignant ascites of other unknown origin	Mucin-producing adenocarcinoma moderately or poorly differentiated (±signet ring cells)
Lungs	
Pulmonary metastases	Adenocarcinoma of various differentiations
Pleural effusions	Adenocarcinoma moderately or poorly differentiated
Bones (solitary or multiple)	Adenocarcinoma of various differentiations
Brain (solitary or multiple)	Adenocarcinoma of various differentiations or squamous cell carcinoma
Neuroendocrine tumours	Poorly differentiated carcinoma with neuroendocrine features (mainly), low-grade neuroendocrine carcinomas, small cell anaplastic carcinomas
Malignant melanoma	Undifferentiated neoplasm with melanoma features

4.2.5. Metastatic CUP to the bones

Almost one fourth of CUP patients present with bone symptoms due to metastases, although bone scintigraphy is positive in more than 50% of these patients. Bony metastases may manifest as multiple lesions or as a single metastatic site. Adenocarcinoma is the most frequent histological diagnosis. Prostate cancer and breast cancer should be suspected in male and female patients, respectively [41,42].

4.2.6. Metastatic CUP to the brain

Metastatic carcinoma of the central nervous system (CNS) from an unknown primary, is diagnosed with either a solitary lesion or with multiple metastases. Up to 15% of all patients with CNS metastases will have no clearly identified primary site despite an intensive investigation. These patients primarily present with neurological dysfunction. Histopathologically, intracranial lesions are most frequently metastatic adenocarcinoma or metastatic squamous cell carcinoma. Patients with solitary lesions are candidates for surgery and have a better survival [43–45].

4.2.7. Metastatic neuroendocrine carcinomas of unknown primary

Neuroendocrine carcinomas of unknown primary site represent a broad spectrum of neuroendocrine malignancies. Three different clinicopathological sub-sets of neuroendocrine tumours have been described. The first sub-set includes low-grade neuroendocrine carcinomas (e.g. metastatic well-differentiated carcinoid or islet-cell tumours) which usually involve the liver and sometimes have symptoms associated with the secretion of vasoactive peptides. The second sub-set includes small cell anaplastic carcinoma, with a histological appearance and clinical behaviour that is similar to small cell lung cancer or extrapulmonary small cell carcinoma. The third group represents the '*poorly differentiated carcinomas*' or '*poorly differentiated adenocarcinomas*' of unknown primary and in these tumours, neuroendocrine features are identified by immunohistochemical staining for chromogranin and/or synaptophysin. These tumours have been termed '*poorly differentiated neuroendocrine tumours*' of unknown primary site. Some of these patients may present with patterns strongly resembling those of an extragonadal germ-cell syndrome [9,28,46].

4.2.8. Metastatic malignant melanoma of unknown primary

The diagnosis of metastatic melanoma of unknown primary origin is estimated to represent 2–6% of all melanoma cases. 10–15% of these cases are believed to be ''amelanotic'' melanomas. Despite some controversies in the literature, it seems that the clinical disease course of patients with metastatic melanoma of an unknown primary site is similar to that of patients with primary cutaneous melanoma when the same clinical stages of the disease are compared [47–49].

5. The biology of CUP

Despite the heterogeneity of these tumours, most follow an aggressive biological and clinical behaviour. This unusual pattern of growth suggests that CUP may progress via a unique series of molecular and biochemical events. To date, CUP has not been extensively investigated on a molecular basis, and the limited information available is controversial and inconclusive. Karyotypic abnormalities were detected in a number of CUP patients including deletion of part or all of 1p, translocations, isochromosome 1q and evidence for gene amplification. Similar changes have also been described in other advanced malignancies [9]. Bar-Eli and colleagues have shown that although CUP represents a highly aggressive and advanced tumour where a high incidence of *p53* mutations was expected, the frequency of mutations was only 26% in the studied cases. They concluded that *p53* mutations may not play a major role in the development and progression of CUP [50].

In contrast, a high overexpression of p53 protein (53%) was observed by immunohistochemistry in another study. In the same publication, Bcl-2 overexpression was detected in 40% of the 47 CUP cases studied, whereas the presence of either oncoprotein was not associated with any clinicopathological variables [51]. Similarly, overexpression of C-myc and Ras oncoproteins were reported in 26 cases studied by a three-step immunoperoxidase technique. In the same study, c-erbB-2 p185 oncoprotein was overexpressed in 58% of the cases [52]; however, in the study of Hainsworth and colleagues c-erbB-2 was overexpressed in only 11% of 100 investigated patients with poorly differentiated carcinoma [53].

Angiogenesis was also studied in 54 CUP cases. The microvessel density, represented by CD-34 and vascular endothelial growth factor (VEGF) expression, were investigated using immunohistochemistry. Although both markers were overexpressed, no association with a number of clinical parameters was found [54].

Since these results can not easily be interpreted probably due to the heterogeneity of CUP syndrome, more comprehensive molecular research is urgently needed to provide a better understanding of the aetiological molecular pathways. In this regard, gene expression profiling of these tumours may eventually establish a primary site and provide clues to effective biologically-targeted therapy.

6. The diagnostic evaluation

The diagnostic evaluation of patients with CUP consists of laboratory or clinical investigations including mainly pathology, imaging and endoscopy studies. Serum tumour markers can contribute, but only in certain cases. Clinicians should follow certain algorithms in searching for the primary tumour, taking into consideration the cost, in terms of time and money, as well as the final benefit in the outcome of these patients.

6.1. The role of the pathologist

An adequate sample of tumour tissue is of paramount importance in order to perform light microscopy, immunohistochemistry, other markers or receptor studies, as well as more specific investigations such as electron microscopy or genetic analysis. Fine-needle aspiration, a common initial diagnostic procedure, often provides insufficient material for optimal pathological evaluation, particularly in patients with poorly differentiated tumours.

The pathologist should always be in close contact with the clinician concerning the patient's medical history, clinical findings, and other laboratory data. There is no doubt that cooperation between the pathologist and clinician optimises the chances of making a specific diagnosis in patients with CUP.

6.1.1. Light microscopy

Light microscopic examination is rarely successful in identifying the site of origin in a patient with CUP. Light microscopy can basically characterise cell morphology and tumour differentiation. Apart from the routine staining with haematoxylin and eosin, additional stains can be employed including mucicarmine, Alcian Blue and periodic acid-Schiff to detect mucin and mucopolysaccharides or trichrome and methyl-green pyronine stains to help rule out sarcomas and lymphomas in poorly differentiated and undifferentiated neoplasms [55]. However, the development of immunohistochemical techniques of greater sensitivity and specificity has limited the value of these histochemical procedures.

6.1.2. Immunohistochemistry

Immunohistochemical studies on metastatic carcinomas of an unknown primary site sometimes results in the identification of the tumour origin, especially if the metastases are poorly differentiated by light microscopy. The ability of immunoperoxidase staining to be performed on formalin-fixed paraffinised tissue facilitates its diagnostic application in the detection of the primary. Several cell components can be identified by a series of monoclonal or polyclonal immunoperoxidase antibodies including enzymes, structural tissue components, hormonal receptors, hormones, oncofetal antigens or other substances [9]. Table 5 lists a screening panel of some of the most commonly used immunoperoxidase staining patterns.

The development of monoclonal antibodies against various cytokeratin (CK) polypeptides has opened up new avenues in investigating the normal and cancerous epithelial cells. Among them, CK7 and CK20 have been extensively studied in solid tumours. CK20 appears to be very useful in diagnosing gastrointestinal adenocarcinomas, while CK7 is more common in respiratory or gynaecological malignancies. In addition, determining the CK7/CK20 phenotype has also been proven to be useful in the diagnosis of certain solid tumours. Overall, the CK7+/CK20− phenotype favours a lung, breast or ovarian primary, the CK7+/CK20+ phenotype favours urothelial-transitional cell carcinoma, the CK7−/CK20+ phenotype favours colorectal or gastric carcinoma, while the CK7−/20− phenotype favours prostatic, renal or liver adenocarcinomas (Table 6) [56,57]. However, the number of false-positives and false-negatives with these staining phenotypes makes a definitive diagnosis of a primary site difficult on this basis alone.

6.1.3. Electron microscopy

Electron microscopy is not widely available, is relatively expensive and can only be recommended for the evaluation of certain poorly differentiated neoplasms. In appropriate clinical situations, electron microscopy is useful in distinguishing lymphoma from carcinoma, adenocarcinoma from squamous cell carcinoma (desmosomes, prekeratin filaments), and in identifying neuroendocrine tumours (neurosecretory granules), melanomas (premelanosomes) or poorly differentiated sarcomas [9]. Electron microscopy should be considered in the evaluation of poorly differentiated neoplasms in

Table 5
The usefulness of immunoperoxidase staining in CUP patients

Tumour type	Immunoperoxidase marker
Carcinoma	Cytokeratin, EMA
Lymphoma	CLA, EMA (±)
Sarcoma	Vimentin, Desmin, Factor VIII Antigen
Melanoma	S-100, HMB-45, Vimentin, NSE
Neuroendocrine	Chromogranin, Synaptophysin, Cytokeratin, EMA, NSE
Germ-cell	Cytokeratin, EMA, HCG, AFP
Prostate cancer	PSA, Cytokeratin, EMA
Breast cancer	Cytokeratin, EMA, ER, PR
Thyroid Cancer	Thyroglobulin, Cytokeratin, EMA, Calcitonin

EMA, epithelial membrane antigen; CLA, common leucocyte antigen; NSE, neuron-specific enolase; HCG, human chorionic gonadotropin; AFP, α-fetoprotein; PSA, prostate-specific antigen; ER, oestrogen receptor; PR, progesterone receptor.

Table 6
Cytokeratin phenotypic expression in adenocarcinomas of several organs

Organ	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−

young patients, particularly when immunoperoxidase stains are inconclusive.

6.1.4. Molecular diagnostics

Conventional or molecular cytogenetics are of limited use in identifying the origin of the primary tumour, since only a few tumour-specific chromosomal abnormalities have been identified. An isochromosome of the short arm of chromosome 12 i(12p) or a deletion in 12p is an abnormality characteristic of testicular carcinoma and other germ cell tumours. In a group of young men with poorly differentiated carcinoma and the clinical features of an extragonadal germ cell tumour, molecular genetic analysis showed the i(12p) abnormality in 25%. These patients proved to have tumours that were highly sensitive to chemotherapy for germ cell tumours [58].

Other chromosomal abnormalities have been found in several carcinomas, lymphomas or sarcomas such as translocation t [11,22] [q 24; q 12] in peripheral neuroectodermal tumour (PNET) and Ewing's sarcoma, *t* [8;14] [q24; q32] in non-Hodgkin's lymphomas, *t* [3;13] in alveolar rhabdomyosarcoma or 3p deletion in small cell lung carcinoma. Cytogenetic analysis should be considered in the evaluation of young patients with poorly differentiated carcinomas or undifferentiated neoplasms potentially responsive to systemic chemotherapy [58–60].

To conclude, extensive pathological investigation by immunohistochemistry, electron microscopy or cytogenetic studies, results in the identification of specific subgroups of CUP patients in almost 20% of the cases [9].

6.2. The role of the radiologist

6.2.1. Conventional radiology

Routine chest radiograph has always been a part of the initial evaluation of the patient with CUP. Based on autopsy studies, however, the chest X-ray was able to differentiate between primary and secondary malignancy in the lungs in only one-third of the cases [61,62]. Barium enemas are of very limited value and therefore, are not recommended at all [63].

6.2.2. Computed tomography

The usefulness of CT scanning of the abdomen and pelvis is very well documented in CUP patients, and results in the detection of a primary site in 30–35% of patients. CT of the chest has not been evaluated as adequately as that of the abdomen or pelvis and an argument can be made to reserve this for patients with chest X-ray abnormalities. However, the mediastinum represents an important site of involvement that is best evaluated by CT. CT can also determine the extent of the metastatic disease and may provide guidance in selecting the optimal site for biopsy [64,65].

6.2.3. Mammography and other breast imaging tests

Mammography has been proposed in women with metastatic adenocarcinoma involving axillary lymph nodes, although its sensitivity is still around 20% [66]. In cases where there is a strong suspicion of a primary breast tumour and if a mammogram and/or ultrasound are not contributory, magnetic resonance imaging (MRI) scan may be requested. Recent reports have shown that MRI is very sensitive for the detection of mammographically- and clinically-occult breast cancers in patients with malignant axillary lymphadenopathy. Some investigators suggest that MRI of the breast should be added to clinical examination and mammography/sonography before defining the breast cancer as occult [67].

6.2.4. Novel nuclear imaging studies: FDG-PET scan and ^{111}In-pentetreotide scan

FDG-PET scan has been studied in the recent years as an additional diagnostic tool in CUP patients. Encouraging results show that a FDG-PET scan is a valuable modern imaging technique for patients with CUP, particularly in patients with squamous cancer found in cervical lymph nodes. In this group, FDG-PET scanning identifies an occult primary site in the head and neck area in approximately one-third of patients [68–72]. FDG-PET scanning may also provide valuable information that influences treatment in patients with metastases evident at one site (e.g. a single lymph node area), in whom local treatment is being considered. Further evaluation of this new diagnostic trial, are well as cost–benefit analyses, are warranted [68–72].

^{111}In-pentetreotide scan, another advanced nuclear imaging technology, might also be useful in the investigation of CUP patients and deserves further evaluation [73].

6.3. The role of the endoscopist

Endoscopies should be used to evaluate CUP patients with specific clinical presentations. Therefore, ENT endoscopy is recommended in patients with isolated cervical node involvement, fibreoptic bronchoscopy is advisable in patients with thoracic indications or pulmonary symptoms, gastrointestinal endoscopies in patients with abdominal symptoms or occult blood in the stool, and proctoscopy and/or colposcopy in patients with inguinal lymph node involvement [36].

6.4. Serum tumour markers

Patients with CUP should have serum β-HCG, AFP and PSA tested (in men) to exclude treatable extragonadal germ cell tumours and to identify metastatic prostate cancer amenable to endocrine treatment. High levels of serum thyroglobulin in CUP patients with bone metastases suggests an occult thyroid cancer. Serum CA 15-3 and CA 125 could be of some help, i.e. in the isolated axillary node adenocarcinomas and in peritoneal papillary adenocarcinomatosis, respectively [74–78]. In all other cases, routine evaluation of commonly used epithelial serum tumour markers (CEA, CA 19-9, CA 15-3, CA 125) has no proven prognostic or diagnostic value, and non-specific elevations of multiple markers occurs in the majority of CUP patients (Fig. 1).

7. How often can the primary site be identified?

Even with an extensive diagnostic work-up using modern pathological and imaging procedures, the frequency of detection of the primary tumour site remains low. Less than 20% of patients have a primary site identified antemortem, while from necropsy data, it was found that almost 70% of autopsied cases remained undiagnosed. Postmortem detection of a primary site may be higher in patients with well-differentiated adenocarcinomas. From a review of 12 studies (1967–1983) with 2029 CUP patients, autopsy was performed in 27% (0–51%) of the cases. The primary tumour was detected in 19% (0–48%) of the patients, in 7% (0–26.4%) antemortem and in 35% (0–85%) postmortem [6,18,63,79–87].

Ultimately, primary sites are most frequently detected in the lung and pancreas, followed by other gastrointestinal and gynaecological malignancies. Primary care physicians and oncologists should be very concerned in overinvestigating CUP patients, taking always into consideration the cost of time and money. A limited diagnostic approach with patient-benefit orientation aiming to recognise patients with good prognostic features is now considered the best approach.

8. Prognostic and predictive factors

In general, it appears that patients with CUP have a limited life expectancy with a median survival approximately of 6–9 months. However, some sub-sets have a better prognosis and enjoy longer survival. Analyses of prognostic and predictive factors in CUP have examined several clinicopathological parameters including age, gender, performance status, weight loss, histopathology, tumour burden, tumour location, number of metastatic sites and serum markers. Several positive and negative prognostic and predictive factors were detected, which helped to define several favourable and unfavourable groups of CUP patients. The features categorised as significant factors—although not consistent in all studies—are certain histological sub-sets (poorly differentiated carcinoma, squamous cell carcinoma, neuroendocrine carcinoma), lymph node involvement

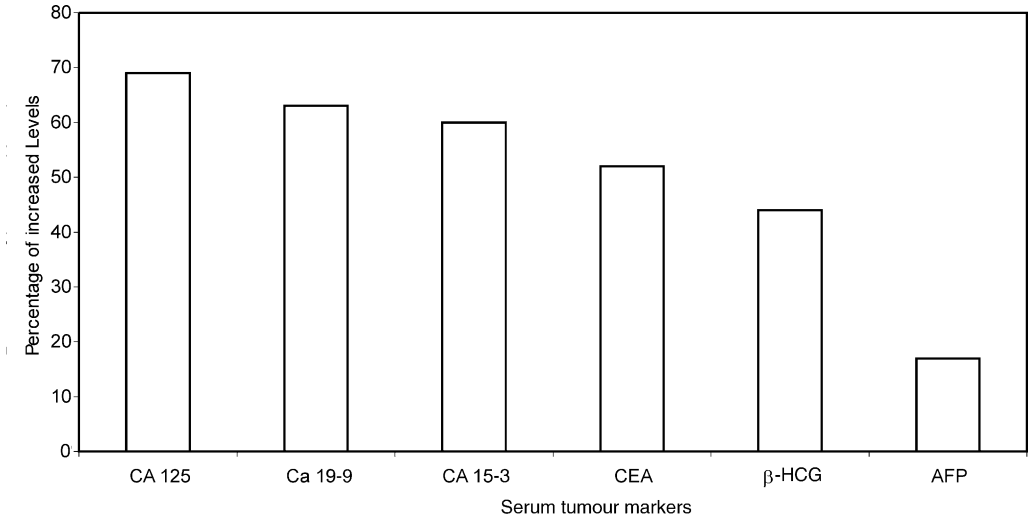

Fig. 1. Frequency of tumour marker elevations in 85 CUP patients.

(except supraclavicular), number of metastatic sites ($\leqslant 2$), female sex, performance status especially in the undifferentiated carcinomas, weight loss, and some serum markers (alkaline phosphatase, LDH, CEA) [8,20,88].

The proposed favourable and unfavourable sub-sets are listed in Table 7.

9. Therapeutic management

The therapeutic strategy for CUP patients should always be individualised according to the clinical subset. The oncologist should recognise whether the patient belongs to any of the favourable or unfavourable groups prior to recommending the appropriate therapy. Based on the clinical presentation, the recommended treatment may be locoregional and/or systemic, and may have curative or palliative intent.

Historically, chemotherapy has been the cornerstone of treatment for patients with CUP. During the last 40 years, almost all cytotoxic drugs have been used either as single agents or in combination regimens. In the 1960s and 1970s, the drugs used were 5-fluorouracil, cyclophosphamide, mitomycin-C, nitrosoureas and vincristine offering a response rate of less than 10%. In the next decade, doxorubicin-containing chemotherapy improved responses to 20–25%, but median survival remained low at 4–6 months. Since platinum became available in 1980s, chemosensitive favourable sub-sets were recognised as being able to achieve significantly better responses and survivals [8,24,46,89–91]. Since 1995, the use of a taxane (paclitaxel or docetaxel) in combination with a platinum compound has provided an additional and probably improved treatment option for the large group of patients who do not fit into any favourable sub-set [92–96].

Tables 8 and 9 summarise the results of the major prospective studies using platinum-based or taxane/platinum-containing regimens. A critical appraisal of the results of various treatments in patients with CUP is difficult because of the great heterogeneity in the patient profiles in the published series.

Second-line chemotherapy (gemcitabine, fluorouracil/leucovorin or the 5-fluorouracil, doxorubicin, cyclophosphamide (FAC) regimen) in patients previously treated with platinum-containing regimens has been generally ineffective [97–99]. In addition, no benefit from high-dose chemotherapy, with or without peripheral stem cell support, was found [100].

10. Treatment of favourable sub-sets

Several sub-sets of CUP patients, easily identified by either clinical or pathological features, require specific treatment approaches and have the potential for an excellent treatment outcome. These sub-sets are summarised in Table 10.

10.1. Poorly differentiated carcinoma with midline distribution (extragonadal germ cell syndrome)

This sub-set of CUP should be treated according to guidelines for poor prognosis germ cell tumours, using platinum-based combination chemotherapy. Overall response rates are more than 50%, with 15–25% complete responders and around 10–15% long-term disease-free survivors [25,28].

10.2. Women with papillary adenocarcinoma of peritoneal cavity

These women should be managed as FIGO stage III ovarian cancer with taxane/platinum-based systemic chemotherapy. Recently, this syndrome is also being recognised in men. In five retrospective studies published between 1988 and 1990, a total of 179 patients were treated with surgical cytoreduction and cisplatin-based chemotherapy. The median complete response rate was 20% (10–39%), the median survival 16 months (11–24%) and the median long-term survival 16% (11–24%). Therefore, optimal management of this sub-set of CUP patients includes aggressive surgical cytoreduction followed by platinum-based postoperative chemotherapy. Survival curves appear to be similar to FIGO

Table 7
Favourable and unfavourable sub-sets of CUP

Favourable sub-sets	Unfavourable sub-sets
1. Poorly differentiated carcinoma with midline distribution (extragonadal germ cell syndrome)	1. Adenocarcinoma metastatic to the liver or other organs
2. Women with papillary adenocarcinoma of peritoneal cavity	2. Non-papillary malignant ascites (adenocarcinoma)
3. Women with adenocarcinoma involving only axillary lymph nodes.	3. Multiple cerebral metastases (adeno or squamous carcinoma)
4. Squamous cell carcinoma involving cervical lymph nodes	4. Multiple lung/pleural metastases (adenocarcinoma)
5. Isolated inguinal adenopathy (squamous carcinoma)	5. Multiple metastatic bone disease (adenocarcinoma)
6. Poorly differentiated neuroendocrine carcinomas	
7. Men with blastic bone metastases and elevated PSA (adenocarcinoma)	
8. Patients with a single, small, potentially resectable tumor	

III ovarian cancer patients. Intraperitoneal chemotherapy or radiotherapy is not recommended [9,37–39].

10.3. Women with adenocarcinoma involving only axillary lymph nodes

Although there are no data from randomised or large prospective studies, locoregional therapy followed by some form of systemic treatment is recommended. Generally, the management of these patients resembles that of stage II or III breast cancer patients. Patients with N1 disease (mobile nodes) should undergo axillary clearance followed by either a simple mastectomy or breast irradiation. Adjuvant chemotherapy in premenopausal women followed by tamoxifen administration in positive oestrogen receptors patients is suggested. No adequate information is available for adjuvant chemotherapy in postmenopausal patients apart from tamoxifen treatment in oestrogen receptor-positive cases. However, it seems reasonable in these patients to follow guidelines for adjuvant treatment of stage II breast cancer. In patients with N_2 disease (fixed nodes), preoperative chemotherapy is recommended, following the guidelines for stage III breast cancer.

Table 8
Prospective studies in CUP patients using platinum-based chemotherapy

Authors/year [Ref.]	Regimen	No. of patients	Response rate (%)	Survival (median (months))
Platinum-based combinations				
Jadeja and colleagues (1983) [101]	FACP	23	17	6
Greco and colleagues (1986) [25]	PveB	56	57	16 (PDC midline pts)
Milliken and colleagues (1987) [102]	PveB	50	39	5
Becouarn and colleagues (1989) [103]	FAPH	85	21	6
Van der Gaast and colleagues (1990) [28]	PEB	34	79	8+ (PDC midline)
Raber and colleagues (1991) [104]	FEP	36	22	11
Lenzi and colleagues (1991) [105]	PFL	25	32	–
Gill and colleagues (1991) [106]	PE	16	19	8
Wagener and colleagues (1991) [107]	P	21	19	5
Falkson and colleagues (1998) [108]	PMiEp	40	50	9.4
Warner and colleagues (1998) [109]	CbE	26	23	5.6
Briasoulis and colleagues (1998) [91]	CbEpE	62	37	10
Lofts and colleagues (1999) [110]	PF	44	27	–
Voog and colleagues (2000) [97]	PE	23	32	8
Guardiola and colleagues (2001) [111]	PAC	22	50	10.7
Saghatchian M and colleagues (2001) [112]	PE→BI	30	40	9.4
	PFI_f	18	44	16.1 (PDC midline)
Macdonald and colleagues (2002) [113]	PMiF	31	27	7.7
Lortholary and colleagues (2002) [114]	PG		42	22%, 1 year-survival
		80		
	PI_R		25	23%, 1 year-survival

A, doxorubicin; B, bleomycin; C, cyclophosphamide; Cb, carboplatin; E, etoposide; Ep, epirubicin; F, fluorouracil; G, gemcitabine; H, hexamethymelamine; L, leucovorin; Mi, mitomycin-C; I, ifosfamide; I_f, interferon-α; I_R, irinotecan; P, cisplatin; Ve, vinblastine; pts, patients; PDC, poorly differentiated carcinoma.

Table 9
Prospective studies in CUP patients using taxane/platinum-based chemotherapy

Authors/year	Regimen	No Patients	Response rate (%)	Survival median (months)
Paclitaxel-based				
Greco and colleagues (2000) [94]	P_LC_bE	71	48	11
Briasoulis and colleagues (2000) [95]	P_LC_b	77	38.7	13
Dowell and colleagues (2001) [115]	C_bE	34	19	8.3
	P_LFL		19	6.4
Greco and colleagues (2002) [116]	P_LC_bG	120	25	9
Gothelf and colleagues (2002) [117]	P_LPG	29	50	–
Docetaxel-based				
Greco and colleagues (2002) [93]	D_xP	26	26	8
	D_xCb	47	22	
Bouleuc and colleagues (2001) [118]	D_xP	22	33	8
Darby and colleagues (2001) [119]	D_x	29	7	6

Cb, carboplatin; Dx, docetaxel; E, etoposide; F, fluorouracil; G, gemcitabine; L, leucovorin; P, cisplatin; P_L, paclitaxel.

Table 10
Recommended therapeutic management for favourable CUP sub-sets

CUP sub-set	Recommended treatment
• Poorly differentiated carcinoma with midline distribution (extragonadal germ-cell syndrome)	Treat similar to germ-cell tumours with platinum-based regimen
• Women with papillary or serous adenocarcinoma of peritoneal cavity	Treat similar to FIGO stage III ovarian cancer
• Women with adenocarcinoma involving axillary nodes	N1 disease: surgery or radiation.Premenopausal: adjuvant CX→TMX if ER (+) Postmenopausal: adjuvant TMX if ER (+), CX? N2 disease: neoadjuvant CX→axillary clearance→TMX if ER (+) *or* radiation (non-responding or elderly pts)→CX *or* TMX if ER (+)
• Squamous cell carcinoma of cervical nodes	Radical radiotherapy±surgery±chemotherapy
• Isolated inguinal lymphadenopathy (squamous cell carcinoma)	Surgical dissection±radiotherapy
• Poorly differentiated neuroendocrine carcinoma	Chemotherapy with platinum/etoposide-based regimen
• Men with blastic bone metastases and elevated PSA	Treat with endocrine treatment as for prostate cancer
• Single metastasis only	Definitive local treatment (surgery or radiation)

CX, chemotherapy; TMX, tamoxifen; ER, oestrogen receptor; pts, patients; FIGO, International Federation of Gynecology and Obstetrics.

However, in non-responding tumours or in elderly patients, radical irradiation should be the treatment of choice. Oestrogen receptor-positive patients should continue on tamoxifen treatment. The 5- and 10-year overall survival rates are 75 and 60%, respectively [29,31,32].

10.4. Squamous cell carcinoma involving cervical lymph nodes

The treatment of this sub-set of patients should follow guidelines for locally advanced head and neck cancer. Locoregional management is the primary recommended treatment. The 5-year survival rates range from 35 to 50% with documented long-term disease-free survivors. Surgery alone is inferior and can be recommended only in selected patients, particularly those with pN_1 neck disease with no extracapsular extension. Regarding locoregional failures, it appears that radiation to the ipsilateral cervical nodes alone is also inferior to extensive irradiation to both sides of the neck and the mucosa in the entire pharyngeal axis and larynx. The impact of this more intensive radiation therapy strategy in prolonging survival in this patient group is undefined [33,34]. However, the strong correlation between locoregional control and survival in patients with head and neck cancer suggests a benefit will be also obtained in this patient group.

The impact of chemotherapy in patients with metastatic squamous carcinoma involving the cervical nodes remains undefined. Although experience remains limited in this CUP sub-set, the emerging superiority of concurrent chemotherapy/radiation for patients with locally advanced head/neck tumours suggests a benefit for this strategy, particularly in patients with an N_2 or N_3 adenopathy.

10.5. Isolated inguinal lymphadenopathy from squamous cell carcinoma

Inguinal node dissection, with or without local radiotherapy, is the recommended treatment for this sub-set of patients. Long-term survival following definitive local therapy has been reported in a few patients [9,35,36]. The role of systemic chemotherapy has not been evaluated in these patients. The emerging role of combined modality therapy for other squamous cancers originating in this region (e.g. anus, cervix, bladder) suggests a future role for this treatment approach in these CUP patients as well.

10.6. Poorly differentiated neuroendocrine carcinomas

Many poorly differentiated neuroendocrine carcinomas are highly sensitive to chemotherapy. In recent studies, the response rates to platinum-based or to

paclitaxel/carboplatin-based chemotherapy were reported to be as high as 50–70%, with more than 25% complete responses and 10–15% long-term survivors. Therefore, patients with poorly differentiated neuroendocrine carcinoma of unknown primary site should enter a trial of combination chemotherapy with either platinum-based or taxane/platinum-based regimens [9,27,46].

10.7. Men with blastic bone metastases and elevated PSA from an adenocarcinoma

It has been reported that endocrine treatment often produces responses in this sub-set of CUP patients. Therefore, these patients should be considered as having metastatic prostate cancer and hormonal therapy should be recommended as the initial treatment of choice [9].

10.8. Patients with a single small metastasis

A small group of patients have only a single small metastasis identified, even after complete clinical and radiological evaluation. Although the location of the single involved site varies, definitive local treatment with either resection and/or radiation therapy should be considered. Choice of treatment should be guided by the tumour location. Many of these patients derive significant palliative benefit from such treatment, and some have a substantial disease-free interval before other metastases appear. Two-year survivals have been demonstrated in patients with various single sites of involvement, including single lymph node groups, lung, liver, adrenal gland and brain. Although unproven, it would be prudent to consider chemotherapy for good performance status patients.

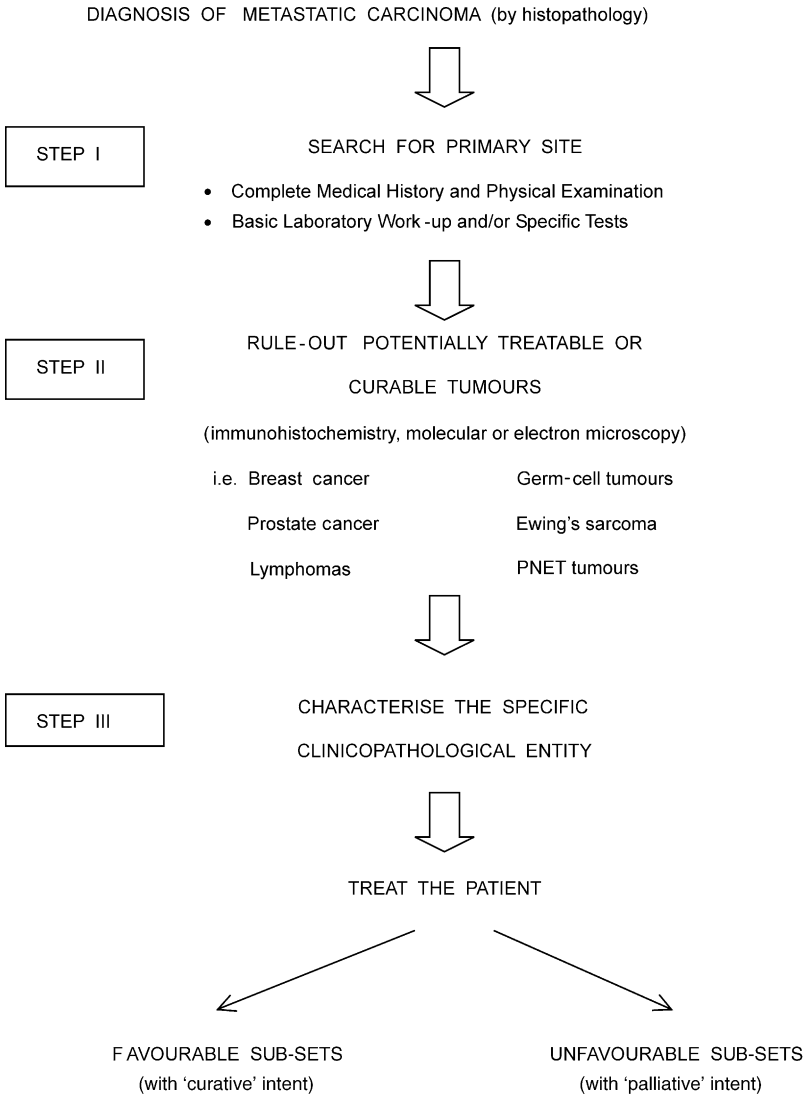

Fig. 2. Steps in the diagnostic and therapeutic management of patients with CUP. PNET, peripheral neuroectodermal tumour.

11. Treatment of unfavourable sub-sets

Patients with favourable sub-sets of CUP constitute a minority. Unfortunately, most carcinomas of unknown origin remain relatively unresponsive to systemic therapy, although chemotherapy has been found to offer clinical benefit to some of these patients. Several platinum or taxane/platinum-based regimens (Tables 8 and 9) have produced higher response rates than were observed with previous regimens, and median survivals in the range of 8–9 months. The 1- and 2-year survivals in large numbers of patients treated with taxane/platinum regimens are approximately 45 and 20%, respectively [94–96]. These survival statistics also seem superior to those reported with earlier chemotherapy regimens or supportive care alone.

Although these recent reports suggest a modest improvement in treatment efficacy, definitive conclusions are difficult due to the heterogeneity of this patient population and the retrospective nature of the comparisons. As with other advanced malignancies, considerable selection is involved as patients enter clinical trials. Population based data from two European registries report median survivals of 2–3 months in an unselected CUP population, while median survival in patients enrolled in clinical studies invariably ranges from 6 to 10 months [2,3]. In addition, median age of unselected CUP patients is around 70 years, while the median age of patients treated in trials is usually below 60 years. However, several favourable sub-sets of patients were not excluded from the registries survival reports, thus tending to improve the overall results. Additional selection factors may also influence the results of clinical studies conducted in single, specialised institutions. Therefore, definitive randomised trials are needed in patients with CUP to confirm the benefit of recent regimens and to better define standard treatment.

The general approach to the diagnosis and treatment of patients with CUP is outlined in Fig. 2. At present, most patients with CUP should enter a treatment trial. For patients who do not fit into a favourable sub-set, a trial of empirical combination chemotherapy should be considered if their performance status is adequate. Patients who are either very elderly or who have a poor performance status are better managed with symptomatic care. Since the benefit of current therapy remains limited in most patients, the evaluation of novel treatment approaches is essential. Promising classes of agents currently in development, including epidermal growth factor receptor (EGFR) inhibitors and anti-angiogenesis agents, should be explored in patients with CUP. Ongoing basic research and focused translational studies are also critical in advancing the understanding and management of patients with these tumours.

12. Online guideline recommendations

The readers of this review article should be aware of the available online guideline recommendations in English, at the following electronic sites:

1. NCI/PDQ: http://www.cancer.gov/cancerinfo/pdq/treatment/unknownprimary/healthprofessional/
2. ESMO Minimal Clinical Recommendations (available in full text/PDF/Palm OS format) http://www.esmo.org/reference/reference.guidelines.htm

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