Cancer of unknown primary site

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Lancet 2012; 379: 1428–35
Published Online March 12, 2012
DOI:10.1016/S0140-6736(11)61178-1

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Cancer of unknown primary site (CUP) is a well recognised clinical disorder, accounting for 3–5% of all malignant epithelial tumours. CUP is clinically characterised as an aggressive disease with early dissemination. Diagnostic approaches to identify the primary site include detailed histopathological examination with specific immunohistochemistry and radiological assessment. Gene-profiling microarray diagnosis has high sensitivity, but further prospective study is necessary to establish whether patients' outcomes are improved by its clinical use. Metastatic adenocarcinoma is the most common CUP histopathology (80%). CUP patients are divided into subsets of favourable (20%) and unfavourable (80%) prognosis. Favourable subsets are mostly given locoregional treatment or systemic platinum-based chemotherapy. Responses and survival are similar to those of patients with relevant known primary tumours. Patients in unfavourable subsets are treated with empirical chemotherapy based on combination regimens of platinum or taxane, but responses and survival are generally poor.

Introduction

Patients diagnosed with cancer of unknown primary site (CUP) present with histologically confirmed metastatic cancer for which clinicians are unable to identify a primary tumour after a standard diagnostic approach (panel 1).[1]

CUP accounts for 3–5% of all human cancers, is reported to be the seventh to eighth most frequent malignant tumour, and is the fourth most common cause of cancer death in both sexes. The overall age-standardised incidence per 100 000 people per year is 7–12 cases in the USA, 18–19 in Australia, 5–7 in the Netherlands, and 4–6 in Switzerland.[1] Median age at presentation is 65–90 years.[2] The disorder is slightly more common in men than in women, and predominantly affects adults (less than 1% of patients with diagnosed solid CUP are children).[2]

Pathophysiology

Some investigators believe that biologically distinct CUP cases exist. Such cases are thought to have a peculiar and poorly understood biology and a metastasis-causing genetic signature independent of that of the primary tumour.[1,3] Here we review the evidence for the existence of such a distinct biology.

Hedley and colleagues[4] reported that 106 (70%) of 152 patients with CUP had aneuploid tumour cells. Additionally, several investigators have used immunohistochemistry to study the oncogenes *MYC* and *RAS*, and human epidermal growth factor receptor-2 proteins, and showed that they were overexpressed in less than a third of CUP cases.[3,4] The transmembrane proteins epidermal growth factor receptor, platelet-derived growth factor receptor, MET, and c-Kit, which contribute to malignant transformation when constitutively activated, are overexpressed in less than 15% of patients with CUP who have no activating mutations.[3,5] Stella and coworkers[6] screened 23 patients with CUP and reported a mutation incidence of 30%, higher than the 4% incidence recorded for other solid tumours.

The so-called guardian of the genome, *TP53*, has been investigated by many groups in studies of CUP, but overexpression rates (40–50%) or mutation rates (25–40%) are not different from those of other solid tumours. Research into immunohistochemical staining of VEGFA (the main protein mediating tumour angiogenesis) and matrix metalloproteinases (enzymes that degrade stroma) showed that the relevant genes are universally expressed and active angiogenesis is present in CUP.[3] Finally, circulating tumour cells in the peripheral blood were recorded in 15 of 24 patients with CUP, with a still unknown effect on prognosis.[7] Overall, the search for a molecular CUP signature has relied on non-systematic studies of one gene or protein, and has not identified a molecular trait that is a consistent CUP characteristic. The complex CUP signature is probably made up of many genes.

Most cases of CUP are carcinomas, which are divided into adenocarcinomas of well or moderate differentiation (60%), undifferentiated or poorly differentiated adenocarcinomas (30%), squamous-cell carcinomas (5%), and undifferentiated neoplasms (5%).[1,2,8] Immunohistochemical studies can help to categorise patients into subsets to receive the appropriate therapeutic management.

Search strategy and selection criteria

We searched Medline with the search terms "cancer", "carcinoma", or "adenocarcinoma", in combination with "unknown primary" or "unknown origin". We mostly selected publications from between 1981 and January, 2011, but did not exclude commonly referenced and highly regarded older reports. We also searched the reference lists of articles identified by this search strategy and selected those we judged relevant. Review articles and book chapters are cited to provide readers with more details and more references. Only reports published in English were included.

Clinical features and clinicopathological subsets

Whether the clinical course of CUP—especially for patients with untreatable subsets—differs substantially from that of known primary tumours is unclear. CUP has several fundamental characteristics: short history with symptoms and signs associated with metastatic

sites, early dissemination in the absence of primary tumour, aggressive clinical course, and occasionally an unpredictable metastatic pattern (frequency and location of metastases different from those of known primary tumours). Additionally, three or more organs are involved at time of diagnosis in a third of patients.[1,2]

Autopsy helps to understand the diagnosis and natural history of CUP. Unfortunately, autopsy rates have been declining during the past three decades in both the USA and Europe.[9] In an analysis of 12 post-mortem cohort studies from 1944 to 2000,[9] the primary tumour was identified in 644 (73%) of 884 patients. The most common primaries were lung (27%) and pancreatic tumours (24%); tumours in the liver or bile duct (8%), kidney or adrenals (8%), colon or rectum (7%), genital system (7%), and stomach (6%) were also reported.

Classification of patients with CUP into several clinicopathological subsets according to age, sex, histopathology, clinical presentation, and organ or site involvement (table 1) helps practising oncologists to investigate and decide on appropriate therapeutic management.[1,2]

Poorly differentiated carcinoma with midline distribution

Poorly differentiated carcinoma with midline distribution predominantly affects young men (age <50 years; rarely reported in women) and has features of extragonadal germ-cell tumours. It mainly involves mediastinal or retroperitoneal lymph nodes, and less frequently supraclavicular or cervical nodes, or lung parenchyma.[1,2,8,10] Histologically, the disorder is characterised as undifferentiated or poorly differentiated carcinoma positive for β human chorionic gonadotropin, α-fetoprotein, placental alkaline phosphatase, or octomer-binding transcription factor 4 with immunoperoxidase stains. Serum concentrations of β human chorionic gonadotropin or α-fetoprotein can be raised in as many as 20% of cases.[1,2,8,10]

Isolated axillary nodal involvement

Adenocarcinoma identified in isolated unilateral axillary lymph nodes without an obvious primary tumour is a unique CUP subset in which the most frequent cause is breast cancer. This subset has similar presentation, biology, and outcome to stage II breast cancer. Its true incidence seems to range from 0·12% to 0·67% of all diagnosed cancers.[1,2,11] Women are almost exclusively affected, with a mean age at diagnosis of 52 years; 66% of patients are postmenopausal women.[1,2,11] Histologically, haematoxylin and eosin light microscopy examination, supplemented by immunohistochemistry (eg, detection of oestrogen receptor, progesterone receptor, cytokeratin [CK] 7, CK20, GCDFP-15, mammaglobin protein expression, or human epidermal growth factor 2 overexpression), can contribute to precise diagnosis.[1,2]

A systematic review[11] showed that, of 689 patients, 358 (52%) individuals had N2 or N3 disease. Histologically, 83% of patients had ductal carcinoma, with oestrogen

Panel 1: **Investigations that should be done before diagnosis of CUP in patients with suspected CUP**

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

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

Laboratory test data 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

	Median age (years)	Sex of patients (M/F)	Histopathology
Lymph nodes			
Mediastinal retroperitoneal	<50	70%/30%	UDF or PDF
Axillary	52	0%/100%	Adenocarcinoma (WDF, MDF, or PDF)
Cervical	57–60	80%/20%	SCC
Inguinal	58	50%/50%	UDF, SCC, mixed SCC and adenocarcinoma
Peritoneal cavity			
Primary peritoneal in women	55–65	0%/100%	Adenocarcinoma (serous papillary)
Ascites of other unknown origin	..	..	Adenocarcinoma (MDF or PDF; mucin; with or without signet ring cells)
Neuroendocrine tumours	63	60%/40%	PDF with neuroendocrine features; low-grade neuroendocrine cancers; small-cell anaplastic cancers
Liver (mainly) or other organs, or both	62	61%/39%	Adenocarcinoma (MDF or PDF)
Lungs			
Pulmonary metastases	..	..	Adenocarcinoma (WDF, MDF, or PDF)
Pleural effusions	..	..	Adenocarcinoma (MDF or PDF)
Bones (one or more)	..	..	Adenocarcinoma (WDF, MDF, or PDF)
Brain (one or more)	51–55	M>F	Adenocarcinoma (WDF, UDF, or PDF); SCC

Data taken from Pavlidis and Fizazi,[1] and Pavlidis et al.[2] M=men. F=women. UDF=undifferentiated. PDF=poorly differentiated. WDF=well differentiated. MDF=moderately differentiated. SCC=squamous-cell carcinoma.

Table 1: **Clinicopathological subsets of patients with cancer of unknown primary site**

receptors present in 43%. Of 13 cases investigated, only four overexpressed human epidermal growth factor 2, or a new protein. An occult breast primary tumour was identified histologically in 321 (72%) of 446 patients undergoing mastectomy.[11]

Squamous-cell carcinoma involving cervical lymph nodes

Squamous-cell carcinoma with involvement of cervical lymph nodes constitutes roughly 5% of all head and neck cancers, with an annual incidence of 0·34 cases per 100 000 people per year.[12] Squamous-cell histology is the most common type of cervical node CUP, representing 75% of cases, and the most common clinical presentation is a painless and unilateral cervical mass.[12,13] Level II lymph nodes—jugulodigastric or upper nodes—are most frequently implicated (30–50% of patients).

Fine-needle aspiration has a diagnostic accuracy of almost 95% and is widely used.[13] Panendoscopy with anaesthesia and a flexible nasopharyngoscope and biopsy is recommended. CT scan can detect the primary tumour of squamous-cell carcinoma in 22% of patients, MRI in 36%, and PET-CT in 28–57%.[14] Patients with squamous-cell carcinoma involving inguinal nodes should undergo careful clinical and endoscopic examination, and biopsy of suspicious lesions in anal vulva, vagina, uterine cervix, penis, or scrotum.[2,8,15]

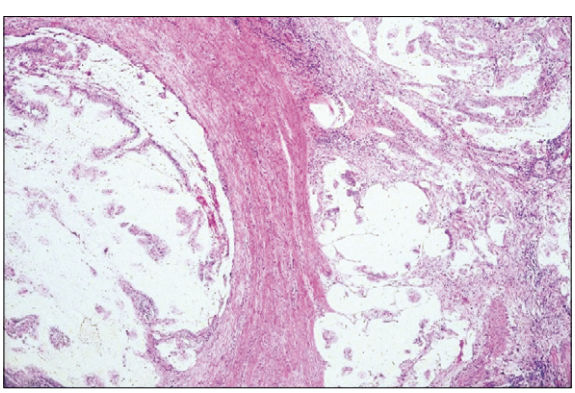

Figure 1: **Mucinous adenocarcinoma of unknown origin seeding the peritoneum**
Haematoxylin and eosin staining, ×40.

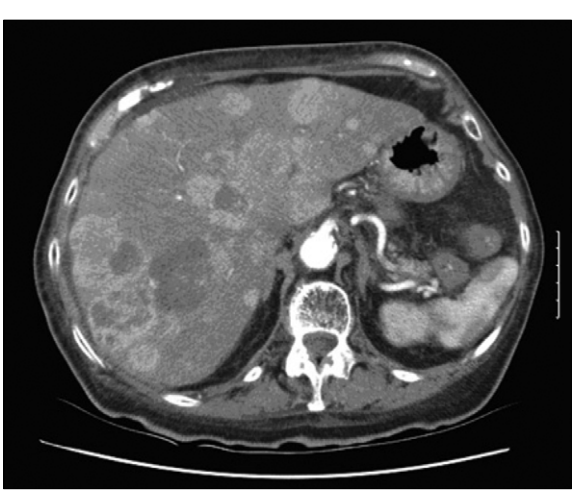

Figure 2: **CT scan of a patient presenting with several liver metastases from adenocarcinoma of unknown origin**

Women with serous papillary peritoneal carcinomatosis

Serous papillary peritoneal carcinomatosis has also been termed primary peritoneal carcinoma. Investigators of a systematic review series of 579 patients[16] noted that the most prominent clinical presentations were pain, abdominal-mass lesions, ascites, and intestinal obstruction. The disease spreads mainly to the peritoneal, mesenteric, and omental surfaces of the abdomen and pelvis.[16] Papillary serous adenocarcinoma might involve psammoma bodies with immunohistochemical expression of *MUC16*, oestrogen receptors, mesothelin, *WT1*, and *KRT7*. Heightened serum MUC16 concentrations are recorded in 70–90% of patients.[2,8] Notably, an ovarian or peritoneal primary tumour might be occult in the presence of undifferentiated, non-papillary peritoneal deposits.[16]

Malignant ascites of non-papillary serous adenocarcinoma

Diffuse carcinomatosis of the peritoneal surfaces of non-papillary serous adenocarcinoma originates predominantly from tumours of the gastrointestinal tract, as well as from other hidden primary sites. Clinicians should suspect a gastrointestinal origin in patients with mucin-producing adenocarcinoma (figure 1), often with signet ring cells.[2]

Metastatic neuroendocrine carcinomas of unknown primaries

Three different neuroendocrine cancers of unknown primary have been recognised (table 1). Patients with low-grade neuroendocrine tumours (10%) have typical, well differentiated carcinoids or islet-cell tumours of unknown primaries. Small-cell anaplastic carcinoma (15% of patients) is clinically similar to small-cell lung cancer, whereas poorly differentiated large-cell neuroendocrine carcinomas (75%) of unknown primary can present at many sites and have an aggressive course. Morphology of neuroendocrine tumours established with haematoxylin and eosin stains can help with diagnosis, as can immunohistochemistry markers such as chromogranin and synaptophysin.[2,8,17,18]

Metastatic visceral or skeletal CUP

Patients with metastatic visceral or skeletal CUP (80%) have poor outlooks. The most commonly involved metastatic sites after the liver (40–50%) are lymph nodes (35%), lungs (31%), bones (28%), and the brain (15%). Figure 2 shows a typical CT image depicting liver metastases of unknown origin. Histological investigation of this subset mostly identifies adenocarcinoma of moderate-to-poor differentiation (64%), followed by undifferentiated (20%), neuroendocrine (9%), and squamous carcinomas (7%).

Age, number of metastatic sites, lactate dehydrogenase concentration, performance status, and neuroendocrine differentiation are independent prognostic factors.[2,19] Men presenting with blastic bone metastases and high serum concentrations of prostate-specific antigen have a better prognosis than do others in this subset and should be managed in the same way as patients with metastatic prostate cancer. In these more favourable cases, immunohistochemical staining of biopsy tissue with prostate-specific antigen is mandatory.[2,8,20] Patients with visceral metastases and a colon-cancer profile (ie, those positive for CK20 and homeobox protein CDX2 but negative for CK7 on immunohistochemical staining) also have a more favourable prognosis.

Panel 2 gives a summary of all subsets that have a favourable prognosis (representing 20% of patients with CUP) and those that have an unfavourable one (80%). More than ten retrospective analyses of univariate and multivariate prognostic factors have been done, involving more than 2500 patients with CUP.[1,2,21–23] Predictors of poor patient survival are male sex, performance status of more than 1, high comorbidity score, age older than 64 years, history of smoking (more than 10 pack-years), weight loss, and laboratory parameters such as lymphopenia, low serum albumin concentrations, and raised serum concentrations of lactate dehydrogenase and alkaline phosphatase.[1,21]

Diagnosis

Histopathology

Three rules are of paramount importance to the diagnosis of CUP. First, the pathologist should receive an adequate tumour tissue or properly processed cytological samples. Second, a stepwise algorithm with immunohistochemical staining should be applied to provide a final diagnosis. Third, close contact with the clinical oncologist to retrieve necessary clinical and laboratory information is pivotal. The immunochemistry of a CUP biopsy should establish three things: whether the cancer is carcinoma, melanoma, lymphoma, or sarcoma; whether the subtype is adenocarcinoma, germ-cell tumour, hepatocellular, renal, thyroid, neuroendocrine, or squamous carcinoma; and the primary site of adenocarcinoma (ie, prostate, lung, breast, colon, pancreas or biliary, or ovarian cancer; table 2).

Cytokeratins are intermediate filaments specific to epithelial cells expressed in some normal human tissues. They have 20 different subunits. Nowadays, cytokeratin-antibody cocktails are widely used to predict the anatomical origin of adenocarcinomas (table 3).[2,24] Although the number of stains available is increasing, immunohistochemistry probably pinpoints the epithelial tissue or origin in less than 30% of CUP cases.

Molecular diagnosis

Every tissue has a different biological function and therefore expresses specific genes. Conservation of this tissue-specific gene-expression profile during carcinogenesis could potentially enable definition of CUP according to primary site. Over the past decade, the success of gene-expression profiling in the classification of tumour types[25] has led to development of commercial tests for biological definition of tissue of origin, with accuracy rates of 33–93%.[26]

Only one such assay, the 1550-gene microarray-based Pathwork Tissue of Origin Test (Pathwork Diagnostics, Redwood City, CA, USA), has been reviewed and cleared by the US Food and Drug Administration.[26–30] Other laboratory-developed tests are available. Theros Cancer-TYPE ID (BioTheranostics, San Diego, CA, USA) is a 92-gene real-time quantitative RT-PCR assay, and the MiRview Mets test (Rosetta Genomics, Philadelphia, PA, USA) is a 48-microRNA quantitative RT-PCR assay. Another microarray-based test, the 1900-gene CupPrint (Agendia BV, Amsterdam, Netherlands), is offered clinically in Europe. Lastly, the CUP assay, a ten-gene quantitative PCR assay (Veridex, La Jolla, CA, USA), has been developed but is not yet clinically available.

Varadhachary and colleagues[27] assessed use of the ten gene CUP assay in a cohort of 120 patients and identified a putative tissue of origin in 61% of patients. Greco and co-workers[28] retrospectively investigated the Cancer Type ID RT-PCR platform in 20 patients with CUP who had their primary tumours identified later in life or during autopsy and reported correct biological diagnosis in 15 cases. Horlings and colleagues[29] applied the CupPrint assay to tumour samples from patients with CUP who were subdivided into three groups. For patients presenting with CUP (n=16), the test agreed with diagnosis of tissue of origin with immunohistochemistry in 94% of cases. For those with CUP with

Panel 2: Prognostic classification of patients with CUP

Favourable subset

- Women with papillary adenocarcinoma of the peritoneal cavity
- Women with adenocarcinoma involving the axillary lymph nodes
- Poorly differentiated carcinoma with midline distribution
- Poorly differentiated neuroendocrine carcinoma
- Squamous-cell carcinoma involving cervical lymph nodes
- Adenocarcinoma with a colon-cancer profile (CK20+, CK7–, CDX2+)
- Men with blastic bone metastases and elevated prostate-specific antigen (adenocarcinoma)
- Isolated inguinal adenopathy (squamous carcinoma)
- Patients with one small, potentially resectable tumour

Unfavourable subset

- Adenocarcinoma metastatic to the liver or other organs
- Non-papillary malignant ascites (adenocarcinoma)
- Multiple cerebral metastases (adenocarcinoma or squamous carcinoma)
- Several lung or pleural metastases (adenocarcinoma)
- Multiple metastatic lytic bone disease (adenocarcinoma)
- Squamous-cell carcinoma of the abdominopelvic cavity

	Diagnosis
Step one	
AE1 or AE3 pan-cytokeratin	Carcinoma
Common leucocyte antigen	Lymphoma
S100; HMB-45	Melanoma
S100; vimentin	Sarcoma
Step two	
CK7 or CK20; PSA	Adenocarcinoma
PLAP; OCT4; AFP; human chorionic gonadotropin	Germ-cell tumour
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; mammaglobulin; ER	Breast
CDX2; CK20	Colon
CDX2 (intestinal epithelium); CK20; CK7	Pancreas or biliary
ER; CA-125; mesothelin; WT1	Ovary

Step one detects broad type of cancer. Step two detects subtype. Step three detects origin of adenocarcinoma. Positive results with any of these stains indicates a tumour is present, but without absolute certainty. PSA=prostate-specific antigen. PLAP=placental alkaline phosphatase. OCT4=octamer-binding transcription factor 4. AFP=α-fetoprotein. pCEA=polyclonal carcinoembryonic antigen. RCC=renal-cell carcinoma antigen. ER=oestrogen receptor. PAP=prostatic acid phosphatase.

Table 2: **Immunohistochemical approaches for diagnosis of different types of cancer of unknown primary site**

	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–

+=positive stain. –=negative stain.

Table 3: **Phenotypic expression of cytokeratins in adenocarcinoma of several organs**

differential diagnosis of two or three sites after immunohistochemistry (n=12), the assay predicted a single origin, concordant with clinicopathological information in eight of 12 cases. Finally, for patients with CUP who had no suspected primary site, the test predicted a single origin, in agreement with the clinical suspicion in six of ten cases. Another study[30] using the same assay showed clinically compatible results in 18 of 21 tumours.

Molecular testing could become an important method in tissue-of-origin identification, to lend support to a suspected diagnosis. Moreover, such methods, by biologically allocating a primary tissue of origin, could allow appropriate specific treatment, including targeted therapies, to be given to patients with CUP, which could improve survival. This principle is being tested in prospective clinical trials. Until the results are reported, molecular platforms have an uncertain role in clinical practice. Because most cases of favourable CUP exhibit biological behaviour and have clinical courses similar to metastatic overt tumours, and should be treated accordingly, molecular diagnosis could contribute to identification of midline nodal CUP cases that are undifferentiated germ-cell, thyroid, lymphoid, or neuroendocrine cancers needing specific treatment. Material could be sent for molecular diagnosis in cases of poor-risk CUP, especially for visceral (to detect a colon cancer profile) or bony metastases (to detect a renal or prostate profile).

Imaging

During the past 30 years, the accuracy of detecting primary tumour by CT or MRI has increased from 11–26% to 33–55%.[31] In a study with 879 participants,[31,32] CT scans provided a diagnosis in 86% of patients with pancreatic cancer, in 36% with colorectal cancer, and in 74% with lung cancer, providing an overall diagnostic accuracy of 55%. No data are yet available for the validity of whole-body MRI in patients with CUP. However, MRI enables detection of occult primary breast cancers in as many as 70% of cases. MRI is the imaging diagnostic test of choice in the subset of women with isolated axillary nodal adenocarcinoma.[33]

Tumour detection rates by fluorodeoxyglucose (FDG) PET range from 25% to 43%.[32,34–36] The most common primaries detected in studies are lung (54–59%) and head and neck cancers (46%). In 27% of cases, previously unrecognised metastases are reported, and clinicians alter clinical management of almost 35% of patients.[32,34,35] In a comparative study in patients with cervical lymphadenopathy,[36] FDG PET/CT was better than was FDG PET in detection of the primary site (55% *vs* 31%). A meta-analysis[14] showed that primary tumour detection rate is 37%, and again the most common primaries were lung (33%), head and neck cancer (27%), pancreatic (5%), breast (4%), and colon cancer (4%).

Use of ^{68}Ga-DOTA-NOC receptor PET/CT is more accurate than is CT, MRI, or OctreoScan in detection of primary neuroendocrine tumours or metastatic lesion.[37] PET scanning would be indicated in solitary, potentially resectable CUP and in head and neck cervical CUP; the indications will probably expand in other subsets because of the enhanced sensitivity of PET/CT. An indirect comparison of CUP frequency recorded before 1990 and in more recent reports suggests that it has decreased from

10–15% to 3–5%, probably because of enhanced accuracy and sensitivity of imaging technology.[9]

Endoscopy

The detection accuracy, sensitivity and specificity of endoscopic procedures are very low. Therefore, endoscopic procedures should be used only in patients presenting with relevant symptoms or signs, or in the presence of specific pathological changes. For example, colonoscopy should be used when a patient has a CK7–, CK20+, or CDX2+ immunohistochemical profile, and brochoscopy when positive for TTF1.

Serum tumour markers

Patients with CUP commonly overexpress several tumour markers in a non-specific way. Concentrations of various serum epithelial tumour markers (carcinoembryonic antigen, CA15-3, CA-125, CA19-9, α-fetoprotein, β-human chorionic gonadotropin) can be raised without any diagnostic, predictive, or prognostic use. Therefore, routine measurement of epithelial tumour markers is not recommended in daily clinical practice.[2] However, in some cases, it might be diagnostically helpful—eg, β human chorionic gonadotropin and α-fetoprotein are increased in patients with poorly differentiated carcinoma of midline distribution, as are prostate-specific antigen in men with bone metastases, CA-125 in women with primary serous peritoneal adenocarcinoma, and CA15-3 in women with isolated axillary adenocarcinoma.[38]

Treatment

Favourable subsets

For the past 50 years, chemotherapy has been the basis of CUP treatment. Generally, treatment recommendations are based mainly on type 3 evidence, and therapeutic modalities are thought to be suitable for individual clinical or investigational use.

Women with serous papillary adenocarcinoma of the peritoneal cavity should be managed similarly to patients with stage III and IV ovarian cancer. Best possible treatment includes maximum surgical cytoreduction followed by chemotherapy with a combination regimen of platinum and paclitaxel. Median response rate is about 80%, with 30–40% patients having complete responses and a median survival of 36 months.[1,8,16]

Patients with poorly differentiated carcinoma with midline distribution should be treated as having a poor-prognosis germ-cell tumour and given platinum-based combination chemotherapy. From ten available reports,[10] the median response rate to this treatment is roughly 45%, with almost 20% of patients having complete responses and a median overall survival of 12 months. This subset is poorly defined, and constitutes a heterogeneous entity with a minority harbouring a typical germ-cell cancer. It warrants further molecular genetic investigation.[8,10]

Patients with poorly differentiated neuroendocrine carcinomas should be treated with platinum-based or platinum-taxane combination chemotherapy. Overall response rate to this treatment is 55% (as many as 21% of patients have complete responses), whereas median overall survival is 15·5 months (IQR 11·6–40).[18] Few patients (13%) might have long-term survival.[17,18] What effect sunitinib or mTOR-inhibitors would have in this group is unknown. VEGFR and mTOR inhibitors were active in foregut or midgut neuroendocrine tumours that were well to moderately well differentiated, but the tissue of origin in CUP (foregut, midgut, hindgut) is unknown and poor differentiation is expected.

A large systematic review of evidence from the past 30 years[11] showed that 633 (92%) of 689 women with adenocarcinoma involving only axillary lymph nodes underwent axillary lymph node dissection, 275 (40%) had mastectomy, 179 (26%) had primary breast radiotherapy, and 131 (19%) had mastectomy with chest-wall radiotherapy. Breast observation only was associated with high locoregional relapse rates (42%) and risk of metastatic spread. 426 (62%) received adjuvant chemotherapy, or hormone therapy, or both. 3 year overall survival was 97% in the group that received adjuvant systemic therapy versus 75% in the untreated group.[1,8,20] Therefore, axillary clearance should be used because it offers local control; mastectomy or breast irradiation are preferred to avoid locoregional relapses; and adjuvant systemic therapy with chemotherapy, hormone therapy, or trastuzumab should be given according to standard indications.

Treatment of patients with metastatic squamous-cell carcinoma involving cervical lymph nodes of an unknown primary origin should be similar to that of patients with locally advanced carcinoma of the head and neck. Recommended management is radical neck dissection, external-beam radiotherapy to the pharyngeal axis and bilateral neck, and concurrent chemotherapy and radiation therapy mainly in N2 or N3 disease (although there are few data for this treatment).[8,13,39–41]

Although little evidence is available for treatment of patients with adenocarcinoma with a colon-cancer profile (CK20+, CK7–, and CDX2+), the disease shows responses and survival similar to those obtained with colon cancer-specific therapies. Median survival is similar to that of metastatic colon cancer (20–24 months). This subset has also been correlated with molecular profiles of colon cancer and tumours might be producing non-papillary serous peritoneal deposits.[42,43]

Men with blastic bone metastases and raised concentrations of prostate-specific antigen should be treated for metastatic prostate cancer, initially with androgen-deprivation treatment. When disease becomes castration-resistant, patients should be given chemotherapy.[2,8] Finally, patients with either isolated inguinal lymph-nodal metastatic squamous-cell carcinoma or with one metastatic lesion are classed as patients with restricted disease.

These patients should be managed with local dissection with or without local radiation treatment. They usually enjoy long, disease-free survival.[14,44]

Unfavourable subsets

Most patients with CUP (80%) belong to prognostically unfavourable subsets, and the most common subset is visceral metastatic disease.[1,2] In a systematic review of more than 700 patients with poor-prognosis CUP and liver metastases histologically diagnosed as adenocarcinoma or undifferentiated carcinoma,[44] response rates were less than 20% and median survival was 6–7 months. Data from non-randomised studies from the past 40 years have shown that the introduction of platinum or platinum-taxane combinations is associated with a doubling of response rates and overall survival. By contrast, a meta-analysis[45] has shown that no type of chemotherapy has been proven to lengthen survival.[46]

Targeted therapy

In one study,[47] 60 patients with CUP were given first-line treatment with carboplatin and paclitaxel, with or without bevacizumab and erlotinib as maintenance treatment. The response rate was 53% and overall survival 13 months. In another investigation,[48] 47 patients received bevacizumab and erlotinib as second-line treatment, and the response rate was 10% and median survival 7 months. Further investigation of targeted treatment in patients with CUP is warranted.

Future prospects and research needs

CUP is a heterogeneous group of metastatic cancers with a distinct biology. However, although our inability to identify a primary tumour is because of clinical or technological inefficiencies in a substantial proportion of patients, sometimes the primary tumour will regress or stay dormant and the malignant clone will metastasise early to several secondary sites. For this subgroup of genuine CUP, research should be focused on the multigene prometastatic signature of these tumours, which might well lead to identification of biomolecules crucial to metastatic dissemination that could be targeted with smart drugs. Moreover, such breakthroughs in biology and therapeutics would benefit not only patients with CUP, but also potentially all patients with cancers prone to metastatic dissemination.

Our best approach to patients with CUP is to identify those with favourable subsets for primary-specific therapy and manage those with unfavourable subsets with palliative chemotherapy or possibly with primary-specific therapy, aided by multigene expression platforms based on microarray of PCR technology. Use of molecular diagnosis to extend survival would first need to be validated in the context of randomised clinical trials.

Contributors
NP and GP did the literature search, interpreted the data, and wrote the report. NP collected the data. GP created the figures.

Conflicts of interest
We declare that we have no conflicts of interest.

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