

Cancer of unknown primary: a diagnostic and therapeutic dilemma

Cancer of unknown primary origin is difficult to manage because, even when the primary can be detected, it behaves differently to cancers of the same type and location that are discovered as primaries. Here, the lead author of ESMO's new guidelines for these tumours reviews their diagnosis and management and looks ahead to the possible role of molecular profiling.

Cancer of unknown primary (CUP) represents a heterogeneous group of metastatic tumours for which medical history, physical examination and standardised diagnostic work-up fail to identify the site of the cancer's origin at the time of diagnosis. It accounts for 3%–5% of all malignancies, so is relatively common.

The natural history of cancer of unknown primary site is quite different to cancers where the primary site is known, with an unpredictable metastatic pattern. For example, a pancreatic cancer with known primary site has a well-defined metastatic pattern, with less than a 5% chance of lung metastasis. However, as a hidden pancreatic CUP, it might have a 30%–40% chance of metastasis to the lungs.

The fundamental characteristics of CUP are:

- Early dissemination
- Clinical absence of primary site at presentation
- Generally quite aggressive
- Unpredictable metastatic pattern



European School of Oncology e-grandround

The European School of Oncology presents weekly e-grandrounds which offer participants the opportunity to discuss a range of cutting-edge issues, from controversial areas and the latest scientific developments to challenging clinical cases, with leading European experts in the field. One of these is selected for publication in each issue of *Cancer World*.

In this issue, Nicholas Pavlidis, Professor of Medical Oncology at the University of Ioannina, Greece, reviews the challenge of diagnosing and treating cancer of unknown primary (CUP). This covers a range of cancers with different histologies where the primary cancer cannot be found. He summarises new ESMO guidelines, which outline key steps in diagnosis and treatment. Daniel Helbling, from the Onkozentrum



Zurich, in Switzerland, poses questions that were sent in by participants during the e-grandround live presentation. The presentation is summarised by Susan Mayor.

The recorded version of this and other e-grandrounds is available at www.e-eso.net

HISTOLOGICAL CLASSIFICATION OF CUP

The most common histological type of CUP is adenocarcinoma, with well- to moderately-differentiated adenocarcinomas accounting for 50% of cases of CUP, and poorly or undifferentiated adenocarcinomas accounting for a further 35%. Squamous cell carcinomas account for 10% of CUP cases, while undifferentiated neoplasms, including neuroendocrine tumours, lymphomas, germ cell tumours, melanomas, sarcomas and embryonic malignancies account for 5%.

CLINICOPATHOLOGICAL ENTITIES OF CUP

CUP is not one disease. The different histological types can be considered by the organ affected:

Liver. Patients with liver metastases often have adenocarcinoma. They sometimes also have metastatic signs in other organs, which is, unfortunately, the most common type of CUP.

Lymph nodes. Patients with lymph node metastases in a mediastinal to retroperitoneal (midline) distribution may have undifferentiated or poorly differentiated carcinoma. Those with metastases to the axillary nodes may have adenocarcinomas, while patients with metastases in the cervical nodes could have squamous cell carcinoma, and those affected in the inguinal nodes could have undifferentiated carcinoma, squamous cell carcinoma (SCC), or mixed SCC/adenocarcinomas.

Peritoneal cavity. CUP with metastases in the peritoneal cavity is termed peritoneal adenocarcinomatosis when found in females, and looks like ovarian cancer. Histologically, these cancers are papillary or serous adenocarcinomas, with or with-

out psammoma bodies (round collections of calcium). Patients may also have malignant ascites of other unknown origin, which are usually mucin adenocarcinomas (with or without signet ring cells).

Lungs. A subset of patients has lung metastases, with either pulmonary metastases or only pleural effusion. These are generally adenocarcinomas.

Bones. Another subset of patients has only bone metastases, either solitary or multiple. These are adenocarcinomas of various levels of differentiation.

Brain. Brain metastases can occur either singly or more than one, and are adenocarcinomas.

Neuroendocrine tumours. These are generally poorly differentiated cancers mainly low-grade, with neuroendocrine features.

Melanoma. Patients have undifferentiated neoplasm with melanoma features, but with no obvious primary site.

Being aware of the subsets of CUP is useful in order to classify patients into appropriate groups for treatment decisions and research purposes.

FINDING THE PRIMARY SITE

Histopathology

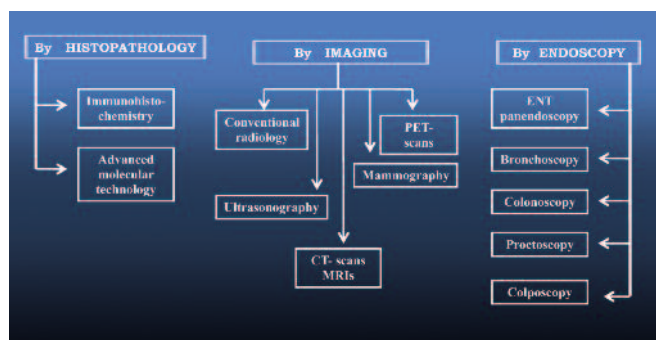
The process of searching for the primary site of CUP of an adenocarcinoma origin

requires good histopathology, especially immunohistochemistry, with 10 key markers generally being tested for. Routine evaluation of commonly used markers has not been shown to be of any prognostic or diagnostic assistance. Non-specific multiple overexpression of adenocarcinoma tumour markers (CEA, CA125, CA15-3, CA19-9) occurs in most CUP patients. Around 70% of CUP patients will have high serum levels of more than one tumour marker, so you cannot be sure about what you are dealing with. However, it is worthwhile to request:

- PSA in men with bone metastatic adenocarcinoma
- B-HCG and AFP in men with undifferentiated tumours (especially mid-line distribution)
- AFP in patients with hepatic tumours
- CA125 in women with papillary adenocarcinoma of the peritoneal cavity
- CA15-3 in women with adenocarcinoma involving only axillary lymph nodes.

The pattern of cytokeratins (CK7 and CK 20 positivity) is also very useful in determining primary cancers (see opposite). Nowadays, we also include advanced molecular technology, using gene expression to detect the primary site. This has an accuracy of 80% in locating the primary site of CUP.

TRACKING DOWN THE PRIMARY



Multiple strategies are needed to find the primary cancer

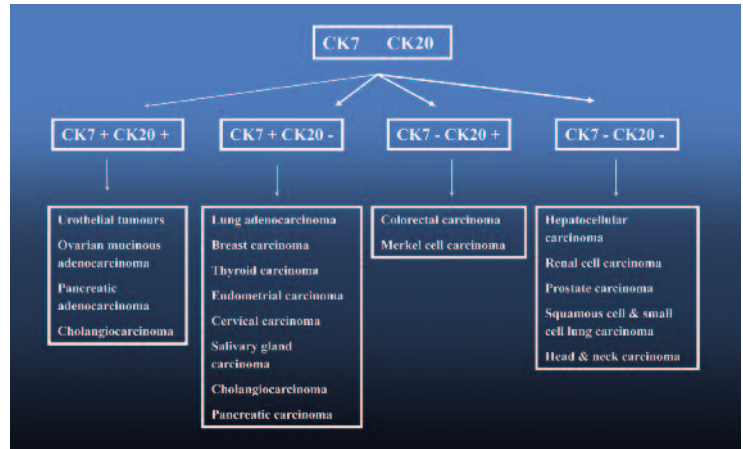
Question: If CUP is discovered, do you ask the pathologist to test all of these markers?

Answer: Not all of them. In a female patient, you do not need a PSA, and GcDFP-15, which checks for hidden breast cancer, is not needed in men. You can find breast cancer in males, but it is not very common. Select markers from the list opposite to rule out the primary site.

WHAT IMMUNOHISTOCHEMISTRY CAN REVEAL

Marker	THE 10 MARKERS	Site of Origin
◇ PSA (Prostate - specific antigen)		Prostate
◇ TTF1 (Thyroid transcription factor 1)		Lung
◇ GcDFP-15 (gross cystic disease fluid protein 15)		Breast
◇ CDX2		Colon
◇ CK20		Ampullary, Colon, Esophageal, Ovarian
◇ CK7		Lung, Pancreas, Breast, Cholangio, Ovarian
◇ ER (Estrogen receptor)		Breast, Ovarian, Endometrial
◇ Mesothelin		Ovarian, Cholangio, Mesothelioma, Endometrial
◇ CA 125		Ovarian, Endometrial, Cholangio, Pancreas
◇ Lysozyme		Cholangio, Stomach, Colon, Pancreas, Lung

WHAT CK COMBINATIONS CAN REVEAL



Source: JL Dennis et al. *Clin Cancer Res* 11: 3766–3772

Question: What is the accuracy of CA125 positive serum as a diagnostic tool for ovarian cancer?

Answer: If you routinely measure epithelial markers in the serum in all patients, 70% will have more than one marker at an elevated level. If you do it in the whole population of CUP patients, it is not helpful at all. However, if you do it in the subset of patients with peritoneal disease with pathology of papillary carcinoma, it is very useful. You must be very selective. The diagnostic accuracy of CA125 alone is not good. However, immunohistochemistry in general is very useful.

Question: Are you looking for these markers during treatment as an indication of the effectiveness of therapy?

Answer: If you are dealing with subsets of CUP, you should look for the markers suggested. For example, if you are dealing with a male with midline differentiated tumour, and B-HCG + AFP levels are raised, it is useful to measure these markers during treatment. However, this occurs in only 20% of patients so is quite rare.

Imaging

Imaging includes conventional radiology, ultrasonography, mammography,

and CT, MRI or PET scans.

A chest X-ray is used as a prerequisite before any further investigations. Barium studies are completely useless in investigating patients with CUP. CT scans are quite useful, with an accuracy of 40%, and can provide useful guidance for biopsy. Mammography is useful in investigating women with breast cancer, but has very low sensitivity. However, an MRI in breast cancer patients can increase accuracy to 60%. FDG-PET scan can be helpful, especially in patients with occult head and neck cancers or lung cancer. These areas are really sensitive to PET scan in finding the primary site.

Endoscopy

Finally, endoscopy is sometimes useful, but not in all patients. Its use should be guided by specific symptoms or signs. For example, ENT panendoscopy should only be requested for a patient with cervical node involvement. Bronchoscopy would be indicated in patients who have a positive chest X-ray or CT scan with a cough. Colonoscopy is useful in patients with relevant symptoms or signs, with the same applying to proc-

toscopy and colposcopy for patients with inguinal node involvement.

Question: How often do you personally use PET scans to diagnose CUPs?

Answer: I do not use it as a routine, and it is not even included in the guidelines to rule out occult head and neck cancer or lung cancer. However, if you have suspicions that your patient might have one of these cancers, you could consider it. It is still not accepted by everybody. If I have a patient with cervical lymph node presentation or some suspicions of lung cancer, I would recommend it. But do not do PET scan in all your patients.

Question: Do you recommend fundoscopy – looking at the back of the eye – as a tool in the search for CUP primary sites?

Answer: This technique would only be used frequently in the search for melanoma of unknown primary. Otherwise, I would only carry out this process in the search for a primary if I had a biopsy of metastases in the liver that showed melanoma and I could not find any skin primary. In this case, I would have to look at the retina to search for primary retinal melanoma.

HOW OFTEN IS A PRIMARY TUMOUR DIAGNOSED?

Available data suggest that the antemortem frequency of detection of primary site by imaging, endoscopy or immunohistochemistry studies remains around 30% (*Eur J Cancer* 39:1990–2005). A study published several years ago by our group compared data from autopsy and microarray (*Eur J Cancer* 43:2026–2036). Reviewing studies from the last 55 years (1944–2000) where autopsy studies were available gave results for 884 autopsies. The primary site was found in 73% of these patients, with the most common primary sites being identified as lung (27%) and pancreas (24%).

Question: *Do you often find small tumours that metastasise very quickly?*

Answer: *Yes, this is quite common. The tissue must be sliced very finely to identify these tumours. A CUP is a tumour that metastasises abnormally quickly.*

Data from recent studies, identifying the primary site by genetic profiling or microarray, show that the accuracy of biological assignment of primaries is 50%–87%. The most common primary

identified was breast cancer (15%) followed by pancreas (12.5%), bowel (12%) and lung (11.5%). It is not clear why the rates differ compared to autopsy studies.

TREATMENT OF CUP

In terms of treatment, there are essentially two subsets of CUP patients: the favourable prognosis subset, with better response rate, more complete responders and survival ranging from 15 to 22 months, and the poor prognosis subset, with median survival of 4 to 10 months. Favourable subsets make up only 20% of CUP patients; 80% belong to the unfavourable prognosis subset.

CUP patients with favourable or good prognosis

The first group of patients with a good prognosis is those with poorly differentiated CUP and midline distribution. Most of these patients are men younger than 50 years who have lymph node involvement in the mediastinum and retroperitoneum, some peripheral lymph nodes and some lung metastases; 20% have elevated serum markers. The clinical evolution is, unfortunately, very rapid tumour growth. Up to 50% of these

patients respond to cisplatin-based chemotherapy and around 20% are complete responders. Median survival is around 13 months, but 15% survive long-term.

The second group is women with peritoneal carcinomatosis, who present with abdominal distension, pelvic masses and ascites. Surgeons find abdominal masses with peritoneal disease and ascites, but normal ovaries with no primary tumour. Histology will show papillary serous carcinoma and patients often have elevated CA125. These patients should be treated in the same way as FIGO III ovarian cancer, with surgical cytoreduction and platinum-based chemotherapy. The response rate is up to 60%, with 30% complete responders. Median survival is around 16 months and 10% will be long-term survivors.

Question: *How should I treat a woman with axillary lymphadenopathy with a diagnosis of adenocarcinoma who has an increased level of CA15-3? Do you treat patients like this as metastatic breast cancer patients?*

Answer: *This type of patient with isolated axillary nodal metastases accounts for 0.3% of all breast cancer patients. Mammography has quite low sensitivity (20%), whereas MRI has sensitivity up to 70%. Most of these patients have N1 disease and invasive ductal carcinomas. Half are positive for ER and PR. There are not yet sufficient data about HER-2 receptors to determine the percentage. Distant metastases occur in only 2% of patients.*

The first step in a patient with axillary lymphadenopathy is to take a biopsy and check for breast cancer. If this is the case, give standard treatment. If the biopsy is negative for breast cancer, you should perform complete axillary dissection, with, or without, breast cytoreductive surgery and radiotherapy. Chemotherapy or endocrine treatment should then be given, depending on age and menopausal status.

FAVOURABLE SUBSETS OF CUP

Poorly differentiated carcinoma with midline distribution (which looks like extragonadal germ cell syndrome)

Women with papillary adenocarcinoma of the peritoneal cavity (which looks a bit like ovarian cancer)

Women with adenocarcinoma involving only the axillary lymph nodes (which looks like breast cancer)

Squamous cell carcinoma of the cervical lymph nodes (looks like head/neck cancer)

Poorly differentiated neuroendocrine tumours

Men with blastic bone metastases and elevated PSA (adenocarcinoma)

Isolated inguinal adenopathy (squamous carcinoma)

Patients with a single, small, potentially resectable tumour

Survival rates are similar to those for stage 2 or 3 breast cancer, although 25% have locoregional recurrence. The overall survival is 75% at five years and 68% at 10 years. There is no difference in survival rate between patients undergoing conservative management and mastectomy procedures. Patients with N2 disease have a worse prognosis than N1 disease.

Question: If you have suspected ovarian cancer and treat the cancer with chemotherapy, and the CA125 comes down nicely, how long will you go on with the treatment? What is the level of CA125 decline required?

Answer: You are talking about primary peritoneal disease. You do the same procedure as with ovarian FIGO III cancer patients, giving six cycles of chemotherapy. If the marker was still dropping after six cycles, I would schedule another two or three cycles to be on the safe side.

The other good prognosis subset is patients with squamous cell cancer involving the cervical lymph nodes. These should be managed in the same way as patients with locally advanced head and neck cancer.

Surgery alone is inferior unless you have a patient with pN1 neck disease with no extracapsular extension. Radiation should be given to both sides of the neck and mucosa (entire pharyngeal axis and larynx).

Chemotherapy remains undefined, but there are encouraging results with platinum-based treatment. The five-year survival rate is 35%–55% after treatment, and there are also some long-term survivors.

Patients who have poorly differentiated neuroendocrine carcinomas should be treated with platinum-based or paclitaxel/carboplatin-based chemotherapy. The response rate is 50%–70%, with up to 25% complete responders. Median survival is around 14 months, with 24% surviving up to three years.

CUP patients with a poor prognosis

The most common subset of patients with a poor prognosis CUP is those with liver metastases without known primary tumour. A summary of the big five trials in these patients ($n=700$) shows a response rate of less than 20% and a very poor median survival, down to five months. (Bull Cancer 78:725–736; JCO 16:2105–2112; Clin Radiol 57:1073–1077; Gastroint Clin Biol 29:1224–1232; Cancer Treat Rev 34:693–700).

Patients who are relatively young and have good performance status should be offered platinum-based chemotherapy for two or three cycles. If there is no response, stop treatment. A patient who is older or has a poor performance status should be given supportive care alone.

Question: Which cisplatin doublet do you use and what do you use as second-line treatment for patients of unfavourable CUP subsets?

Answer: The most common first-line doublet is platinum–taxane, except for patients with a neuroendocrine tumour, where you might use etoposide at the same time. Data for second- and third-line therapy are poor. We have only data for gemcitabine and other chemotherapy. Response rates to these therapies are very poor and survival is not good. Second-line therapy still remains unsuccessful in the treatment of CUP.

Question: In a 65-year-old woman with metastatic pleural effusion and elevated CA125 but no evidence of ovarian cancer on the MRI, and no ascites, what further procedures would you do and how would you treat her? Would you do a diagnostic laparoscopy?

Answer: If a CT scan or MRI is negative, I am not going to do laparoscopy to find the primary tumour. Sometimes in primary lung cancer you might have increased serum CA125, but we never look for this. If I have a patient with pleural effusion as an

unknown primary, I do a bronchoscopy first of all, to rule out lung cancer.

This patient belongs, by definition, to the bad prognosis subset. The two most possible good prognosis groups are breast cancer or ovarian cancer. However, if you rule out both via CT or MRI and have an MRI of the breast with no sign of tumour, I would treat this patient as belonging to the poor prognosis subset.

DOES MOLECULAR PROFILING IMPROVE OUTCOMES?

We are still unsure as to whether molecular profiling has any impact on patients' outcome, but there are two or three randomised studies investigating this. Hainsworth and colleagues in the US are conducting a phase II study in which they perform CUP investigation after conventional work-up, followed by gene expression profiling (JD Hainsworth, www.clinicaltrials.gov). They then split the patients into two groups. The first group includes patients with a specific diagnosis from gene expression profiling, who are treated accordingly. The second group is patients with no specific diagnosis, who are treated empirically for CUP with agents including platinum or a taxane. Results will be analysed to see whether guidance of treatment in patients in which gene expression profiling shows a specific primary site improves outcomes.

A retrospective study of 47 CUP patients treated with regimens for colorectal cancer showed that those with proven colorectal cancer had higher response rates (60%) and median survival (22 months) compared to those who were also treated with colorectal regimens but who had unknown primary tumours (10% response rate; six months median survival).

If prospective data show that gene profiling predicts the effectiveness of treatment, this will be very useful in determining the most appropriate treatment for these patients.

Question: Do you have experience of pancreatic carcinoma in young individuals presenting as CUP? Would you treat them differently from advanced pancreatic carcinoma in the elderly? A randomised phase III trial published recently by a French group used folfirinnox [5FU/leucovorin/irinotecan/oxaliplatin] against gemcitabine. There was a clear advantage in survival for individuals in the folfirinnox group over three years. Would you treat CUP suspected to derive from the pancreas in young patients differently than in more elderly patients?

Answer: If you are talking about patients who had a molecular or gene profile that proved they had pancreatic cancer, it is a completely different question than suspecting a pancreatic cancer in a patient without gene profiling. You have to differentiate it. If you have patients whom you believe may have pancreatic cancer but you never proved that, you do not treat them as pancreatic cancer patients because you do not have data to support this.

I would give 'umbrella' treatment with platinum–taxane and treat them as a poor prognosis patient. I would not be expecting to have good results. However, if data from ongoing randomised studies show that a gene profiling diagnosis can be used to treat patients as routine patients, I would treat these patients as pancreatic cancer patients. The challenge with CUP is that there is no approved drug for its treatment and expensive drugs used to treat cancers with known primary tumours may be ineffective against CUP.

Question: In the future, will we be able to link treatment directly to the patient's genetic profile?

Answer: This is the principle. However, at the same time, we believe that patients with CUP of unfavourable prognosis (e.g. liver metastases), regardless of the discovery of the primary tumour, have

low response rates. Each patient will have a specific molecular profile that can be linked to treatment, but they will not respond in the same way as those with known primary tumours. CUP patients are carrying a molecular signature that gives different behaviour, and probably respond differently to those with known primary tumour.

A phase II trial in the US using a combination of bevacizumab and erlotinib in CUP treatment showed a fairly poor response rate, with 10% having a partial response and 61% stable disease. The median survival was 7.4 months and 33% survived up to one year (JCO 25:1747–1752). This answers the question of targeting treatment in these patients.

DIAGNOSIS AND MANAGEMENT: IN SUMMARY

The new clinical practice guidelines published by ESMO for the diagnosis, treatment and follow-up of cancers of unknown primary site (*Ann Oncol* 21 (suppl 5):v228-v231) set out what you need to know in order to manage these patients. They point out that CUP patients may have a different natural

history to those with known primary tumours. CUP patients do not suffer from one disease but often have more than one, and it is essential to differentiate clinical and pathological subsets.

Immunohistochemistry is the cornerstone of CUP diagnosis. Molecular profiling is very useful as far as sensitivity is concerned, but we do not yet know if this will improve patients' outcomes. In terms of imaging, a CT scan and MRI are useful, especially in the detection of primary breast tumours. A PET scan is useful in finding hidden head/neck and lung cancers.

It is important to avoid spending unnecessary time and money in investigating and treating all CUP patients, as there is no benefit in this. Patients should be classified into favourable prognosis and poor prognosis subsets. For favourable subsets, locoregional treatment should be given to patients with isolated axillary lymph metastases and those with squamous cell cancer of cervical nodes.

Some of these patients – including those with poorly differentiated carcinomas of midline distribution, peritoneal adenocarcinomatosis in female patients and poorly differentiated neuroendocrine carcinomas – may also be very sensitive to chemotherapy. A combination of platinum, with or without a taxane, may achieve a response rate of 40%–70% and some prolongation of survival.

However, this is mainly in patients with good prognosis CUP and not in non-favourable subsets. In a young patient with poor prognosis CUP but with good performance status, it may be useful to provide platinum-based chemotherapy. However, you need to keep in mind that these patients have a very dismal prognosis.

STEP BY STEP SUMMARY

