Unknown primary tumours

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Abstract

Unknown primary tumours (UPTs) are defined by the absence of a primary tumour in biopsy proved metastatic cancer. These tumours have a specific biology with clinical characteristics of rapid progression and random atypical metastases. Cytogenetic abnormalities have been demonstrated, particularly deletion of chromosome 1p. Diagnostic evaluation that includes pathology review, physical examination, chest radiography, computed tomography of the abdomen, and mammography is directed at the identification of treatable subsets. Based on clinicopathological criteria, therapy responsive subsets of patients with UPTs can be defined. These subsets have a better prognosis than the average median survival time of four months in patients with UPTs.

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In about 4% of all cancer patients, metastases of an unknown primary site are found. Consequently, unknown primary tumours (UPTs) have a higher incidence than ovarian cancer, non-Hodgkin's lymphoma, or rectal carcinoma. Many of these patients have tumours that respond poorly to available treatments and, in general, the clinical course of UPTs is progressive and fatal.[1–3]

The diagnosis of UPTs poses diagnostic and therapeutic problems. It is difficult to determine the appropriate treatment without knowledge of the primary tumour. Yet it remains controversial whether the prognosis in UPTs improves when the primary tumour is identified by intensive diagnostic search.

Recent clinical research has provided arguments for an evidence based clinical strategy in UPTs. Guidelines for the diagnosis and the treatment of UPTs have been developed on the basis of their specific biology, and particularly of the identification of treatable subsets.[4] The present diagnostic and therapeutic strategy in UPTs is reviewed in this paper. For this review a number of different search strategies were used to identify eligible papers in Medline (1966 to October 1999) and EMBASE (1980 to 1999). The keywords unknown primary, tumours, carcinoma, metastatic cancer were used in a free text search with combinations of these words, restricted to the English language. Additional reports were identified from reference lists of retrieved reports, review articles, and textbooks.

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Box 1: Diagnostic evaluation for UPTs

- Biopsy proved metastatic cancer
- No primary

Therefore evaluate by:

- History
- Physical examination
- Laboratory: basic evaluation
- Radiology: chest radiography, computed tomography of the abdomen, mammography
- Additional diagnostic tests: indicated by positive findings, to find treatable subgroups

Definition and specific biology

UPTs are defined as biopsy proved metastases in the absence of an identifiable primary site after complete history and physical examination, basic laboratory studies, chest radiography, computed tomography of the abdomen and mammography, with additional directed studies only indicated by positive findings during the initial evaluation.[4]

In 30% of all patients no primary tumour is identified, even after postmortem examination. The primary site becomes obvious in only 25% of patients during their lifetime. At necropsy, however, the primary tumour can be identified in 70% of all patients.[5 6] The most common sites of origin are the lung (30%) and the pancreas (20%). Furthermore, primary tumours are regularly found in the large bowel, the kidney, and the breast.[5 6] Due to the specific biology of UPTs, the primaries, when identified, are small and asymptomatic in the majority of patients. Clinical manifestations of the specific biology of UPTs are the short medical history, typically less than three months, and a rapid progression of the disease.[7 8] A clinical hallmark is the unusual pattern of metastasis. In the majority of patients, metastases are found at different sites. The classical correlation between the origin of the primary tumour and the site of metastasis is lacking in UPTs. For example in UPT patients with lymph node metastasis in the left supraclavicular region (Virchow's node) the primary tumours are found at necropsy as often above as below the diaphragm.[5–9] This clinical pattern is related to the specific phenotype of the malignant cells in UPTs. These cells are characterised by autotrophic growth, independent of the homing organ. Partial or complete loss of chromosome 1p may be a specific karyotypic abnormality in UPTs.[10] A hypothesis is that chromosome 1p carries a metastasis suppressor gene. Deletion or mutation of this gene would cause the metastatic phenotype. In the UPT this phenotype is

Box 2: Specific biology of UPTs

- Clinical characteristics: short history, small asymptomatic primary, rapid growth of metastases, atypical random metastatic pattern
- Autotrophic growth
- Cytogenetic abnormalities

Box 3: Clinical presentation of UPTs

- Short history
- Local signs/symptoms
- Constitutional symptoms: weight loss, anorexia, fatigue
- Physical examination: obvious abnormal findings, one metastatic site (40%), ≥3 metastatic sites (30%)

manifested early in the disease, in such a way that the primary tumour is dominated by a clone of cells with structural change of chromosome 1.[11] These cells have most likely acquired the capacity to metastasise directly and to grow autotrophically in different organ systems.[12] The essential concept, derived from basic research, is that UPTs have a specific biology and are not merely variants of common tumours in which the primary tumour just cannot be found.

Clinical presentation

The diagnosis of UPT is usually suspected after the history and the initial physical examination.[9] Characteristic clinical features include:

- A short history of local symptoms (pain, swelling, cough).
- A short history of constitutional symptoms (weight loss, malaise, fatigue, and fever).
- Obvious abnormalities at physical examination, palpable lumps at a single site and more commonly at different sites.

UPTs are diagnosed more often in men than in women (ratio 5:4). In unselected series the median age at diagnosis is about 65 years, with only 10% of the patients younger than 50 years. Major sites of metastases are the liver, lung, bone, and lymph nodes. In 30% of patients multiple metastases are already present at diagnosis.[5–9]

Diagnostic evaluation

In all patients a full history and a complete physical examination should be carried out. This may bring forward eventual clues regarding a primary site. Several retrospective series have shown that extensive laboratory and radiological studies in UPTs are not meaningful for diagnosis and treatment in the majority of patients.[5 7 13 14] The diagnostic procedure should be focused on distinguishing treatable from untreatable UPTs. In most clinics the first evaluation will be restricted to basic haematological and biochemical surveys. These will reveal such aspecific abnormalities as anaemia and raised alkaline phosphatase and lactate dehydrogenase.[4] The routine study of tumour markers is not indicated. In general the sensitivity and specificity of available tumour markers (CEA, CA 15-3, CA 19-9) are too low to define reliably a primary site in UPTs.[9 15]

Box 4: Pathological classification of UPTs

- Adenocarcinoma
- Squamous cell carcinoma
- Poorly differentiated carcinoma/ adenocarcinoma
- Undifferentiated neoplasm

However four specific tumour markers are useful both for diagnosis and for following the response to therapy in treatable subsets of UPTs. These are prostate specific antigen in men with predominant skeletal metastases, CA-125 in women presenting with malignant ascites, the β subunit of human chorionic gonadotrophin and α-fetoprotein in young men with poorly differentiated UPTs.[9 15 16] Initial radiological examination can be limited to chest radiography and mammography in women. There is controversy about computed tomography of the abdomen and pelvis in women. In 20%–30% of computed tomograms of the abdomen, primary tumours are found, mostly in the pancreas, but these findings have no effect on the clinical outcome. At present, only the detection of primary tumours in the breast and the ovaries leads to a survival advantage in patients with UPTs.[4]

Pelvic ultrasonography and pelvic computed tomography have similar sensitivities in detecting pelvic masses in women with UPTs.[17] Considering cost effectiveness, ultrasound of the pelvis may be preferred as the first radiological evaluation to find treatable ovarian cancer.[4]

By far the most important step in the diagnostic procedure is biopsy of the most accessible lesion for pathological examination.

Pathological evaluation

In UPTs, four pathological subgroups can be identified by light microscopic examination: adenocarcinoma 50%–60%, squamous cell carcinoma 5%–8%, poorly differentiated neoplasm 2%–5%, and poorly differentiated adenocarcinoma 30%–40%.[18 19] The clinical presentation, diagnostic procedure, treatment, and prognosis vary considerably between the four subgroups.

In the last two groups with undifferentiated tumours of uncertain origin, extension of the pathological evaluation to include immunohistochemical analysis is necessary.[18–20] Commonly used antibodies to define tumour lineage are: common leucocyte antigen (lymphoma), cytokeratin (carcinoma), S-100 protein (melanoma), and vimentin (mesenchymal tumours). Specific tumours can be identified by such antibodies as prostate specific antigen, oestrogen receptors (breast), neuron specific enolase (neuroendocrine carcinoma)

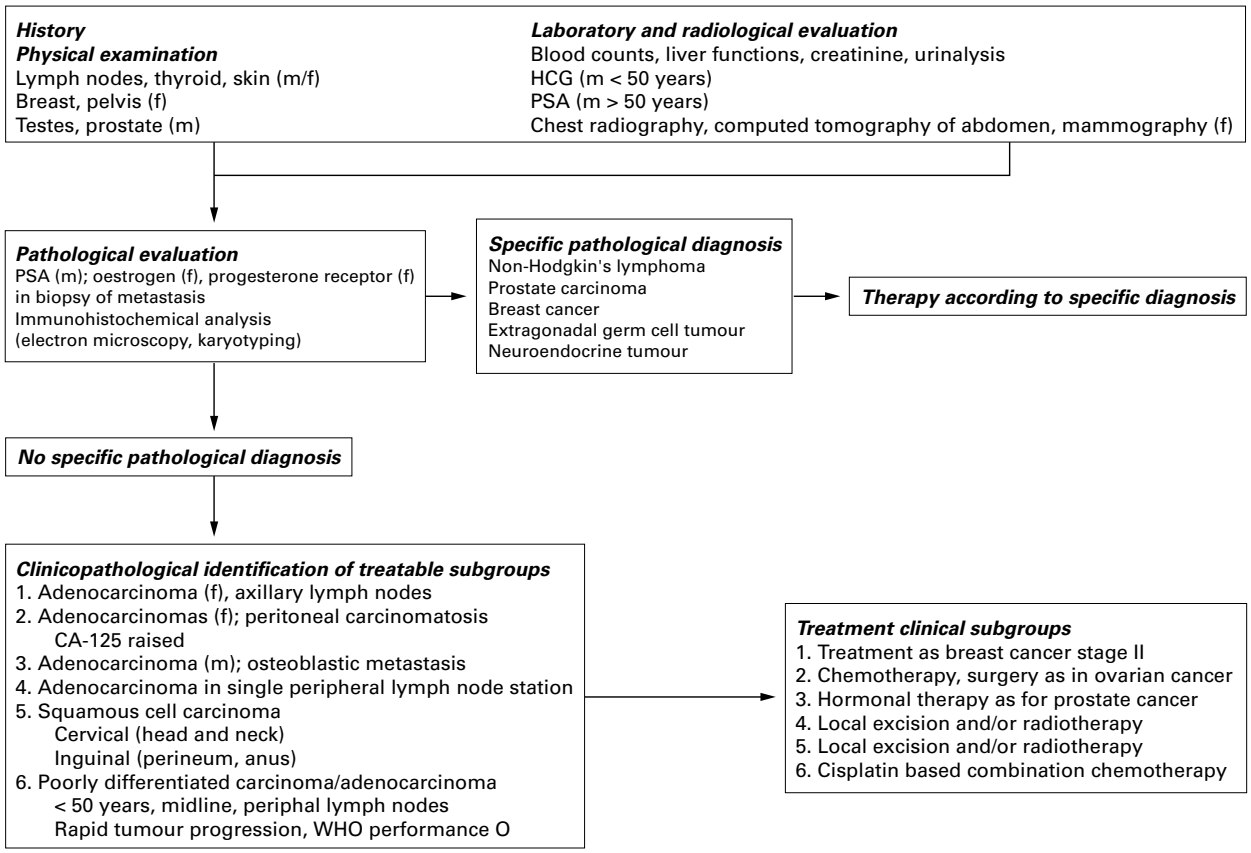

Figure 1 Guidelines for diagnosis and treatment in metastases of UPTs (HCG = human chorionic gonadotrophin; PSA = prostate specific antigen; WHO = World Health Organisation; m = male; f = female).

and β-human chorionic gonadotrophin (germ cell tumours).[18–20]

After immunohistochemical evaluation 30%–70% of the *undifferentiated neoplasms* appear to be non-Hodgkin's lymphomas, positive for leucocyte antigen.[20] In 10%–20% a diagnosis of melanoma or sarcoma is apparent. In young patients, additional electron microscopy or karyotyping may prove useful. Neurosecretory granules are specifically detected by electron microscopy in neuroendocrine tumours. Abnormalities of chromosome 12 are associated with germ cell tumours. Both tumours can present as poorly differentiated UPTs. The identification of these subsets is important because they are responsive to cisplatin based chemotherapy.[4 20 21]

Clinical identification of treatable subgroups

Once the pathological diagnosis is established, additional clinical investigation should only be performed to identify treatable subgroups (fig 1).

ADENOCARCINOMA

In general, the prognosis of patients with adenocarcinoma in metastasis of UPTs is very poor. The median survival of this group is only four months.[1–3] Some clinical subgroups, however, have a better prognosis because they respond to specific treatment:

- Men with raised serum prostate specific antigen or prostate specific antigen staining of the tumour should be treated for metastatic prostate cancer, in spite of an atypical pattern of metastases.[20 22]
- Women with oestrogen receptor positive UPTs should receive a trial of hormonal therapy as in metastatic breast cancer.
- Women with isolated axillary metastasis may have curable breast cancer. Directed diagnostic investigations reveal occult breast cancer in 40%–70% of these patients. Diagnosis and treatment should be performed as in stage II breast cancer.[23 24]
- In about 50% of women with peritoneal carcinomatosis, an ovarian carcinoma is found by further clinical evaluation. Many of these women present with ascites. Aspiration and cytology is the least invasive diagnostic procedure to obtain the diagnosis of adenocarcinoma. Ultrasound and computed tomography of the abdomen, measurement of CA-125, and gynaecological examination should be carried out for further diagnosis.[4 20] A variant in this group is the syndrome of peritoneal papillary serous carcinoma. This syndrome is characterised by diffuse peritoneal involvement with microcalcifications on computed tomography, pelvic adenopathy, normal ovaries, raised CA-125 and the occurrence of psammomabodies in the malignant cells. In this subgroup, cytoreductive surgery of the tumour mass and combination chemotherapy with cisplatin should be considered. Response rates of 35% have been reported, with some longlasting, complete remissions.[25]

● Solitary lymph nodes metastasis, cervical, axillary, or inguinal should be treated by local excision and/or radiotherapy.[26]

However, for a major group of patients with adenocarcinoma in UPTs, not belonging to one of the clinical subgroups, we have no effective treatment at present. The prognosis does not improve by an extensive search for the primary tumour and by treatment directed at this primary tumour. Results of empirical chemotherapy in patients with adenocarcinoma of unknown primary sites were disappointing (response <30%, median survival <6 months).[27 28] New combination chemotherapy (paclitaxel, carboplatin, etoposide) may increase response rate and duration. This is currently being tested in a phase II trial.[28]

SQUAMOUS CELL CARCINOMA

● Patients with squamous cell carcinoma in cervical lymph node metastasis constitute an important clinical subgroup. Often these patients have an occult primary tumour in the head or neck. Diagnostic investigation by panendoscopy and biopsies should be performed by an experienced ear, nose, and throat specialist. Even when the primary tumour is not found, surgery and/or radiotherapy are effective.[29]

● In patients with inguinal nodes containing squamous cell carcinoma, the primary tumour has to be sought in the perineal or anorectal area. This subgroup has a relatively favourable prognosis after local treatment with lymph node excision and radiotherapy.[4 20]

POORLY DIFFERENTIATED CARCINOMA OR POORLY DIFFERENTIATED ADENOCARCINOMA

Pathological evaluation has to be extended to exclude potentially curable tumours like lymphoma (leucocyte common antigen positive) or extragonadal germ cell tumours (chorionic gonadotrophin, α-fetoprotein positive).[20]

A clinical subgroup highly responsive to cisplatin based chemotherapy can be identified among patients with poorly differentiated tumours. This subgroup is characterised by the following clinical features: predominant tumour location in the mediastinum or retroperitoneum, younger age (<50), rapid tumour progression, and probably a normal performance score and a normal alkaline phosphatase serum level. Treatment with combinations of cisplatin and etoposide have resulted in a complete response rate of 26% and 10 year disease-free survival in 16% of the patients.[20 28]

Conclusion

Metastatic tumours of unknown origin have a unique clinical presentation due to a specific biology. The results of clinical research support the use of a limited diagnostic evaluation. Pathological and clinical data identify the major patient subsets responsive to specific therapy. Unfortunately, the majority of patients have unresponsive UPTs, with a very poor prognosis. Insight into the molecular biology of UPTs will be essential for the development of more effective treatments.

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