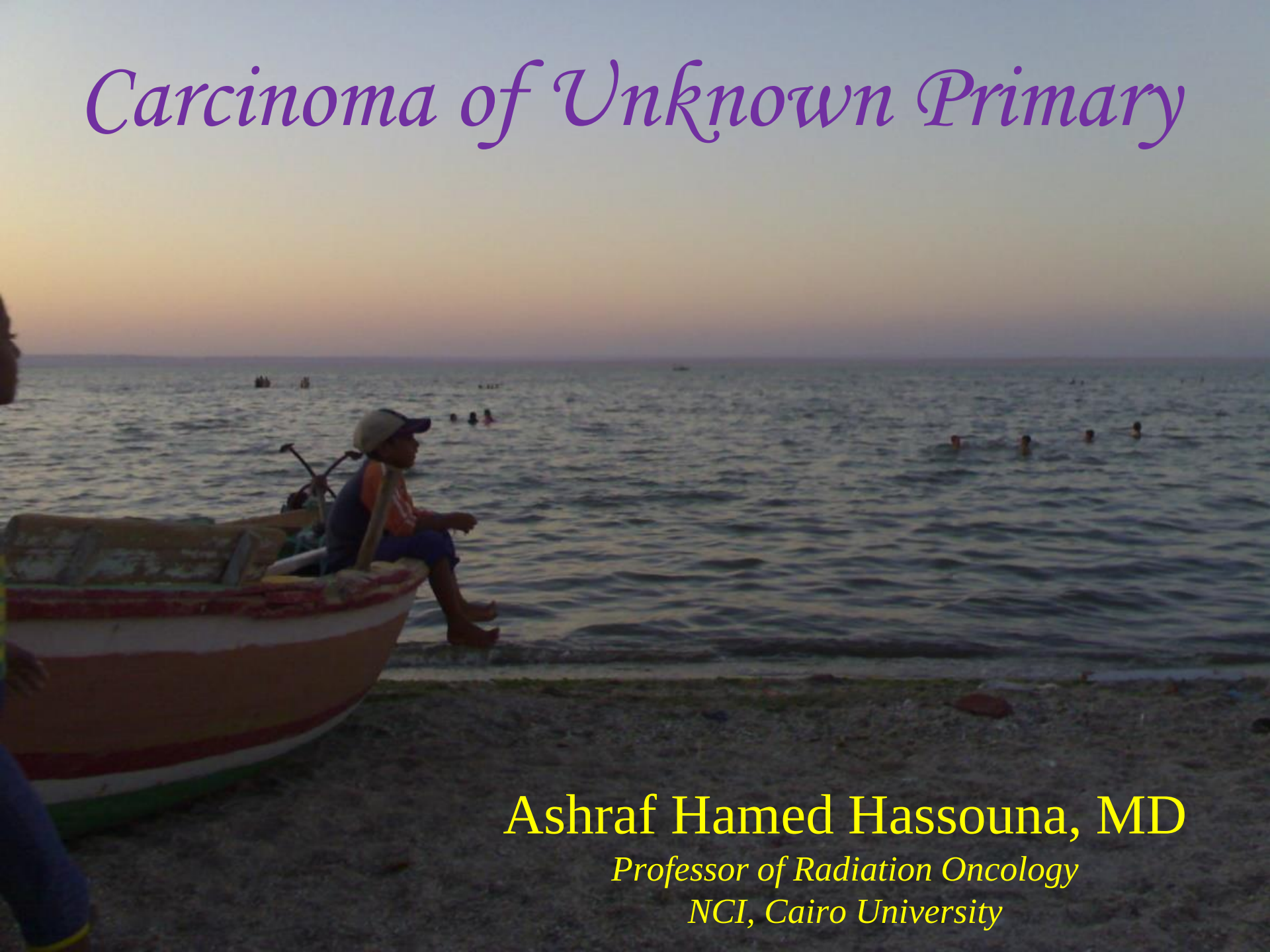

بسم الله الرحمن الرحيم

Carcinoma of Unknown Primary



Ashraf Hamed Hassouna, MD

Professor of Radiation Oncology

NCI, Cairo University

Definition

A biopsy-proven metastasis of a malignancy in the absence of an identifiable primary site after:

- Complete history
- Physical examination
- Basic laboratory studies
- Chest X-ray
- Additional directed studies, indicated by positive findings during the initial work-up

Histologically confirmed metastatic cancer without a primary site at diagnosis

MUO & CUP

- Metastasis of unknown origin (MUO) includes any metastatic neoplasm for which the anatomic site of origin is unidentified.
- In the most common scenario, the tumor type is epithelial, and the syndrome is therefore termed carcinoma of unknown primary (CUP).
- Other examples of MUO may represent melanoma, sarcoma, or other tumors that are so poorly differentiated as to be truly unclassifiable.

Incidence

- 2% of all cancer patients, decreasing.
- 8th most common malignant tumor
- 4th most frequent cause of cancer death
- Median age is 65 years
- Slight predilection for males

Pathology

- Adenocarcinoma
  - well or moderate differentiation (50%)
  - Un- or poorly differentiated (30%)
- Squamous cell carcinoma (15%)
- Undifferentiated neoplasm (5%)

- The primary lesion, which has escaped detection by radiographic and endoscopic studies, is rarely identified during the subsequent patient lifetime.
- In historical studies, only 15% of CUPs were associated with a definite primary neoplasm.
- Primary lesions are found postmortem in 51-85%.

The “parent” neoplasm by autopsy

- Lung (17–23%)
- Pancreas (20–37%)

- Large bowel (4–10%)
- Liver (3–11%)
- Stomach (3–8%)
- Kidney (4–6%)

- Breast (2%)
- Ovaries (3–4%)
- Prostate (3–4%)

Tissue Markers

	Immunoperoxidase stains
Tumor type	
Carcinoma	Pan-Cytokeratin, EMA
Lymphoma	CLA, (CD45RB), occasionally EMA
Sarcoma	Vimentin, desmin, S100, alpha-smooth muscle actin, myoD1, CD34, c-kit, CD99
Melanoma	S100, HMB45, Melan-A
Carcinoma type	
Adenocarcinoma	Light microscopy, PAS, CK7, CK20
Squamous cell carcinoma	CK5/6, p63
Neuroendocrine carcinoma	Chromogranin, synaptophysin, PGP9.5, CD56
Germ-cell carcinoma	PLAP, OCT4, AFP, HCG
Adenocarcinoma type	
Breast cancer	ER, GCDFP-15, mamaglobulin, CK7+/CK20-
Prostate cancer	PSA, PAP, CK7−/CK20−
Ovarian cancer	CA125, mesothelin, WT1, ER, CK7+/CK20−
Endometrial cancer	CK7+/CK20−, CA125, ER
Colon cancer	CDX2, CEA, CK7−/CK20+
Stomach cancer	CDX2, CK7−/CK20+
Pancreatic cancer	CK7+/CK20±, CA125, mesothelin
Liver cancer	Hepar-1, AFP, polyclonal CEA, CD10, CD13
Lung cancer	TTF1, CK7+/CK20−
Kidney cancer	RCC, CD10, CK7−/CK 20−
Thyroid cancer	TTF1, thyroglobulin

CUP ???

- Metastases in patients in whom the primary tumor has not been found and which did not result in clinical signs of disease.
- Separate group of cancers harboring genetic and phenotypic characteristics that underlie their unique clinical presentation.
- Unusual primary tumors mimicking metastatic disease (in the case of one identified tumor site).

- It is hypothesized that:
  - The primary acquires a metastatic phenotype soon after transformation and stays small either by inborn errors within the primary, leading to involution or an extremely slow growth rate, or by metastases inhibiting the growth of the primary.
  - Aggressive tumor cells can leave a relatively mild tumor early and circulate through the blood and form metastases in other organs.
- None of the biological hypotheses is confirmed. So, the question as to whether CUP are really different from tumors of known primaries remains unanswered.

Although CUP comprise a heterogeneous group of tumors, the clinical picture demonstrates common characteristics:

(1) short history of non-specific complaints (anorexia, weight loss, etc.). In most cases, the primary tumor remains unidentified during the patient's lifetime, but if found during their lifetime or by autopsy, it is a small asymptomatic tumor often localized in the lung or pancreas. Even after thorough evaluation at autopsy, only 80% of the primaries have been found.

(2) 30% of patients with CUP present with $\geq$ 3 organs involved. This obviously differs from the percentage of patients with $\geq$ 3 involved organs in metastasized known primaries, which is below 15%.

(3) unusual metastatic pattern. A relatively high number of metastases are found in the kidneys, adrenal gland, skin and heart when compared with expected sites of metastases. In addition, in patients where the primary tumor had been found during autopsy, differences in metastatic localization were observed when the metastatic pattern of the CUP was compared with the common sites of tumor spread of known primary tumors.

(4) identification of the primary tumor by intensive radiological and/or endoscopic examination, by PET scan or by IHC did not improve survival in the majority of patients, mainly due to a lack of alternative therapeutic strategies.

Prognosis

- With the exception of some treatable subgroups, CUP usually exhibit a relatively high resistance to available CT.
- Patients with CUP have a very poor prognosis of 3-4 months in an unselected population with <25% alive 1 year.
- However, new, more effective CT agents are available, and in more recent studies with selected patients from poor prognostic groups, MST of 9-13 months is reached, with >40% alive 1 year.

Adverse prognostic factors

- PS
- Number of metastatic sites
- Liver metastases
- Poorly differentiated histology
- Male
- Age >64 years

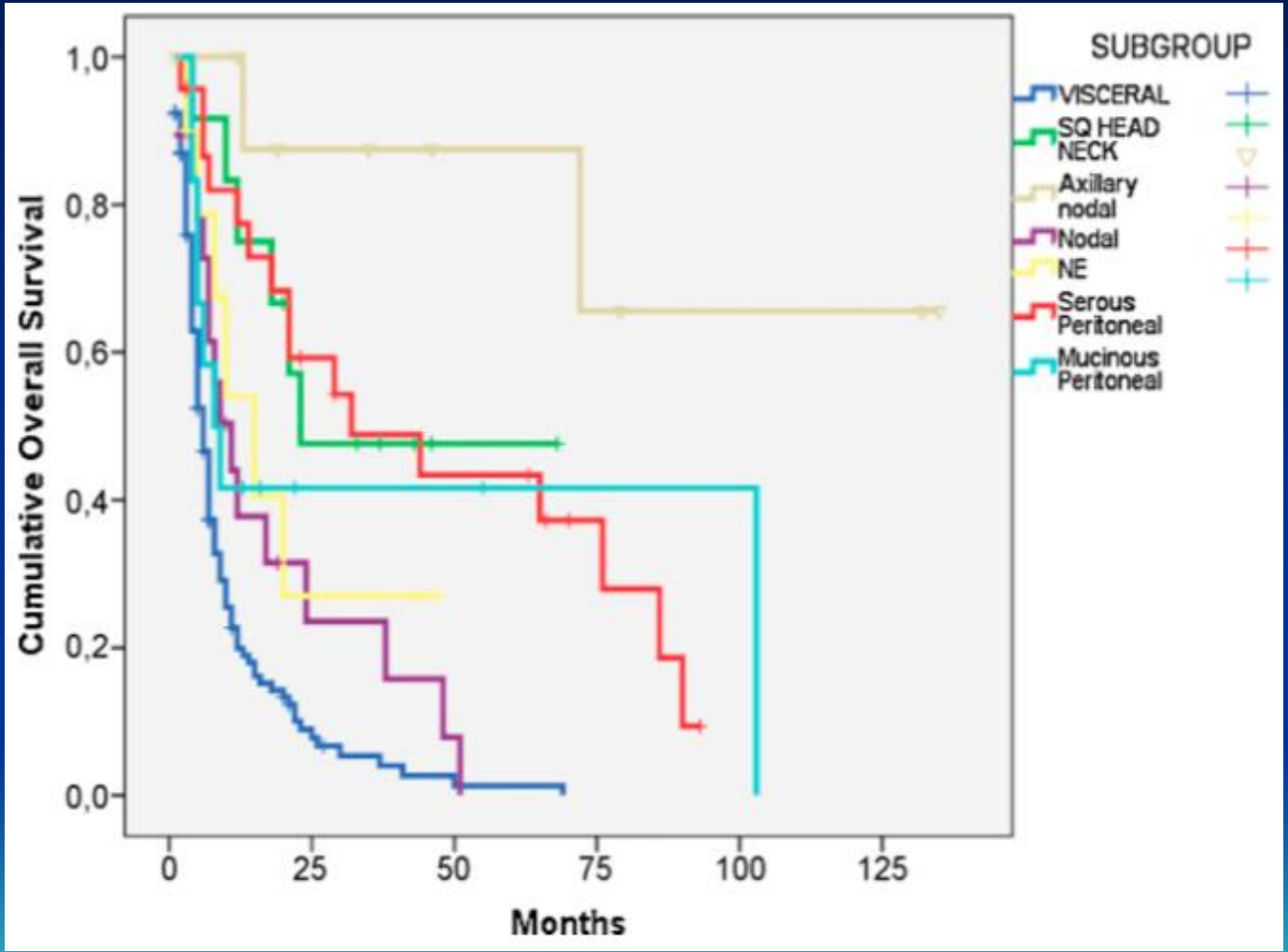
- Weight loss
- Lymphopenia
- Elevated LDH
- Elevated ALK
- Low albumin levels


Classifications

Clinico-pathological subsets of CUP

Organ	Histopathology
Lymph nodes	
Mediastinal – retroperitoneal	UDF or PDF
Axillary	AdenoCa (WDF/MDF/PDF)
Cervical	SCC
Inguinal	UDF, SCC, mixed SCC/adenoCa
Peritoneal cavity	
Primary peritoneal in females	AdenoCa (papillary/serous)
Ascites of other unknown origin	AdenoCa (MDF/PDF, mucin, ±signed ring cells)
Neuroendocrine tumors	PDF with neuroendocrine features, low-grade neuroendocrine Cas, small cell anaplastic Cas
Liver (mainly) and/or other organs	AdenoCa (MDF/PDF)
Lungs	
Pulmonary metastases	AdenoCa (WDF/MDF/PDF)
Pleural effusions	AdenoCa (MDF/PDF)
Bones (solitary or multiple)	AdenoCa (WDF/MDF/PDF)
Brain (solitary or multiple)	AdenoCa (WDF/UDF/PDF), SCC
Malignant melanoma	UDF neoplasm with melanoma features

OAS according to clinico-pathologic subgroup



CUP Subsets

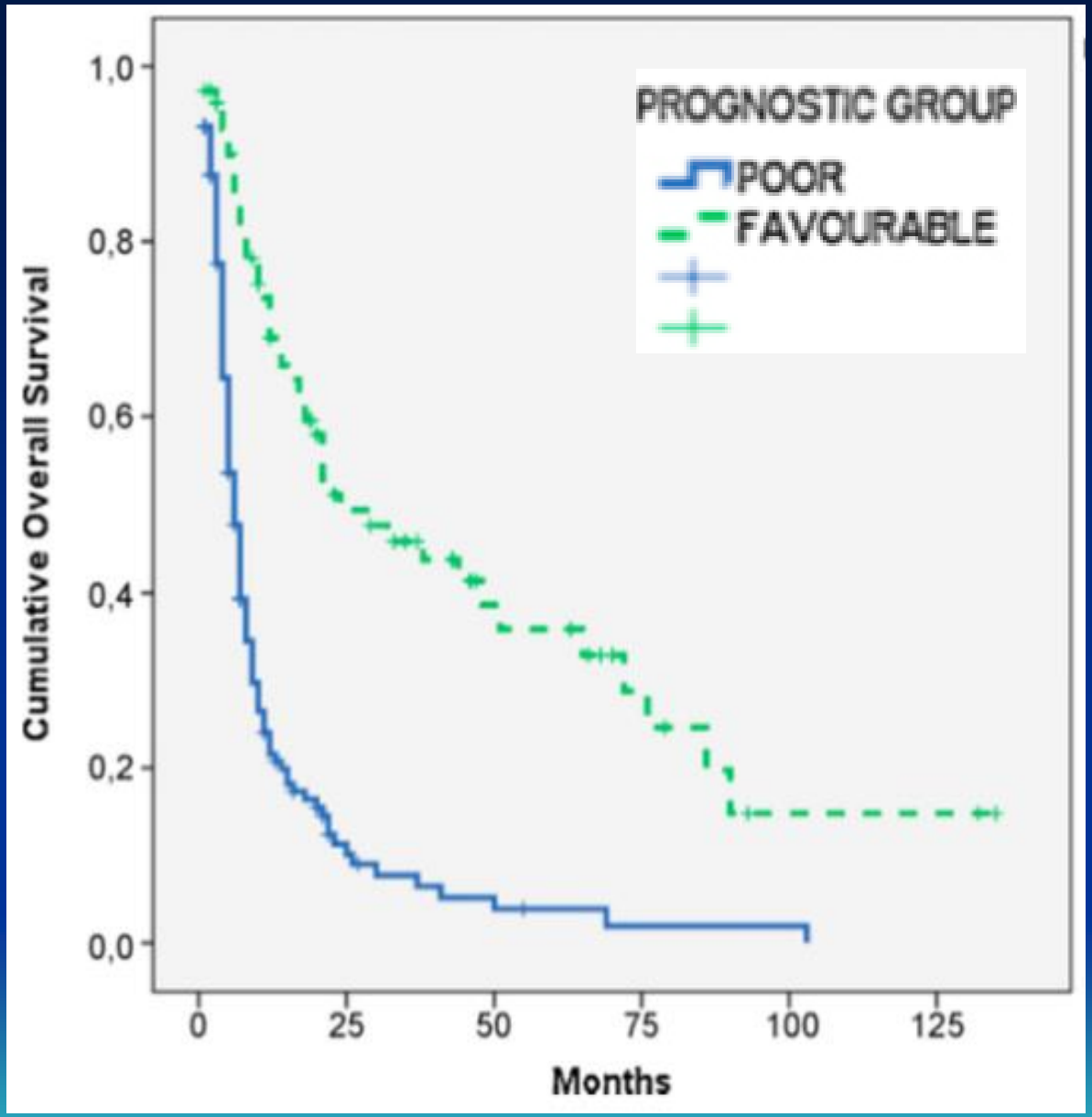
- CUP subsets have been categorized to:
  - Favourable (good prognosis) group
  - Unfavourable (poor prognosis) group

- Unfortunately, the unfavourable group represents the 70-80% of all CUP cases

Favorable

vs

Unfavorable



- 20-30% are included to the good prognosis group and could respond to locoregional or systemic treatment.

- Unfortunately, patients with poor prognosis although they might demonstrate moderate response to CT, the OAS is poor ranging between 6-9 months.

Favorable subsets of CUP

- Single lesion or oligometastasis amenable to local ablative treatment (single-site or oligometastatic CUP).
- Women with isolated axillary LN metastases (breast-like CUP).
- Women with peritoneal carcinomatosis of a serous papillary adenocarcinoma (ovary-like CUP).
- SCC involving non-supraclavicular cervical LNs (head and neck-like CUP).
- Men with blastic bone metastases and/or IHC or serum PSA expression (prostate-like CUP).
- Adenocarcinoma with colorectal IHC or molecular profile (colon-like CUP).
- Carcinoma with renal-cell histological and IHC profile (renal-like CUP).

Unfavorable subsets of CUP

- Adenocarcinoma metastatic to liver or other organs.
- Non-papillary malignant ascites (adenocarcinoma).
- Multiple brain metastases.
- Multiple lung/pleural metastases.
- Multiple bone metastases not expressing PSA.

Radiology

- CT accuracy of 55% (36-74%) mainly in pancreatic, colorectal and lung cancer.
- MRI is very sensitive in detecting primary breast cancers in 70% of cases.
- FDG-PET accuracy in CUP ranges between 25-43%. The most common primary sites detected by PET are lung cancer (33%), head and neck cancers (27%), followed by pancreatic, breast and colon cancers (4-5%).

Endoscopy

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

Serum tumor markers

- Elevated epithelial serum tumor markers can be overexpressed in CUP patients. In almost 70% of them 2-3 markers can be concomitantly increased in a non-specific way.
- CA 125, CA 15.3, CA 19.9, CEA can be raised without any diagnostic, prognostic or predictive value. Therefore, routine request of these tumor markers is not recommended.
- However, in specific cases it might offer diagnostic aid such as:
  - PSA in men with osteoblastic bone metastases
  - CA125 in females with primary serous papillary peritoneal adenocarcinoma
  - CA 15.3 in women with isolated axillary adenocarcinoma

Molecular profiling

- There is a rising consensus in recommending molecular profiling for tissue-of-origin prediction. Small non-coding RNAs and epigenetic modifications are particularly appealing.
- Such biomarkers could potentially endorse the access to more specific therapies and improve patients' life expectancy.
- Molecular diagnostics, combined with genetic profiling, might become the standard of care for future CUP management.


Management

- Favorable CUP patients harbor metastatic tumors from occult primaries with biology not drastically different from that of corresponding metastatic tumors from overt primaries.
- They should receive primary-specific therapy, matched to that of the equivalent known primary tumor, as they often enjoy long-term disease control.

- Unfavorable CUP patients are probably affected by a distinct clinical entity characterized by regression/dormancy of the primary, early high-volume systemic spread to uncommon sites and resistance to CT.
- Have a dismal outcome and should be treated in the context of trials evaluating new cytotoxic and targeted therapies.
- Even when biologically assigned to a tissue of origin, often behaves differently from metastatic tumors of known origin.

Management of Favorable CUP Subsets

CUP subset	Recommended treatment
Women with serous papillary adenocarcinoma of the peritoneal cavity	Optimal surgical debulking followed by platinum-based chemotherapy
Women with isolated axillary nodal metastases from adenocarcinoma	Axillary nodal dissection, mastectomy or breast irradiation and adjuvant chemohormonotherapy
Squamous cell carcinoma involving cervical lymph nodes	Neck dissection and/or irradiation of bilateral neck and head-neck axis for advanced stages induction chemotherapy with platinum-based combination or chemotherapy
Adenocarcinoma with a colon-cancer profile	Colorectal chemotherapy regimen
Metastatic melanoma of unknown primary site	Surgical treatment for localized disease followed by chemoimmunotherapy. Systemic treatment for disseminated disease. Local radiotherapy is optional as postoperative treatment
Men with osteoblastic metastases and elevated serum PSA	Hormonal therapy with LHRH agonists and/or antiandrogons.
Patients with limited disease	Local excision with or without radiotherapy

Women with peritoneal carcinomatosis of a serous papillary adenocarcinoma (ovary-like CUP)

Clinical picture:

As stage III/IV ovarian cancer characterized by abdominal pain and distention, palpable mass, ascities or incomplete intestinal obstruction. Elevated serum CA 125 in 70-90%.

Management:

Optimal surgical debulking (residual <1cm) then Platinum/Taxane combination CT (addition of bevacizumab is optional) and poly (ADP-ribose) polymerase (PARP) inhibitor maintenance therapy in responding patients.

- Overall RR is up to 60%, with 30% CR.
- MST is ~16 months with 10% 5-year survivors.
- Survival is inferior to that of ovarian cancer by 2-6 months.

Women with isolated axillary lymph node metastases (breast-like CUP)

Clinical picture: The detection rate by mammography (20%), MRI (60%), and by mastectomy (70%) of the cases.

Management:

- Axillary lymph node dissection
- Mastectomy or breast RT as alternative
- Adjuvant systemic treatment for N+ve breast cancer.

- Mastectomy or RT provided 75-80% LRC.
- OAS at 5 and 10 years is 75% and 60%, respectively.


الفاتح
الحاجرى

Squamous-cell carcinoma involving non-supraclavicular cervical lymph nodes (head and neck-like CUP)

Clinical picture: upper or middle cervical lymph nodes

Management: Local RT to the pharyngeal axis and bilateral neck ± neck dissection. CCRT is also used in many centers

- LRC is 80-90%.
- 5-year OAS up to 65%.

Adenocarcinoma with colorectal or molecular profile (colon-like CUP)

Clinical picture:

Liver or peritoneal metastasis but also other metastatic sites are present i.e. lungs, bones, ovary, etc. Colonoscopy remains normal in all patients.

Management:

Colorectal CT regimens.

Men with blastic bone metastases and/or IHC or serum PSA expression (prostate-like CUP)

Clinical picture:

Blastic bone metastasis with localized or diffuse bone pains and elevated PSA.

Histopathology:

Adenocarcinoma with +ve staining for PSA.

Management:

Androgen suppression therapy

Carcinoma with renal-cell histological and IHC profile (renal-like CUP)

Clinical picture:

Small subset of patients appear to display a histological and IHC profile truly compatible with RCC in the absence of any renal lesion.

Management:

According to the rapidly evolving kidney cancer protocols.

Single metastatic deposit or oligometastatic disease amenable to local ablative treatment (single-site and/or oligometastatic CUP).

Definition:

- Local ablative treatment of all lesions by surgery and/or RT is feasible.
- Oligometastatic state confirmed by imaging including PET-CT and brain MRI.
- Number of metastases ≤ 5.
- No involvement of a diffuse organ such as malignant pleural, pericardial, peritoneal or leptomeningeal carcinomatosis.

Histopathology: Adenocarcinoma of various differentiation, squamous cell carcinoma or poorly differentiated carcinoma.

Management:

Local surgery and/or RT.

There is insufficient evidence to provide recommendations regarding the treatment modality (surgery vs RT) or the administration of (neo)adjuvant CT or immunotherapy.

Management of unfavorable CUP

- Platinum-based CT is the standard of care.
- No high-level evidence that gene expression profiling-directed therapy leads to an improvement in patient outcomes. So, such strategies are not recommended outside of clinical trials.
- For patients with ovary-like and colon-like CUP and isolated peritoneal carcinomatosis, peritonectomy without HIPEC might be an option.
- Inclusion in clinical trials is encouraged.

what is the optimal treatment and final outcome for unfavorable CUP?

- Dismal prognosis despite platinum and/or taxane based CT.
- Although CT can offer clinical benefit to some of these patients, OAS remains poor.
- From phase II studies as well as from some randomized trials the overall RR was 25-50%; MST was 6-14 months.
- Meta-analysis of 10 randomized trials (683 cases) showed no significant survival benefit for any CT regimen over others.

- According to guidelines, patients of relatively young age and good PS could be offered the chance of platinum-based CT or accrual in clinical trials.
- Alternatively, BSC could be recommended.

New regimens under trials

- Site-directed therapy by molecular tissue of origin prediction.
- Molecular targeted therapy.
- ICIs.
  - MSI-H or mismatch repair-deficient CUP.
  - TMB-high CUP.
  - PD-L1-high CUP.


Thank You

Please Visit This Page

http://scholar.cu.edu.eg/?q=ashrafhassouna

Publications

Bio

Classes

Images

Ashraf Hamed Mohamed Hassouna

Professor of Radiation Oncology

(email)

CAIRO UNIVERSITY

Bio

Biography | *Curriculum Vitae*

M.D.
in Radiation Oncology

NCI, Cairo University,

You Can Get This Presentation …. and ….More