

Cancers of unknown primary : Knowing the unknown

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Definition

Cancers of unknown primary site (CUPs)

- Represent a heterogeneous group of metastatic tumours,
- When a standardised diagnostic work-up fails to identify the site of origin at the time of diagnosis

Definition

- Most investigators limit CUP to epithelial cancers and
- Do not include -
- *Lymphomas, metastatic melanomas, and metastatic sarcomas*
 - These cancers have specific histology- and stage-based treatments

Epidemiology

- Accounting for 3-5% of all cancers
- Approximate equal incidence for men and women
- **Median age** - ranges from 59-66 years
- **Median survival** – 11weeks to 11 months
- **5-year survival** - about 11%

Etiology

- Reasons cancers present as CUP remain unclear.

One hypothesis -

- The primary tumor either regresses after seeding the metastasis
or
- Remains so small that it is not detected

Clinical presentation

- Clinical presentation of cancer of unknown primary origin
 - Extremely variable
- Most patients present with ***multiple areas of involvement*** in multiple visceral sites
- ***Most common***
 - Lung, bone, lymph nodes, and liver.

Clinical presentation

- **Clinical manifestations may suggest the primary site :**

Clinical presentation

- **Ascites:**
 - Search for *gastrointestinal or ovarian primary*
- **Axillary mass in a female :**
 - Search for *breast cancer*
- **Cervical lymphadenopathy :**
 - Should lead to *otolaryngologic examination*

Clinical presentation

- **Brain metastasis :**
 - Search *for lung, breast or kidney* primary
- **Bone metastasis :**
 - Search for *prostate, breast, lung, renal, or thyroid* primary
- **Testicular mass**

CLINICAL EVALUATION

- **Initial CUP evaluation has two goals:**
 - 1. Search for the primary tumor***
 - Based on pathologic evaluation of the metastases
 - 2. Determine the extent of disease***

CLINICAL EVALUATION

- **A thorough medical history is essential**
- ***Paying particular attention to :***
 - Previous surgeries
 - Removed lesions
 - Family history to assess potential hereditary cancers

CLINICAL EVALUATION

Adequate physical examination

- Based on clinical presentation
- Should include
 - Head, neck, chest & abdomen
 - Pelvic and breast examinations in women
 - Digital rectal examination(DRE) & testicular examination in men

Diagnostic work-up

- An appropriate diagnostic work-up can help to identify a minority of CUP patients who can expect to benefit from directed therapy

Diagnostic work-up

A minimal basic workup comprises :

- Basic blood and biochemical analyses
 - Complete blood cell count (iron deficiency > occult gastrointestinal malignancy)
 - Liver and renal function tests
- Urinalysis (microscopic hematuria > occult genitourinary malignancy)

Diagnostic work-up

A minimal basic workup comprises :

- Stool for occult blood
- Chest radiograph
- CT scan of abdomen and pelvis
- Mammography in women, and
- Measurement of PSA in men.

Diagnostic work-up

- **Further investigations are dictated by**
 - any positive findings on initial evaluation

Diagnostic work-up

- Depending on the clinical situation, further tests may include
 - Chest CT
 - Breast magnetic resonance imaging
 - Upper or lower endoscopy

Diagnostic work-up

- In suspected head and neck malignancies,
 - Panendoscopy of upper aerodigestive pathways
 - Blind biopsies of the lymphoid tissue
 - Diagnostic tonsillectomy may be done

Diagnostic work-up

18F-FDG-PET :

- Used in evaluation of suspected head and neck malignancies
- Guide the biopsy
- Lacks specificity
- High cost and false-positive rate of 20%
- Combination of PET/CT may reduce the false-positive rate

Role of Serum Tumor Markers

- Most tumor markers :
 - Nonspecific and
 - Not helpful in determining primary site
- Should be limited to cases in which a particular primary site is favored.
- Men with adenocarcinoma and osteoblastic metastasis
 - Should undergo a PSA

Role of Serum Tumor Markers

| Tumor Marker | Indication |
|--------------|--|
| PSA | In men with bone metastatic adenocarcinoma |
| B-HCG & AFP | In men with undifferentiated tumor |
| AFP | Patients with hepatic tumors |
| CA 125 | Women with papillary adenocarcinoma of peritoneal cavity |

Role of Pathologic Studies

- The pathologist has an indispensable role in the evaluation of CUP
- Tumors provided for pathological review should come from tissue that has whenever possible been excised
- Needle biopsy specimens may provide insufficient tissue

Role of Pathologic Studies

- **Pathologic evaluation typically consists of :**
 - Hematoxylin and eosin stains
 - and
 - Immunohistochemical tests

MAJOR HISTOLOGIES IN CARCINOMA OF UNKNOWN PRIMARY

| Histology | Proportion, % |
|---|---------------|
| Well to moderately differentiated adenocarcinoma | 60 |
| Squamous cell cancer | 5 |
| Poorly differentiated adenocarcinoma, poorly differentiated carcinoma | 30 |
| Neuroendocrine | 2 |
| Undifferentiated malignancy | 3 |

Role of Pathologic Studies

- Majority of cancers of unknown primary origin are adenocarcinomas or undifferentiated tumors

Role of Pathologic Studies

- In the approximately 30% of cancers of unknown primary origin a full workup establishes a clear pathological diagnosis
- Most common epithelial malignancies are lung (15%), pancreas (13%), colon/rectum (6%), kidney (5%), and breast (4%).

ROLE OF IMMUNOHISTOCHEMICAL ANALYSIS

- Immunohistochemistry:
- Help define tumor lineage by using peroxidase-labeled antibody against specific tumor antigens.
- Include stains for :
 - keratin, leukocyte common antigen and S-100 (expressed in melanomas)

ROLE OF IMMUNOHISTOCHEMICAL ANALYSIS

- Thyroid transcription factor–1 (TTF-1)
 - for lung and thyroid cancer
- Prostate-specific antigen (PSA)
- Human chorionic gonadotropin (hCG)
 - for germ cell tumors

ROLE OF IMMUNOHISTOCHEMICAL ANALYSIS

- Alpha-fetoprotein (AFP)
 - for germ-cell tumors and hepatomas
- Estrogen receptors, progesterone receptors, and human epidermal growth factor receptor 2 (HER2)
 - for breast cancer.

ROLE OF IMMUNOHISTOCHEMICAL ANALYSIS

- **Cytokeratin (CK) intermediate filaments**
 - >20 subtypes
 - Different molecular weights and
 - Differential expression in various cell types and cancers
- **Commonly used CK stains in adenocarcinoma CUP**
 - CK7 and CK20

ROLE OF IMMUNOHISTOCHEMICAL ANALYSIS

CK7 :

- Found in tumors of :
 - Lung
 - Ovary
 - Endometrium
 - Breast and
 - Upper gastrointestinal tract including pancreaticobiliary cancers

ROLE OF IMMUNOHISTOCHEMICAL ANALYSIS

CK20

- Normally expressed in :
 - Gastrointestinal epithelium
 - Urothelium and
 - Merkel cells

ROLE OF IMMUNOHISTOCHEMICAL ANALYSIS

Nuclear CDX-2 transcription factor :

- Product of a homeobox gene necessary for intestinal organogenesis
- Often used in the diagnosis of ***gastrointestinal adenocarcinomas***

ROLE OF IMMUNOHISTOCHEMICAL ANALYSIS

Thyroid transcription factor 1 (TTF- 1) nuclear staining :

- Positive in *lung and thyroid cancers*
- Helps differentiate a lung primary tumor from metastatic adenocarcinoma

ROLE OF IMMUNOHISTOCHEMICAL ANALYSIS

Gross cystic disease fibrous protein-15(GCDFP-15):

- A 15 -kDa monomer protein
- ***Marker of apocrine differentiation***
- Detected in 62-72% of ***breast carcinomas***

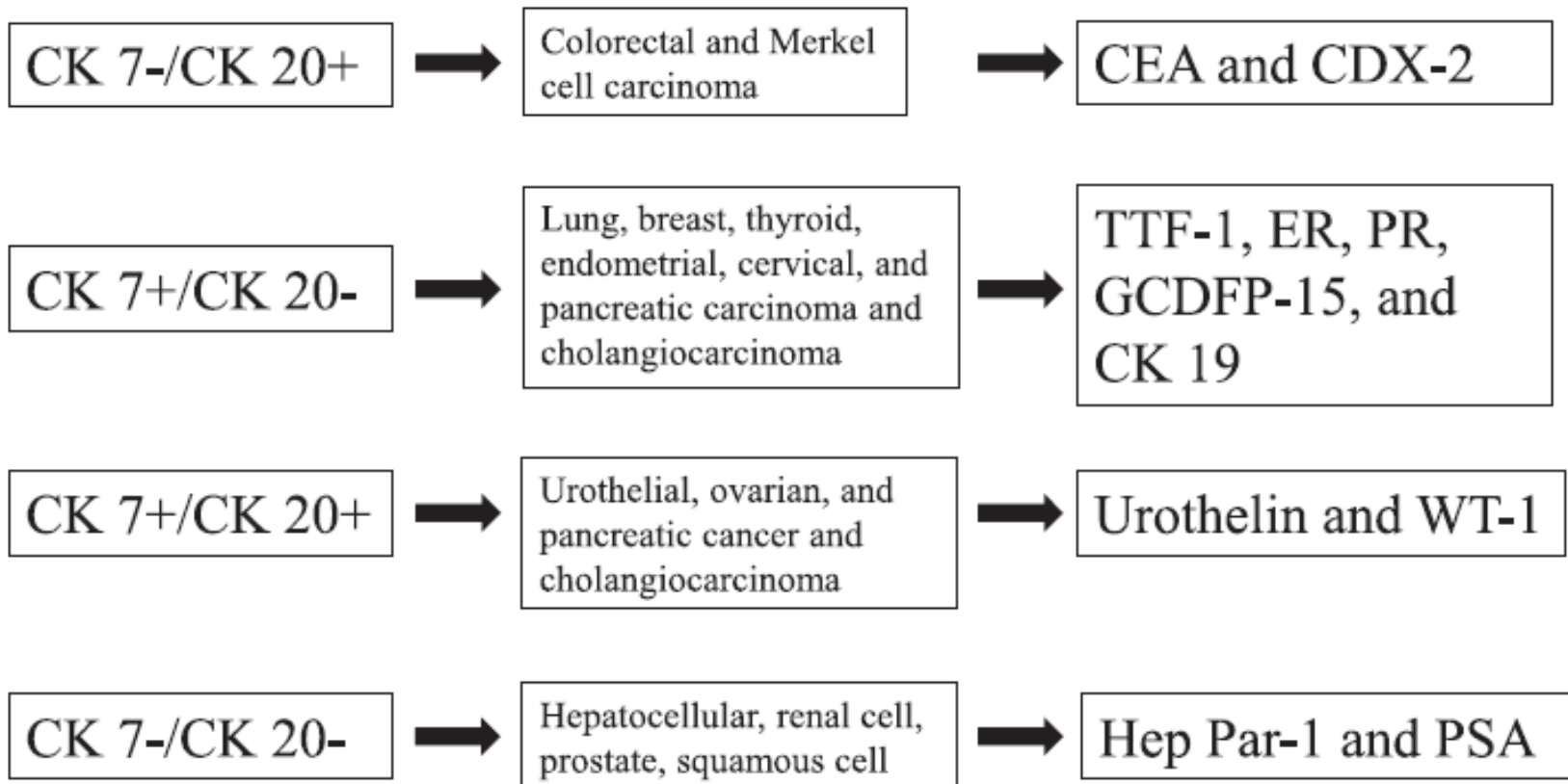
ROLE OF IMMUNOHISTOCHEMICAL ANALYSIS

- **Markers used to diagnose lesions of *urothelial origin* :**
 - URO III
 - High-molecular-weight cytokeratin
 - Thrombomodulin, and
 - CK20

Basic immunohistochemical work-up

Primary markers

Additional markers



ROLE OF IMMUNOHISTOCHEMICAL ANALYSIS

- IHC, when used in groups, gives rise to patterns that are strongly indicative of certain profiles.
- For example:
 - TTF – 1+ /CK7+ phenotypes > ***lung cancer***
 - CK20+/CDX-2+/CK7- phenotypes > ***lower gastrointestinal cancer***

ROLE OF TISSUE OF ORIGIN MOLECULAR PROFILING

- Gene expression profiles are most commonly generated using :
 - Quantitative reverse transcriptase polymerase chain reaction (RT-PCR) or
 - DNA microarray
- Using these measures, the assays suggest a plausible primary in -70% of patients

ROLE OF TISSUE OF ORIGIN MOLECULAR PROFILING

- At this time, the National Comprehensive Cancer Network (NCCN) does not recommend gene signature profiling for tissue of origin for standard management of CUP.
- NCCN advises that although these tests may offer diagnostic benefit, they do not necessarily provide clinical benefit.

Treatment

Patients of favourable-risk subsets

- Should be treated similarly to patients with equivalent known primary tumours with metastatic dissemination
- These patients achieve long-term disease control in 30%–60% of cases.

Treatment

Poor-risk CUP

- Have a dismal prognosis
- Low-toxicity chemotherapy regimens should be administered to reasonably fit poor-risk CUP patients

Conclusion

- Identification of primary tumour may provide valuable information regarding treatment and prognosis
- But aggressive diagnostic work up is of little value and not cost effective.
- Recommended approach is to do limited directed diagnostic tests to identify favourable subset

Thank You