Cancer of Unknown Primary Site

The Unfavourable Subset with Liver Metastases

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Greece

Barcelona, June 2009

Cancer of Unknown Primary (CUP)

1) Definition
2) Epidemiology
3) Biology
4) Pathology
5) Natural History
6) Diagnostic Approach
7) Treatment

Is There a Definition for Cancer of Unknown Primary Origin?

In 1970's

All patients presented with histologically confirmed metastatic carcinoma in whom a complete medical history, careful physical examination, chest x-ray, full blood count, stool occult blood testing and urinalysis did not identify the primary site.
CLINICAL AND LABORATORY DATA REQUIRED TO DEFINE A PATIENT AS HAVING A CUP

- Histologically confirmed metastatic cancer
- Detailed medical history
- Complete physical examination (plus pelvic and rectal exam)
- Chest radiography
- Full blood count
- Biochemistry
- Urinalysis
- Stool occult blood testing
- Histopathology review and use of immunohistochemistry
- Computed tomography of chest, abdomen and pelvis
- Mammography or MRI (in certain cases).
- PET–scan (in certain cases).
**What is the Incidence of Cancer of Unknown Primary Site?**

**Epidemiology of Cancer of Unknown Primary**

<table>
<thead>
<tr>
<th>Geographical area</th>
<th>Source</th>
<th>Frequency (%)</th>
<th>Period</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA</td>
<td>SEER</td>
<td>2.3</td>
<td>1973-1987</td>
</tr>
<tr>
<td>Australia</td>
<td>New South Wales</td>
<td>4.0</td>
<td>1970-1990</td>
</tr>
<tr>
<td>Netherlands</td>
<td>Eindhoven Cancer Registry</td>
<td>4.0</td>
<td>1984-1992</td>
</tr>
<tr>
<td>Finland</td>
<td>IARC</td>
<td>2.5</td>
<td>-</td>
</tr>
<tr>
<td>Germany</td>
<td>-</td>
<td>7.0</td>
<td>1968-1984</td>
</tr>
<tr>
<td>Russia</td>
<td>-</td>
<td>3.0</td>
<td>-</td>
</tr>
<tr>
<td>Switzerland</td>
<td>Local registries</td>
<td>2.3</td>
<td>1984-1993</td>
</tr>
<tr>
<td>Japan</td>
<td>IARC</td>
<td>3.0</td>
<td>-</td>
</tr>
</tbody>
</table>

**Don't Forget That**

- CUP represents the 7th – 8th most frequent type of cancer and the 4th commonest cause of cancer death.
- It is considered to be more common than non-Hodgkin’s lymphoma.

**The Biology of Cancer of Unknown Primary**

**Translation Research on Oncogenes / Oncoproteins in CUP**

- Oncogenes
- Oncoproteins
- Tumor Suppressor Genes
- Angiogenesis
- Proteolysis

<table>
<thead>
<tr>
<th>Author, Method</th>
<th>N</th>
<th>Results</th>
<th>Correlations with clinicopathological parameters and outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pavlidis et al, IHC</td>
<td>26</td>
<td>C-myc expression 96%, overexpression 23%</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ras expression 92%, overexpression 23%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>HER2 expression 65%, overexpression 27%</td>
<td></td>
</tr>
<tr>
<td>Briasoulis et al, IHC</td>
<td>40</td>
<td>BCL2 expression in 15%, overexpression in 15%</td>
<td>None</td>
</tr>
</tbody>
</table>
## Tumour Suppressor Genes in CUP

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Method</th>
<th>Results</th>
<th>Correlations with clinicopathological parameters and outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Briasoulis et al</td>
<td>40</td>
<td>IHC</td>
<td>P53 expression 74%, overexpression 15%</td>
<td>Correlation with BCL2 and P53 predicts the response to platinum</td>
</tr>
<tr>
<td>Dova et al</td>
<td>50</td>
<td>PCR-SSCP</td>
<td>One case with exon 242C &gt; G mutation (P811R)</td>
<td>Not reported</td>
</tr>
</tbody>
</table>

## Oncogenes / Oncoproteins in CUP

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Method</th>
<th>Results</th>
<th>Correlations with clinicopathological parameters and outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dova et al</td>
<td>50</td>
<td>IHC</td>
<td>EGFR expression 74%, overexpression 15%</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PCR-SSCP</td>
<td>Wild-type exon 18, 19, 21 EGFR gene in 96%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>qPCR</td>
<td>1 case with exon 21 SNP, 93%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>IHC</td>
<td>1 case with exon 19 intronic splicing variant TNS19+24G&gt;A</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>IHC</td>
<td>1 case with exon 21 SNP: R836R</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>IHC</td>
<td>1 case with exon 19 intronic splicing variant TNS19+24G&gt;A</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>PCR-SSCP</td>
<td>c-KIT expression 81%, overexpression 13%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>IHC</td>
<td>PDGFRa expression 50%, overexpression 2%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>PCR-SSCP</td>
<td>c-KIT expression 81%, overexpression 13%</td>
<td></td>
</tr>
</tbody>
</table>

## Angiogenesis and Proteolysis in CUP

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Method</th>
<th>Results</th>
<th>Correlations with clinicopathological parameters and outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Karavasilis et al</td>
<td>80</td>
<td>IHC</td>
<td>CD34 microvessel density 59 microvessels/mm²</td>
<td>Positive correlation of VEGF and inverse correlation of TSP1 with microvessel density. Increased microvessel density in unfavourable group CUP</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IHC</td>
<td>VEGF expression 100%, overexpression 83%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>IHC</td>
<td>Stromal TSP1 expression 83%, overexpression 20%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>qPCR</td>
<td>MMP2 expression 69%, overexpression 49%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>IHC</td>
<td>MMP9 expression 49%, overexpression 36%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>IHC</td>
<td>TIMP1 expression 79%, overexpression 44%</td>
<td></td>
</tr>
</tbody>
</table>

## THE NATURAL HISTORY OF CANCER OF UNKNOWN PRIMARY SITE

- Early dissemination
- Clinical absence of primary at presentation
- Aggressiveness
- Unpredictable metastatic pattern
**UNPREDICTABLE METASTATIC PATTERN**

- Refers to the differences in the incidence of metastatic sites at diagnosis between known and unknown primary carcinomas

**Examples**

1. **Lung cancer** presenting as CUP involves the bones in 4%, while presenting as a known primary the osseous involvement is 30-50%.

2. **Pancreatic cancer** presenting as CUP has 4-fold higher incidence to affect bones, and 30% incidence to appear with lung metastasis.

3. **Prostate cancer** presenting as CUP has a 3-fold less incidence to affect bones compared to the known primary prostate cancer.

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**HISTOLOGICAL CLASSIFICATION**

<table>
<thead>
<tr>
<th>HISTOLOGY</th>
<th>INCIDENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenocarcinoma</td>
<td></td>
</tr>
<tr>
<td>Well to moderately differentiated</td>
<td>50 %</td>
</tr>
<tr>
<td>Poorly or undifferentiated</td>
<td>35 %</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>10 %</td>
</tr>
<tr>
<td>Undifferentiated neoplasms</td>
<td>5 %</td>
</tr>
<tr>
<td>Not specified carcinoma</td>
<td></td>
</tr>
<tr>
<td>Neuroendocrine tumors</td>
<td></td>
</tr>
<tr>
<td>Lymphomas</td>
<td></td>
</tr>
<tr>
<td>Germ cell tumors</td>
<td></td>
</tr>
<tr>
<td>Melanomas</td>
<td></td>
</tr>
<tr>
<td>Rhabdomyosarcoma</td>
<td></td>
</tr>
<tr>
<td>Embryonal malignancies</td>
<td></td>
</tr>
</tbody>
</table>

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**CLINICOPATHOLOGICAL ENTITIES OF CUP**

<table>
<thead>
<tr>
<th>ORGAN</th>
<th>HISTOLOGY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver (mainly)</td>
<td>AdenoCa M or P diff and/or organs</td>
</tr>
<tr>
<td>Lymph nodes</td>
<td>U or P diff Ca</td>
</tr>
<tr>
<td>Mediastinal – Retroperitoneal (midline distribution)</td>
<td>AdenoCa W to P diff</td>
</tr>
<tr>
<td>Axillary</td>
<td>SCC Ca</td>
</tr>
<tr>
<td>Cervical</td>
<td>U Ca, SCC, mixed SCC / adeoCa</td>
</tr>
<tr>
<td>Inguinal</td>
<td></td>
</tr>
</tbody>
</table>

**Peritoneal cavity**

- Peritoneal adenocarcinomatosis in females
- Malignant ascites of other unknown origin

**Lungs**

- Pulmonary metastases
- Pleural effusion

**Bones**

- Various diff

**Brain**

- Various diff or squamous cell Ca

**Neuroendocrine tumors**

- P diff Ca with neuroendocrine features (mainly), low-grade neuroendocrine Ca, small cell anaplastic Ca

**Melanoma**

- U neoplasm with melanoma features

W = well, M = moderately, P = poorly, U = undifferentiated
WHAT IS THE OPTIMAL INVESTIGATIONAL DIAGNOSTIC APPROACH FOR THE IDENTIFICATION OF THE PRIMARY TUMOR?

By HISTOPATHOLOGY

IMMUNOHISTOCHEMISTRY IN CUP
DIAGNOSTIC ALGORITHM FOR ADENOCARCINOMA

THE 10 MARKERS

- PSA (Prostate - specific antigen)
- TTF1 (Thyroid transcription factor 1)
- GcDFP-15 (gross cystic disease fluid protein 15)
- CDX2
- CK20
- CK7
- ER (Estrogen receptor)
- Mesothelin
- CA 125
- Lysozyme

Site of Origin

- Prostate
- Lung
- Colon
- Ovarian
- Breast
- Cholangio
- Endometrial
- Ampullary, Colon, Esophageal, Ovarian
- Lung, Pancreas, Breast, Cholangio, Ovarian
- Breast, Ovarian, Endometrial
- Ovarian, Cholangio, Mesothelioma, Endometrial
- Ovarian, Endometrial, Cholangio, Pancreas
- Cholangio, Stomach, Colon, Pancreas, Lung

CYTOKERATINS (CKS)

Monoclonal antibodies against cytokeratin polypeptides CK7 and CK20
PANELS OF IMMUNOHISTOCHEMICAL MARKERS HELP DETERMINE PRIMARY SITES OF METASTATIC ADENOCARCINOMA

Markers

<table>
<thead>
<tr>
<th>TTF-1</th>
<th>MUC 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDX 2</td>
<td>MUC 5AC</td>
</tr>
<tr>
<td>CK 7</td>
<td>SMAD 4</td>
</tr>
<tr>
<td>CK 20</td>
<td>ER</td>
</tr>
<tr>
<td>CEA</td>
<td>GCDFP - 15</td>
</tr>
</tbody>
</table>

TUMOUR TYPES

MOLECULAR ANALYSIS [Microarray Platforms]

around 80% accuracy

VALIDATION OF A MICROARRAY-BASED DIAGNOSTIC TEST FOR CUP (GENE EXPRESSION PROFILING)

<table>
<thead>
<tr>
<th>Reference</th>
<th>Microarray platform (tissue)</th>
<th>Validation in metastases from CUP (N)</th>
<th>Primary Sites</th>
</tr>
</thead>
<tbody>
<tr>
<td>AACR 2007</td>
<td>cDNA/Frozen + FFPE</td>
<td>&gt; 50% (± 500)</td>
<td>B (14%), P (21%), C (33%), L (14%), Lb (12%), G (14%), S (12%), R (15%), O (15%), Ov (12%), Pr (15%), O (15%)</td>
</tr>
<tr>
<td>Cancer Res 2005</td>
<td>cDNA/Frozen</td>
<td>84.5% (11/33)</td>
<td>L (31%), B (23%), R (15%), C (7.5%), O (18%)</td>
</tr>
<tr>
<td>J Mol Diagn 2006</td>
<td>cDNA/FFPE</td>
<td>77% (37/48)</td>
<td>L (30%), B (27%), R (18%), C (14%), O (18%), P (15%), Ov (15%), Pr (15%)</td>
</tr>
<tr>
<td>ASCO 2007</td>
<td>VeriS 10-gene qRT-PCR</td>
<td>81% (42/52)</td>
<td>L (20%), B (18%), R (12%), C (8%), O (12%), Pr (8%), Ov (8%), P (8%)</td>
</tr>
<tr>
<td>ASCO 2007</td>
<td>cDNA/FFPE</td>
<td>87% (34/39)</td>
<td>L (20%), B (18%), R (12%), C (8%), O (12%), Pr (8%), Ov (8%), P (8%)</td>
</tr>
</tbody>
</table>

B = breast, P = pancreas, C = colon, L = lung, Lb = liver/bile, G = genital, S = stomach, R = renal, O = others, Ov = ovary, Pr = prostate

MicroRNAs accurately identify cancer tissue origin

Abstract

“.... they may be used in identifying the tissue in which cancers of unknown primary origin arose. .... We measured miRNA expression levels in 400 paraffin-embedded and fresh-frozen samples .... Two-thirds of samples were classified with high confidence, with accuracy >90% .... Our findings demonstrate the effectiveness of miRNAs as biomarkers for tracing the tissue of origin of cancers of unknown primary origin.”
IMAGING STUDIES

Chest X-ray
✓ A prerequisite test

Barium Studies
✓ Non contributory to the detection of 1st
  (very low sensitivity)
✓ Should only rarely if ever be used

CT-scans
✓ Offers an additional diagnostic accuracy of 40%
✓ Provides guidance to biopsy procedure

Mammography
✓ Basic test in women with metastatic adenoCa in
  axillary nodes
✓ However, sensitivity was found to be low

FREQUENCY OF MRI-DETECTED BREAST CA IN PATIENTS WITH CUP AXILLARY ADENOPATHY

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>N</th>
<th>N (%) with MRI-Detected Ca</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stumper, 1999</td>
<td>8</td>
<td>2 (25.0%)</td>
</tr>
<tr>
<td>Henry-Tillman, 1999</td>
<td>8</td>
<td>8 (100.0%)</td>
</tr>
<tr>
<td>Orel, 1999</td>
<td>22</td>
<td>19 (86.4%)</td>
</tr>
<tr>
<td>Obdeijn, 2000</td>
<td>20</td>
<td>8 (40.0%)</td>
</tr>
<tr>
<td>Olson, 2000</td>
<td>40</td>
<td>28 (70%)</td>
</tr>
<tr>
<td>Buchanan, 2005</td>
<td>64</td>
<td>31 (48.4%)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>162</strong></td>
<td><strong>96 (59.3%)</strong></td>
</tr>
</tbody>
</table>

FDG-PET SCAN
(18-F-FUORODEOXYGLUCOSE)
✓ Diagnostic accuracy: 26% - 45%
✓ More sensitive for occult head-neck and lung tumors

✓ Meta-analysis (1994-2001) on 298 patients
✓ FDG PET showed detection of the primary in 43% of pts
✓ Occult: lung 42%, head-neck 36%, GI 6%, Others 17%
**ENDOSCOPY**

- Should always be symptoms - or signs oriented investigational procedures

- ENT panendoscopy: in cervical node involvement
- Bronchoscopy: in radiographic indications or symptoms
- Colonoscopy: in relevant symptoms and signs
- Proctoscopy: in inguinal node involvement
- Colposcopy: in inguinal node involvement

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**SERUM TUMOR MARKERS**

- Routine evaluation of current commonly used markers have not been proven of any prognostic or diagnostic assistance
- A non-specific multiple overexpression of the adenocarcinoma markers (CEA, CA 125, CA 15-3, CA 19-9) has been observed in the majority of CUP patients.
- Worthwhile to request:
  - PSA in men with bone metastatic adenocarcinoma
  - B-HCG & AFP in men with an undifferentiated tumor
  - AFP in patients with hepatic tumors
  - CA 125 in women with papillary adenocarcinoma of peritoneal origin
  - CA 15-3 in women with adenocarcinoma involving only axillary lymph nodes.

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**Published Clinical Experience on Serum Tumour Marker use in CUP**

<table>
<thead>
<tr>
<th>Author</th>
<th>Number of CUP patients N</th>
<th>Markers studied</th>
<th>Diagnostic utility</th>
<th>Predictive/prognostic utility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Koch</td>
<td>32</td>
<td>CEA</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Varadhachary</td>
<td>147</td>
<td>CEA</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Fritzsche</td>
<td>41</td>
<td>CEA</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Gupta</td>
<td>15</td>
<td>CEA, CA 19-9</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Pavlidis</td>
<td>85</td>
<td>CEA, CA 19-9, CA 125, CA 15-3, B-HCG, AFP</td>
<td>No</td>
<td>No</td>
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<tr>
<td>Milovic</td>
<td>46</td>
<td>CEA, CA 19-9, CA 15-3, CA 125</td>
<td>No</td>
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<tr>
<td>Yonemori</td>
<td>93</td>
<td>CEA, CA 19-9, CA 15-3, CA 125, PSA, AFP, B-HCG</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

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**HOW OFTEN CAN THE PRIMARY TUMOR BE IDENTIFIED?**

The antemortem frequency of detection of primary site by imaging, endoscopy or immunohistochemistry studies remains around 30%.
IDENTIFICATION OF PRIMARY SITE AT AUTOPSY FROM ALL PUBLISHED SERIES

Years of Publications: 1944 - 2000
No of Autopsies: 884
Primary Site Found: 73 % (644 / 884)

Primary Sites Identified:
- Lung: 27%
- Pancreas: 24%
- Liver/bile duct: 8%
- Kidney/adenals: 8%
- bowel: 7%
- Genital system: 7%
- Stomach: 6%
- Bladder/ureter: 0.01%
- Breast: 0.007%
- Other: 10%

IDENTIFICATION OF PRIMARY SITE BY GENETIC PROFILING (MICROARRAYS) FROM ALL PUBLISHED CUP SERIES

Years of Publications: 2005-2007
No of Samples: > 500 (cDNA)
Biological Assignment of Primaries (Accuracy): 50 – 87 %

Primary Sites Identified:
- Breast: 15%
- Pancreas: 12.5%
- Bowel: 12%
- Lung: 11.5%
- Genital system: 9%
- Liver/bile duct: 8%
- Kidney/adenals: 6%
- Bladder/ureter: 5%
- Stomach: 3%
- Other: 18%

WHAT IS THE OPTIMAL THERAPEUTIC APPROACH OF CANCER OF UNKNOWN PRIMARY?

HISTORICAL OVERVIEW 1960 - 2008

<table>
<thead>
<tr>
<th>DECADE</th>
<th>REGIMEN (based)</th>
<th>RESPONSES (%)</th>
<th>SURVIVAL (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1960 – 1970</td>
<td>5-Fluorouracil</td>
<td>8 (5-12)</td>
<td>6 (4-9)</td>
</tr>
<tr>
<td>1970 – 1980</td>
<td>Anthracyclines</td>
<td>16 (0-37)</td>
<td>7 (3-13)</td>
</tr>
<tr>
<td>1980 – 1990</td>
<td>Platinum</td>
<td>30 (17-79)*</td>
<td>8 (5-72)**</td>
</tr>
<tr>
<td>1990 - &gt; 2000</td>
<td>Taxanes / Platinum</td>
<td>39 (7-50)*</td>
<td>8 (6-48)**</td>
</tr>
</tbody>
</table>

*CRs were seen  ** Long survivors

HELENIC COOPERATIVE ONCOLOGY GROUP EXPERIENCE WITH PHASE II TRIALS

<table>
<thead>
<tr>
<th>References</th>
<th>Regimens</th>
<th>Favourable Subsets</th>
<th>Unfavourable Subsets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ann Oncol 1992</td>
<td>Platinum-containing</td>
<td>32 (32)</td>
<td>15</td>
</tr>
<tr>
<td>Oncology 1998</td>
<td>Carbo/Epi/Eto</td>
<td>65 (18)</td>
<td>15.5</td>
</tr>
<tr>
<td>J Clin Oncol 2000</td>
<td>Carbo/Taxol</td>
<td>58 (36)</td>
<td>14</td>
</tr>
<tr>
<td>Cancer Chemother Pharmacol 2007</td>
<td>Oxal/CPT-11</td>
<td>77 (15)</td>
<td>13 (9)</td>
</tr>
<tr>
<td>Acta Oncologica 2008</td>
<td>Carbo/Docetaxel</td>
<td>46 (21)</td>
<td>22.6</td>
</tr>
</tbody>
</table>
DO WE HAVE EFFECTIVE DRUGS FOR CANCER OF UNKNOWN PRIMARY

OR

WE JUST HAVE RESPONSIVE SUBSETS OF PATIENTS?

WHAT IS CANCER OF UNKNOWN PRIMARY?

Lung-hidden CUP
Pancreas hidden CUP
Kidney-hidden CUP
Gastric-hidden CUP
Liver-hidden CUP
Prostate hidden CUP
Breast-hidden CUP

THE FAVOURABLE SUBSETS
OR
GOOD PROGNOSIS SUBSETS

FAVOURABLE OR
GOOD PROGNOSIS SUBSETS

UNFAVOURABLE OR
POOR PROGNOSIS SUBSETS

Favourable Subsets

1. Poorly differentiated carcinoma with midline distribution (extragonadal germ cell syndrome).
2. Women with papillary adenocarcinoma of peritoneal cavity.
3. Women with adenocarcinoma involving only axillary lymph nodes.
4. Squamous cell carcinoma involving cervical lymph nodes
5. Poorly differentiated neuroendocrine carcinomas.
6. Men with blastic bone metastases and elevated PSA (adenocarcinoma).
7. Isolated inguinal adenopathy (squamous carcinoma).
8. Patients with a single, small, potentially resectable tumor.
**CHARACTERISTICS OF PATIENTS WITH POORLY DIFFERENTIATED CUP**

**GENDER / AGE**: Men / < 50 yrs

**TUMOR INVOLVEMENT**: Mediastinum

**Lungs**

**Retroperitoneum**

**Lymph nodes**

**TUMOR MARKERS**: Elevated serum levels of β-HGC or AFP

**CLINICAL EVOLUTION**: Rapid tumor growth

**RESPONSE TO Rx**: Favourable response to Cisplatin - based chemotherapy. RR 50% (CRs: 15-25%)

**SURVIVAL**: Median: 12 months

15% long-term survivors

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**PERITONEAL CARCINOMATOSIS IN FEMALES**

**THE NATURAL HISTORY**

**Incidence**: 10% of invasive serous ovarian Ca, 10% of CUP patients

**Mean Age (yrs)**: 60 (25 – 80)

**Clinical Picture**: Abdominal distension, pelvic masses, ascites

**Surgical Picture**: Abdominal masses, peritoneal disease, ascites, with normal ovaries

**Histology**: Papillary serous carcinoma (+ psammoma bodies)

**Serum Ca-125**: Often abnormal or markedly elevated.

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**WOMEN WITH PAPILLARY ADENOCARCINOMA OF PERITONEAL CAVITY**

(Peritoneal Adenocarcinomatosis)

**Treatment**: * As FIGO III ovarian cancer.

* Surgical cytoreduction.

* Platinum – based chemotherapy.

**Response Rate**: 40 – 60% (CR: 30%)

**Survival**: Median: 16 months

**Long-term survival**: 5-yr: 10%
**TREATMENT RECOMMENDATIONS**

**AXILLARY LYMPH NODE**

- **Surgical Biopsy**
  - Compatible with Breast Cancer
  - Mammogram/US/MRI
  - Other Neoplasm

  **+++ for Breast Cancer**
  - Complete Axillary Dissection ± BC Surgery + Radiotherapy

  **-/- for Breast Cancer**
  - Standard treatment

  **Chemotherapy or hormonotherapy depending on age and menopausal status**

  **ISOLATED AXILLARY NODAL METASTASES**
  - FROM AN OCCULT PRIMARY BREAST CANCER

  **SURVIVAL RATES**
  - Similar to stage II or III breast cancer
  - Locoregional recurrence rate: 25%
  - Overall survival: 75% at 5yrs, 68% at 10yrs
  - No survival difference between conservative management (breast preservation + RT) and mastectomy.
  - N₂ disease has worse prognosis than N₁.

**SQUAMOUS CELL CANCER INVOLVING CERVICAL LYMPH NODES**

**Treatment:**
- As locally advanced head-neck cancer.
- Surgery alone is inferior except pN₁ neck disease with no extracapsular extension.
- Radiation: both sides of neck and mucosa (entire pharyngeal axis and larynx).
- Chemotherapy remains undefined (despite encouraging results with Platinum-based).

**Survival:**
- 5-year survival 35–50%.
- Documented long-term disease-free survivors.

**POORLY DIFFERENTIATED NEUROENDOCRINE CARCINOMAS**

**Treatment:**
- Platinum–based or paclitaxel/carboplatin–based chemotherapy

**Response:**
- 50–70% (CR: 25%)

**Survival:**
- Median: 14.5 months
- 3-yr: 24%

**OTHER FAVOURABLE CUP SUBSETS**

- Men with adenocarcinoma blastic bone metastases (and elevated PSA)
  - **Rx = Treat as metastatic prostate cancer**
- Isolated inguinal lymphadenopathy from squamous cell carcinoma
  - **Rx = Dissection ± radiotherapy**
- Single metastatic site
  - **Rx = Dissection ± radiotherapy**

**THE UNFAVOURABLE SUBSETS OR POOR PROGNOSIS SUBSETS**
**UNFAVOURABLE SUBSETS**

1. Adenocarcinoma metastatic to the liver or other organs
2. Non-papillary malignant ascites (adenocarcinoma)
3. Multiple cerebral metastases (adeno or squamous Ca)
4. Multiple lung/pleural metastases (adenocarcinoma)
5. Multiple metastatic bone disease (adenocarcinoma)

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**HISTOLOGIC SPECTRUM OF LIVER METASTASES**

<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>Adenocarcinoma</td>
<td>79%</td>
<td>65%</td>
<td>79.8%</td>
<td>68%</td>
<td>69%</td>
<td>79% (597)</td>
</tr>
<tr>
<td>Undifferentiated</td>
<td>12%</td>
<td>27%</td>
<td>3.8%</td>
<td>28%</td>
<td>24%</td>
<td>20% (144)</td>
</tr>
<tr>
<td>Neuroendocrine</td>
<td>-</td>
<td>9%</td>
<td>9%</td>
<td>14%</td>
<td>9%</td>
<td>9% (53)</td>
</tr>
<tr>
<td>Squamous</td>
<td>4%</td>
<td>3%</td>
<td>4.5%</td>
<td>4%</td>
<td>0%</td>
<td>4% (28)</td>
</tr>
<tr>
<td>Others</td>
<td>4%</td>
<td>1%</td>
<td>3.5%</td>
<td>4%</td>
<td>-</td>
<td>3% (22)</td>
</tr>
</tbody>
</table>

---

**OVERALL RESULTS OF CHEMOTHERAPY IN CUP PATIENTS WITH LIVER METASTASES**

- N° of patients: 711
- Response rate: < 20%
- Median survival: 5.5 months

---

**HOW SHOULD WE TREAT PATIENTS WITH UNFAVOURABLE CUP?**

- Patients with relatively young age and good P.S. could offer a chance of platinum-based chemotherapy
- Alternatively, best supportive care should be recommended.
**IRINOTECAN-CONTAINING REGIMENS IN CUP**

<table>
<thead>
<tr>
<th>Reference</th>
<th>N</th>
<th>Regimen</th>
<th>ORR</th>
<th>Med. Survival</th>
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</thead>
<tbody>
<tr>
<td>ASCO 2002</td>
<td>80</td>
<td>Cisplatin/Gemcitab</td>
<td>42%</td>
<td>22%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>vs</td>
<td>vs</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cisplatin/IRINO</td>
<td>25%</td>
<td>23%</td>
</tr>
<tr>
<td>JCO 2003</td>
<td>80</td>
<td>Cisplatin/Gemcitab</td>
<td>55%</td>
<td>8 mos</td>
</tr>
<tr>
<td></td>
<td></td>
<td>vs</td>
<td>vs</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cisplatin/IRINO</td>
<td>38%</td>
<td>6 mos</td>
</tr>
<tr>
<td>Oncologist 2004</td>
<td>132</td>
<td>Taxol/Carbo/VP-16</td>
<td>30%</td>
<td>9.1 mos</td>
</tr>
<tr>
<td>Cancer Chem Pharm 2007</td>
<td>47</td>
<td>Oxaliplatin/IRINO</td>
<td>13%</td>
<td>9.5 mos</td>
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</tbody>
</table>

**COMPARATIVE ACTIVITY OF CHEMOTHERAPY BETWEEN PTS WITH METASTATIC BREAST OR COLORECTAL CANCER & CUP PTS**

<table>
<thead>
<tr>
<th>Reference</th>
<th>N</th>
<th>Regimen</th>
<th>ORR</th>
<th>OS (median)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metastatic Colorectal Cancer</td>
<td>7 (R)</td>
<td>FU-based OvRx-based Irin-based</td>
<td>39%</td>
<td>19 months</td>
</tr>
<tr>
<td>CUP and Colorectal Type of CX</td>
<td>8 (II+R)</td>
<td>FU-based OvRx-based Irin-based</td>
<td>14%</td>
<td>5.5 months</td>
</tr>
<tr>
<td>Metastatic Breast Cancer</td>
<td>5 (R)</td>
<td>A-based T-based</td>
<td>41%</td>
<td>22 months</td>
</tr>
<tr>
<td>CUP and A-based CX</td>
<td>10 (II+R)</td>
<td>A-based T-based</td>
<td>29%</td>
<td>7 months</td>
</tr>
</tbody>
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**DOES THE IDENTIFICATION OF PRIMARY SITE BY MOLECULAR PROFILING IMPROVE PATIENTS’ OUTCOME?**

1. Gene profiling can detect the primary site in up to 85% of the cases
2. The assigned tissue of origin is compatible with response to relevant chemotherapy regimens, i.e. hidden colorectal cancer
3. These patients merit a survival benefit after systemic chemotherapy

**THE BENEFIT OF GENE PROFILING IN CUP: THE BOXING GAME**

**THE SUPPORTERS**

1. Gene profiling can detect the primary site in up to 85% of the cases
2. The assigned tissue of origin is compatible with response to relevant chemotherapy regimens, i.e. hidden colorectal cancer
3. These patients merit a survival benefit after systemic chemotherapy

**THE NON-SUPPORTERS**

1. The distinction between favourable and unfavourable subsets can be adequately performed by clinicopathological approach
2. Favourable subsets can be treated accordingly and responses are almost similar to the corresponding primary tumours
3. Although gene profiling can detect the primary site in up to 85% of the cases, responses and survival to relevant cytotoxic combinations are not similar to those with known primary tumours
4. CUP patients, especially those with unfavourable subsets, carry a unique biological and clinical behaviour (genetic signature ?)
5. High cost
**STEPS IN DIAGNOSTIC AND THERAPEUTIC MANAGEMENT**

**DIAGNOSIS OF METASTATIC CARCINOMA (by histopathology)**

**STEP I**
- Complete Medical History and Physical Examination
- Basic Laboratory Work-up and/or Specific Tests

**STEP II**
- Rule-out Potentially Treatable or Curable Tumors
  (Immunohistochemistry, molecular or electron microscopy)
- i.e., Breast Cancer, Germ-cell Tumors, Prostate Cancer, Ewing Sarcoma, Lymphomas, PNET Tumors

**STEP III**
- Characterize the Specific Clinico-pathological Entity
- Treat the patient
  - Favourable Subsets [With “Curative” Intent]
  - Unfavourable Subsets [With “Palliative” Intent]

**CARCINOMA OF UNKNOWN PRIMARY**

**A HUMAN MODEL FOR METASTATIC DISEASE**

**CANCER OF UNKNOWN PRIMARY SITE**

The entire oncology in a single disease

- Hidden Lung Ca
- Hidden Breast Ca
- Hidden Prostate Ca
- Hidden Ovary Ca
- Hidden Head/Neck Ca
- Hidden Liver Ca
- Hidden Colon Ca
- Hidden Germ Cell Ca

**IMAGING**
- CT, MRI, PET

**PATHOLOGY**
- Immunohistochemistry, Molecular