CANCER OF UNKNOWN PRIMARY: A Diagnostic and Therapeutic Dilemma

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Emeritus Professor, University of Ioannina, Greece
ESO Coordinator on Career Development Programme

Berlin, ESO MCO, March 2019
What is the incidence of cancer of unknown primary site?
INCIDENCE AND MORTALITY OF CUP

- CUP accounts for 3-5% of all human cancers

- It is considered to be the 8th most frequent malignant tumor

- In Europe the incidence decreased from 14 per 100,000 person in 2000 to 7.0 in 2012 (EJC 101:77-86, 2018)

- In USA the incidence decreased since 1980’s by 3.6% per year (Cancer Causes Control 25:747-757, 2014)
WHAT ARE THE INTERPRETATIONS?

- Improved diagnostics (immunohistochemistry, molecular gene expression profiling and imaging technology) have improved the ability to detect the primary site.

- Better smoking control in US.
Risks of being diagnosed with CUP was strongly related to smoking.

i) Current smokers (relative risk: 3.66) and
ii) Heavy smokers (26+ cigarettes/d) (relative risk: 5.12) died within 12 months.

Int J Cancer 135: 2475, 2014
CLINICAL PRESENTATION OF CUP
THE NATURAL HISTORY OF CANCER OF UNKNOWN PRIMARY SITE

FUNDAMENTAL CHARACTERISTICS
FUNDAMENTAL CHARACTERISTICS

❖ Early dissemination
❖ Clinical absence of primary at presentation
❖ Aggressiveness
❖ Unpredictable metastatic pattern
Cancer of Unknown Primary Site:

One or more Diseases?
<table>
<thead>
<tr>
<th>HISTOLOGY</th>
<th>INCIDENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adenocarcinoma</strong></td>
<td>50%</td>
</tr>
<tr>
<td>Well to moderately differentiated</td>
<td></td>
</tr>
<tr>
<td>Poorly or undifferentiated</td>
<td>35%</td>
</tr>
<tr>
<td><strong>Squamous cell carcinoma</strong></td>
<td>10%</td>
</tr>
<tr>
<td><strong>Undifferentiated neoplasms</strong></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>Sarcomas</td>
<td></td>
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<tr>
<td>Embryonal malignancies</td>
<td></td>
</tr>
</tbody>
</table>
## CLINICOPATHOLOGICAL ENTITIES OF CUP

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

*W = well, M = moderately, P = poorly, U = undifferentiated*
**Peritoneal cavity**

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

**Lungs**

- Pulmonary metastases
- Pleural effusion

\[ \text{AdenoCa various diff} \]
\[ \text{AdenoCa M or P diff} \]

\[ \text{Papillary or serous adenoCa} \]
\[ (\pm \text{psammoma bodies}) \]

\[ \text{Mucin adenoCa M or P diff} \]
\[ (\pm \text{signet ring cells}) \]

\[ W = \text{well}, \quad M = \text{moderately}, \quad P = \text{poorly}, \quad U = \text{undifferentiated} \]
<table>
<thead>
<tr>
<th><strong>Bones</strong></th>
<th>AdenoCa of various diff</th>
</tr>
</thead>
<tbody>
<tr>
<td>(solitary or multiple)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Brain</strong></th>
<th>AdenoCa of various diff or squamous cell Ca</th>
</tr>
</thead>
<tbody>
<tr>
<td>(solitary or multiple)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Neuroendocrine tumors</strong></th>
<th>P diff Ca with neuroendocrine features (mainly), low-grade neuroendocrine Ca, small cell anaplastic Ca</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th><strong>Melanoma</strong></th>
<th>U neoplasm with melanoma features.</th>
</tr>
</thead>
</table>

\[ W = \text{well,} \quad M = \text{moderately,} \quad P = \text{poorly,} \quad U = \text{undifferentiated} \]
WHAT IS THE OPTIMAL INVESTIGATIONAL DIAGNOSTIC APPROACH FOR THE IDENTIFICATION OF THE PRIMARY TUMOR?
How do we search for the primary?

By Histopathology:
- Immunohistochemistry
- Advanced Molecular Technology

By Imaging:
- Conventional Radiology
  - Ultrasonography
  - CT-scans
  - MRIs
  - PET-scans
  - Mammography

By Endoscopy:
- ENT panendoscopy
- Bronchoscopy
- Colonoscopy
- Proctoscopy
- Colposcopy
By
HISTOPATHOLOGY
And
IMMUNOCHEMISTRY

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Cytokeratins (CKS)

Monoclonal antibodies against cytokeratin polypeptides CK7 and CK20
CK7   CK20

CK7 + CK20 +
  - Urothelial tumors
  - Ovarian mucinous adenocarcinoma
  - Pancreatic adenocarcinoma
  - Cholangiocarcinoma

CK7 + CK20 -
  - Lung adenocarcinoma
  - Breast carcinoma
  - Thyroid carcinoma
  - Endometrial carcinoma
  - Cervical carcinoma
  - Salivary gland carcinoma
  - Cholangiocarcinoma
  - Pancreatic carcinoma

CK7 - CK20 +
  - Colorectal Carcinoma
  - Merkel cell carcinoma

CK7 - CK20 -
  - Hepatocellular carcinoma
  - Renal cell carcinoma
  - Prostate carcinoma
  - Squamous cell & small cell lung carcinoma
  - Head & neck carcinoma
MOLECULAR ANALYSIS
[Microarray Platforms]

> 80 - 90% accuracy
# Gene expression profiling

<table>
<thead>
<tr>
<th>Assays</th>
<th>Platform</th>
<th>Tissue</th>
<th>No. of Tumor types</th>
<th>Number of genes</th>
<th>Accuracy in known tumors (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Veridex RT-PCR mRNA FFPE</td>
<td>6 and &quot;other&quot;</td>
<td>10</td>
<td>76</td>
<td></td>
<td>76</td>
</tr>
<tr>
<td>Pathwork Diagnostics Tissue</td>
<td>cDNA microarray</td>
<td>Frozen/FFPE</td>
<td>15</td>
<td>1500</td>
<td>89</td>
</tr>
<tr>
<td>MiReview met RT-PCR miRNA FFPE</td>
<td>22</td>
<td>48 miRNAs</td>
<td>86</td>
<td></td>
<td>86</td>
</tr>
<tr>
<td>Rosetta Genomics CancerType ID RT-PCR mRNA FFPE</td>
<td>39 (including subtypes)</td>
<td>92</td>
<td>86</td>
<td></td>
<td>86</td>
</tr>
</tbody>
</table>
LIQUID BIOPSY IN CUP

Liquid biopsy opens a new diagnostic, predictive and prognostic window in CUP that may lead to substantial improvement in the management of patients with CUP.

El Rassy, H Khaled, N Pavlidis, Eur J Cancer 105:28-32, 2018
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
<table>
<thead>
<tr>
<th>Imaging Study</th>
<th>Diagnostic Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest X-ray</td>
<td>Prerequisite test</td>
</tr>
<tr>
<td>Barium studies</td>
<td>Useless</td>
</tr>
<tr>
<td>CT-scans</td>
<td>40% accuracy / Guidance to biopsy</td>
</tr>
<tr>
<td>Mammography</td>
<td>Low sensitivity</td>
</tr>
<tr>
<td>MRI (breast)</td>
<td>60% accuracy</td>
</tr>
<tr>
<td>FDG-PET SCAN</td>
<td>43% accuracy / more sensitive for occult H+N (80-85%) and Lung Ca</td>
</tr>
</tbody>
</table>
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 women with papillary adenocarcinoma of peritoneal cavity.
  - CA 15-3 women with adenocarcinoma involving only axillary lymph nodes.
WHAT IS THE OPTIMAL THERAPEUTIC APPROACH OF CANCER OF UNKNOWN PRIMARY?
DO WE HAVE **EFFECTIVE DRUGS** FOR CANCER OF UNKNOWN PRIMARY

OR

WE JUST HAVE **RESPONSIVE SUBSETS** OF PATIENTS?
DIAGNOSTIC AND THERAPEUTIC MANAGEMENT OF CANCER OF AN UNKNOWN PRIMARY

N. Pavlidis, E. Briasoulis, J. Hainsworth, E.A. Greco
CUP

FAVOURABLE OR GOOD PROGNOSIS SUBSETS

UNFAVOURABLE OR POOR PROGNOSIS SUBSETS
THE FAVOURABLE SUBSETS OR GOOD PROGNOSIS SUBSETS

20% of all CUP Cases
**Favourable Subsets**

1. Women with adenocarcinoma involving only *axillary* lymph nodes.
2. Women with *papillary* adenocarcinoma of peritoneal cavity. (Primary peritoneal carcinoma)
3. Squamous cell carcinoma involving cervical lymph nodes
4. Poorly differentiated *neuroendocrine* carcinomas.
5. Men with blastic bone metastases and elevated PSA (adenocarcinoma)
6. Isolated *inguinal* adenopathy (squamous carcinoma).
7. Patients with a *single*, small, potentially resectable tumor.
Subset 1

WOMEN WITH OCCULT PRIMARY BREAST CARCINOMA PRESENTING AS AXILLARY LYMPHADENOPATHY
Subset 1

Women with adenocarcinoma involving axillary nodes

- Mostly ductal adenocarcinoma (ER/PR 40%, HER2 30%)
- Mean age 52 years. Postmenopausal 66%.
- Should be managed as stage II breast cancers (axillary dissection, ipsilateral breast radiotherapy, adjuvant chemo/hormone therapy)
- Distant metastases in < 2%
- 5-year survival: 72%
Subset 2

WOMEN WITH SEROUS PAPILLARY PERITONEAL CARCINOMA (Primary Peritoneal Carcinoma)
**Subset 2**

Women with primary papillary adenocarcinoma peritoneal cavity

- **Similar** presentation with advanced ovarian cancer.

- Median age **60** years

- Histopathology: **serous or papillary adenocarcinoma**

- Serum **CA 125** is frequently **increased**

- Should be treated as stage **III-IV ovarian cancer** (cytoreduction, followed by platinum / taxanes)

- **Responses**: **80% (CR: 30-40%)**, **Median survival**: **36 months**
Subset 3

SQUAMOUS CELL CARCINOMA OF AN UNKNOWN PRIMARY SITE INVOLVING CERVICAL LYMPH NODES
Squamous cell carcinoma involving cervical nodes

• It constitutes the 5% of all head-neck cancers. Age 60 yrs

• INVESTIGATION OF PRIMARY SITE
  i) bilateral tonsillectomy (?) or tongue base mucosectomy (80% sensitivity)
  ii) PET-scan to detect the primary has 80% sensitivity

• TREATMENT:
  ▪ $N_1$ or $N_{2a}$ disease without extracapsular extension: surgery alone

    [locoregional control: 80 – 90%, 5-yr survival: 65%]

  ▪ $\geq N_{2b}$ stage or with extracapsular extension: Postoperative ChemoRT
HPV – RELATED SCCUP

• **DIAGNOSIS**: p16 expression and HPV-DNA (by PCR or in situ hybridization)

• **TREATMENT**: to date, the current treatment of HPV-SCCUP should not differ from the standard management of the rest of the SCCUP

• **PROGNOSIS**: from retrospective studies HIV-related SCCUP patients have a better prognosis compared to the non HIV-related SCCUP. Ongoing prospective trials are warranted

Rassy E, Pavlidis N, Head and Neck (in press), 2019
POORLY DIFFERENTIATED NEUROENDOCRINE CARCINOMA OF AN UNKNOWN PRIMARY SITE

TREATMENT OF NEUROENDOCRINE CUP

**Data** : 1988 – 2010, 515 patients

**Chemotherapy (Platinum based)** : 65% treated

**Response rate** : 50-60% (CR: 20 - 30%)

**Median survival** : 15.5 months (11.6 – 40)
NEWLY IDENTIFIED FAVOURABLE CUP SUBSET WITH IMMUNOHISTOCHEMISTRY OR MOLECULAR PROFILING

1. Colon carcinoma of unknown primary (CK20+, CK7-, CDX2+)

2. Merkel cell carcinoma of unknown primary

3. Renal cell carcinoma of unknown primary

4. Lung carcinoma of unknown primary (?)

5. Metastatic melanoma of unknown primary
Subset 1a

ADENOCARCINOMA WITH A COLON–PROFILE (CK 20⁺, CK 7⁻, CDX 2⁺, CEA⁺) OF AN UNKNOWN PRIMARY SITE
Treatment and Survival of CUP with a Colon Profile (CK20+, CK7-, CDX2+)

- Should be treated as advanced colorectal cancer with chemotherapy / targeting treatment
- Response Rate: 50% (CR 15%, PR 35%)
- Median Survival: 21-37 months

Clin Colorectal Cancer 11(2): 112-8, 2012
Subset 2a

Renal Cell Carcinoma Presenting as CUP
N Pts : 52       Median Age : 64 yrs

Histology : Clear Cell  39%
            Papillary  31.5%
            Unspecified  29.5%

IHC: Vimentin, CK(AE1/AE3), CD10,CK8/18 Pax8

Targeted Rx : Sunitinib, Pazopanib, Everolimus, Temsirolimus

RR : 40-50%   PR

Mean PFS : 8.5 months

Mean Survival : 6-16 months
Merkel Cell Carcinoma of Unknown Primary of Stage III B

88 patients with Merkel tumors treated with Avelumab:
RR 33% (CR 11%)
Unknown primary Merkel cell carcinoma: 23 new cases and a review

Tina I. Tarantola, MD, Laura A. Vallow, MD, Michele Y. Halyard, MD, Roger H. Weenig, MD, Karen E. Warschaw, MD, Amy L. Weaver, MSc, Randall K. Roenigk, MD, Jerry D. Brewer, MD, and Clark C. Otley, MD

Rochester and Minneapolis, Minnesota; Jacksonville, Florida; and Scottsdale, Arizona

- At 2 years, overall survival of patients with stage IIIB unknown primary MCC was significantly improved compared with patients with stage IIIB known primary MCC: 76.9% to 36.4% (P = .028).

![Graph showing overall survival](image)

**Fig 1.** Overall survival among 18 patients with stage IIIB unknown primary Merkel cell carcinoma (MCC) and 27 patients with stage IIIB known primary MCC from same time period. Kaplan-Meier estimates are provided at 1, 2, 3, 4, and 5 years. Number at risk are included in parentheses.
METASTATIC MELANOMA OF UNKNOWN PRIMARY
MALIGNANT MELANOMA OF UNKNOWN PRIMARY SITE:
TO MAKE THE LONG STORY SHORT.
A SYSTEMATIC REVIEW OF 4,348 PATIENTS

Kamposioras K, Pentheroudakis G, Pavlidis N

CONCLUSIONS:

<table>
<thead>
<tr>
<th></th>
<th>5 - YRS OS</th>
<th>10 - YRS OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>MUP (Unknown)</td>
<td>76 %</td>
<td>63 %</td>
</tr>
<tr>
<td>MKP (Known)</td>
<td>29 %</td>
<td>19 %</td>
</tr>
</tbody>
</table>

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Metastatic Melanomas of Unknown Primary Show Better Prognosis than those of Known Primary: A Systemic Review and Meta-Analysis

*J Am Acad Dermatol* 2015;72:59

**METHODS**

- Meta-analysis/systematic review of 18 studies
- 2084 pts with melanoma of unknown primary (MUP)
- 5894 pts with melanoma of known primary (MKP)

**RESULTS**

- MUP had a better overall survival compared with MKP in stage III (p=0.010) and stage IV (p = 0.008)
THE UNFAVOURABLE SUBSETS
OR
POOR PROGNOSIS SUBSETS

80 % of all CUP Cases
UNFAVOURABLE SUBSETS
(80% OF CUP CASES)

1. Metastatic Carcinoma to the liver and 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)
OVERALL RESULTS OF CHEMOTHERAPY IN CUP PATIENTS WITH LIVER METASTASES

Número of patients : 711
Response rate : < 20%
Median survival : 5.5 months
SURVIVAL OUTCOME DIFFERENCES BASED ON TREATMENTS USED AND KNOWLEDGE OF THE PRIMARY TUMOUR SITE FOR PATIENTS WITH CANCER OF UNKNOWN AND KNOWN PRIMARY IN ONTARIO

Current Oncol 2018

- From **Ontario Cancer Registry**: 2000-2005
  - 45,347 (96.3%) pts with known metastatic disease and
  - 1,743 (3.7%) pts with CUP

- Median Survival
  - a) **Known Primary**. Treated vs untreated pts: 19.0 vs 2.2 mo
  - b) **CUP**. Treated vs untreated pts: 3.6 vs 1.1 mo (p<0.0001)

- Overall Median Survival
  - Known vs CUP pts: 11.9 vs 1.9 mo
Molecular Gene Expression Profiling to Predict the Tissue of Origin and Direct Site-Specific Therapy in Patients With Carcinoma of Unknown Primary Site: A Prospective Trial of the Sarah Cannon Research Institute

John D. Hainsworth, Mark S. Rubin, David R. Spigel, Ralph V. Boccia, Samuel Raby, Raven Quinn, and F. Anthony Greco

Conclusion

✓ The **median survival time of 12.5 months** for patients who received assay-directed site-specific therapy compares favorably with previous results using empiric CUP regimens.

✓ Molecular tumor profiling contributes to the management of patients with CUP and should be a part of their standard evaluation.
OVERALL SURVIVAL: Assay-directed treatment vs. empiric treatment

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>Empiric Treatment</th>
<th>Assay-directed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Survival (mo)</td>
<td>4.7</td>
<td>12.5</td>
</tr>
</tbody>
</table>

p = 0.02

PRESENTED BY: F. Anthony Greco, MD
Epigenetic profiling to classify cancer of unknown primary: a multicentre, retrospective analysis

Sebastian Moran, et al

Based on the microarray DNA methylation signatures (EPICUS)

Interpretation: We show that the development of a DNA methylation based assay can significantly improve diagnoses of cancer of unknown primary and guide more precise therapies associated with better outcomes. Epigenetic profiling could be a useful approach to unmask the original primary tumour site of cancer of unknown primary cases and a step towards the improvement of the clinical management of these patients.
Figure: Outcome of patients with cancer of unknown primary who receive a site-specific treatment that matches the EPICUP prediction.
# Ongoing Phase III Randomized Trial with the Use of Molecularly Assigned Therapy

<table>
<thead>
<tr>
<th>Trial</th>
<th>Sponsor</th>
<th>Design</th>
<th>Arms</th>
</tr>
</thead>
<tbody>
<tr>
<td>GEFCAP 104</td>
<td>GEFCAPI, France</td>
<td>RCT Phase III</td>
<td>cDDP + Gemcitabine vs Pathwork test – Based Therapy</td>
</tr>
</tbody>
</table>
Randomized Phase II Trial Comparing Site-Specific Treatment (SST) Based on Gene Expression Profiling With Empirical Carboplatin/Paclitaxel (ECP) for Patients with CUP [OSAKA JAPAN]

- The primary end point was 1-year survival rate.
- 130 pts were randomly assigned.

### RESULTS

<table>
<thead>
<tr>
<th></th>
<th>SST (site specific)</th>
<th>ECP (empirical)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS</td>
<td>5.1 m</td>
<td>4.8 m</td>
</tr>
<tr>
<td>OS</td>
<td>9.8 m (p=0.890)</td>
<td>12.5 m (p=0.550)</td>
</tr>
<tr>
<td>1-YR OS</td>
<td>44%</td>
<td>54.9% (p=0.264)</td>
</tr>
</tbody>
</table>

### CONCLUSION:

- Site-specific treatment that was based on microarray profiling did not result in a significant improvement in 1-year survival compared with empirical PC.
• (2019) ... Until more robust outcomes and comparative effectiveness data are available, pathologists and oncologists must collaborate on the judicious use of these modalities (IHC and GEP) on a case–by–case basis, with the best possible individualized patient outcome in mind...
TARGETED THERAPY IN PATIENTS WITH CANCER OF UNKNOWN PRIMARY ORIGIN:

Where do we stand today?

Rassy E, Pavlidis N  Cancer Treat Rev 67:21-28,2018
GENOMIC ALTERATIONS IN CUP

Cancer Medicine 7:4814-4824, 2018

• METHODS: 10 peer-reviewed publications (2013-2018) of comprehensive genomic profiling in CUP patients

• FINDINGS: 85% clinically relevant mutations or targetable biomarkers were identified, of which 13%-64% may benefit from currently available drugs
THE FUTURE OF TARGETED THERAPY IN CUP
With Positive Biomarkers

• There are only anecdotal cases with TKIs, monoclonal antibodies or immune check inhibitors in patients with CUP

• There are no prospective ongoing studies with targeted treatments

• There is one prospective Phase II trial with Pembrolizumab, that has not yet recruiting
CRITICAL QUESTIONS ON DIAGNOSTIC AND THERAPEUTIC UTILITY OF MOLECULAR PROFILING (MP) IN CUP PATIENTS

Q 1: Does MP assay, increases accuracy of identifying the primary site?

Q 2: Does MP helps in utilizing targeted treatment?

Q 3: Does identification of primary site improves patient outcome (survival)?
STEPS IN DIAGNOSTIC AND THERAPEUTIC MANAGEMENT

DIAGNOSIS OF METASTATIC CARCINOMA (by histopathology)

SEARCH FOR PRIMARY SITE

STEP I
Clinical, immunohistochemistry, imaging, endoscopy studies

RULE-OUT POTENTIALLY TREATABLE OR CURABLE TUMORS
(Immunohistochemistry or other studies)

STEP II
i.e. Breast Cancer, Germ-cell Tumors, Lymphomas

CHARACTERIZE THE SPECIFIC CLINICOPATHOLOGICAL ENTITY

STEP III

TREAT THE PATIENT

FAVOURABLE SUBSETS
[Similarly to relevant primaries with "Curative Intent"]

UNFAVOURABLE SUBSETS
[With empirical chemotherapy with "Palliative Intent" or with specific Rx following gene profiling]
Thank you