Carcinoma of Unknown Primary (CUP)

Four Decades of Evolution in Diagnostic Evaluation and Management

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Disclosure

• Dr. Greco is on the Speaker’s Bureau for bioTheranostics.
Four Decades of Changing Clinical Landscape In CUP

1. 1976-1986: Decade of Recognition of Favorable Clinicopathologic Subsets

2. 1986-1996: Decade of Improved Clinical Diagnostic Techniques/Testing

3. 1996-2006: Decade of Empiric Chemotherapy

4. 2006-2014: Decade of Improved Pathologic and Genetic Diagnostic Technologies and Better Outcomes for Many CUP patients
Agenda

• Cancer of Unknown Primary (CUP) Background
  – Historical Standard of Care: Recognition of favorable subsets; Empiric chemotherapy CUP Trials
  – Improving Clinical Evaluation and finding anatomical primary sites

• Immunohistochemical (IHC) and Gene Expression-Based Diagnostic Approaches
  – Overview of Clinical Data
  – Outcomes-Based Investigations

• A Prospective Outcomes Trial

• Summary
Background: Cancer of Unknown Primary

• Wide heterogeneity of clinical and pathologic presentations
• About 50,000 patients per year in USA
• Most patients have carcinoma and most of these adenocarcinomas
• Autopsy studies reveal small clinically undetectable primary tumor sites in 75% of patients (lung, pancreas, biliary tract, colorectal, kidney most common, but most tumors represented)
• Favorable subsets established; represent ~20% of CUP:
  – Squamous cell in the neck → Head & Neck Primary
  – Squamous cell in the inguinal region → Anal/Cervical Primary
  – Adenocarcinoma in the Axilla (women) → Breast Primary
  – Peritoneal carcinoma (women) → Ovary/fallopian tube/ primary peritoneal
  – Extragonadal Germ Cell Tumor Syndrome → Germ Cell
  – Neuroendocrine carcinoma → well or poorly differentiated- Many sites
  – Single metastasis → Many sites
Background

- **Cancer of Unknown Primary (CUP) Definition**
  - Metastatic cancer in the absence of a clinically-detectable anatomically-defined primary tumor site after an adequate diagnostic evaluation.

- CUP diagnosis can be considered a result of diagnostic failure.

- Improved clinical diagnostic techniques (CTs, MRI, PET, endoscopies) find anatomical primary sites more often than in the past.

- Many anatomical primary sites are too small to identify despite improved clinical diagnostic testing.

- The pathology (including modern IHC) and genetic testing of CUP biopsies has enabled a tissue of origin diagnosis in most patients despite an inability to identify the anatomical primary tumor site.
INITIAL DIAGNOSTIC EVALUATION

- Complete history: including detailed review of systems
- Complete physical examination: including pelvis examination, stool for occult blood
- Complete blood cell count, comprehensive metabolic panel, lactate dehydrogenase, urinalysis
- Computed tomography scans of chest, abdomen, and pelvis
- Mammography in women
- Serum prostate-specific antigen in men
- Positron emission tomography scan in selected patients
- Pathology-including screening immunohistochemistry marker stains (CK7, CK20, TTF-1, CDX2)
- Molecular Cancer Classifier as necessary
Background

- CUP patients within favorable subsets treated with “site-specific” therapy have a better prognosis than the group as a whole.
- In the absence of a definitive diagnosis, 80% of patients (unfavorable prognosis group) with CUP traditionally have been treated as a single entity, usually with taxane/platinum or gemcitabine/platinum chemotherapy
- Patient prognosis is poor, with median survivals of approximately 9 months.

<table>
<thead>
<tr>
<th><em>Reference</em></th>
<th>Treatment</th>
<th># of Patients</th>
<th>Median Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Piga et al., Br J Cancer. 2004;90(10):1898-904.</td>
<td>Carboplatin/Doxorubicin /Etoposide</td>
<td>N=102</td>
<td>9.0 months</td>
</tr>
<tr>
<td>Hainsworth et al., Cancer J. 2010;16(1):70-5.</td>
<td>Paclitaxel/Carboplatin/ Etoposide vs Gemcitabine/Irinotecan</td>
<td>N=198</td>
<td>7.4 months</td>
</tr>
</tbody>
</table>

*CUP studies with patient populations greater than 100.
Evolving Role of IHC in Tissue of Origin Diagnosis in CUP

<table>
<thead>
<tr>
<th>Tissue Type</th>
<th>IHC Markers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung, adenocarcinoma/large cell</td>
<td>CK7+, CK20-, TTF-1+</td>
</tr>
<tr>
<td>Lung, neuroendocrine (small cell/large cell)</td>
<td>Chromogranin+, Synaptophysin +, TTF-1+</td>
</tr>
<tr>
<td>Colorectal</td>
<td>CK7-, CK20+, CDX-2+</td>
</tr>
<tr>
<td>Breast</td>
<td>CK7+, ER+, GCDFP-2+, Mammoglobulin+</td>
</tr>
<tr>
<td>Prostate</td>
<td>CK7-, CK20-, PSA+</td>
</tr>
<tr>
<td>Ovary</td>
<td>CK7+, ER+, WT-1+</td>
</tr>
<tr>
<td>Melanoma</td>
<td>S100+, Melan-A+, HMB45+</td>
</tr>
<tr>
<td>Renal</td>
<td>RCC+, Vimentin+, CD10+, PAX-8+</td>
</tr>
<tr>
<td>Liver</td>
<td>Hepar 1+, CD10+, CD13+</td>
</tr>
<tr>
<td>Germ Cell</td>
<td>PLAP+ and/or OCT-4+</td>
</tr>
<tr>
<td>Adrenal</td>
<td>Alpha-inhibin+, Melan-A (A103)+</td>
</tr>
<tr>
<td>Thyroid (follicular/papillary)</td>
<td>TTF-1+, Thyroglobulin+</td>
</tr>
</tbody>
</table>

Single Tissue of Origin Diagnosed in 35% of CUP Cancers by IHC
## Molecular Cancer Classifiers for CUP-Performed on Biopsies

<table>
<thead>
<tr>
<th>Platform</th>
<th>bioTheranostics CancerTYPE ID</th>
<th>Pathwork Dx Tissue of Origin</th>
<th>Rosetta Genomics Cancer Origin Test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Real-time RT-PCR mRNA</td>
<td>Microarray mRNA</td>
<td>Microarray miRNA</td>
</tr>
<tr>
<td>Tumor Types Classified</td>
<td>28 Main types, 50 Subtypes</td>
<td>15 types</td>
<td>42 types</td>
</tr>
<tr>
<td>Specimen Requirements</td>
<td>FFPE; Minimum 300-500 cells</td>
<td>FFPE; 6 slides 10 µM thick</td>
<td>FFPE; 3-10 slides 10 µM thick</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td>87%</td>
<td>88%</td>
<td>86%</td>
</tr>
<tr>
<td>Specificity</td>
<td>99%</td>
<td>99%</td>
<td>99%</td>
</tr>
</tbody>
</table>
Molecular Cancer Classification: General Approach

- In recent years, molecular cancer classification has emerged as a standardized, objective technique to help identify tumor type in patients with CUP
- Concept: neoplasms retain gene expression profile based on cellular origin; this profile can be exploited to identify tumor type

**Molecular Cancer Classification: General Approach**

- Patient biopsy
- RNA extraction
- Measure Gene expression
- Compare patient profile to gene expression profile of known tumors from a reference database
- Algorithm compares sample to Reference Database
- Predict Tumor Type

Quantification of differential gene expression from a patient’s tumor

Compare patient profile to gene expression profile of known tumors from a reference database
Major Questions regarding the 92-gene RT-PCR Assay

1) Accuracy in predicting primary tumor site?
2) What is the evidence that this assay can accurately identify tumor type in patients with CUP?
3) Will site-specific therapy based on the molecular assay diagnosis improve the outcome of patients with CUP?
Is the 92-gene RT-PCR assay accurate in predicting primary tumor site?

- Sensitivity = 87% (95% CI, 0.84 to 0.89)
- Accuracy stable in metastatic tumors, high-grade tumors, and cases with limited tissue

This assay demonstrated excellent performance for classification of a diverse set of tumor histologies in known tumors.
Major Questions regarding the 92-gene RT-PCR Assay

What is the evidence that this assay can accurately identify tumor type in patients with CUP?*

1. Evaluated biopsy specimens in patients found to have latent primary tumor sites months to years after initial presentation

2. Evaluated biopsy specimens in CUP patients with a single suspected diagnosis made by IHC

3. Evaluated directed IHC and clinical/histologic findings after molecular diagnosis known in attempt to confirm molecular diagnosis

*See – Journal of the National Cancer Institute – 2013, June 5; 105 (11); 782-90.
1. Accuracy of 92-gene RT-PCR assay in Patients with Latent Occult Primary Tumors

- CUP patients that had latent primary tumors discovered during their follow-up
- The latent primary tumor site served as the reference known site of origin
- Original biopsy tissue tested by 92-gene assay (CancerTYPE ID)
- Molecular diagnosis was accurate in 18 of 24 cases
  - Sensitivity = 75%

This assay demonstrated high accuracy in CUP patients with latent primary tumors
2. 92-gene RT-PCR assay Concordance with suspected IHC diagnosis in CUP Patients

171 specimens from CUP patients referred to SCRI and tested by this assay

Single suspected diagnosis after initial IHC

- Molecular diagnosis concordant with IHC diagnosis in 40 of 52 cases (77%)

2 – 3 suspected diagnoses after initial IHC

- Clinical features validated molecular diagnosis prediction in 34 of 43 cases

43 of 97, assay prediction matched 1 of the Dx

54 of 97, assay prediction did not match the IHC Dx

- Molecular diagnosis consistent with clinical features in 41 of 54 cases
- Molecular diagnosis prediction validated with additional IHC and clinical findings in 26 of 35 cases (74%)

Correlative study demonstrated 92-gene RT-PCR had high concordance with suspected IHC diagnoses and provided additional objective diagnostic information when IHC was inconclusive. This molecular cancer classifier is about 80% accurate in determining the tissue of origin and complements standard pathology in CUP diagnosis.
3. 92-gene RT-PCR Assay Colorectal Diagnoses in CUP: Retrospective Outcomes

| Carcinoma of Unknown Primary Site: Outcomes in Patients with a Colorectal Molecular Profile Treated with Site-Specific Chemotherapy |
| Jornal Cancer Thery 2012;3;37-43 |
| F. Anthony Greco, Wayne J. Lennington, David R. Spigel, Gauri R. Varadhachary, John D. Hainsworth |

- Retrospective analysis of 32 patients with CUP who were diagnosed by molecular assay with Colorectal Cancer (CRC).
- 29 patients received CRC-specific regimen.
- Median overall survival with CRC-specific regimens was 21 mo.

| A Retrospective Study of Treatment Outcomes in Patients with Carcinoma of Unknown Primary Site and a Colorectal Cancer Molecular Profile |
| Clin Colorectal Cancer. 2012; 11(2):112-8 |
| John D. Hainsworth, MD, Catherine A. Schnabel, PhD, Mark G. Erlander, PhD, David W. Haines III, BS, F. Anthony Greco, MD |

- Retrospective analysis of 42 patients with CUP who were diagnosed by CancerTYPE ID with Colorectal Cancer.
- 50% of patients treated with CRC-specific regimen had objective response while only 17% of patients treated with empiric therapy had an objective response (p= 0.02).
- Median overall survival with CRC-specific regimens was 27 mo.

Responses and survivals are similar to known advanced CRC and compares favorably to empiric chemotherapy for CUP patients.
IHC Colorectal Diagnosis in CUP: Retrospective Outcomes

Carcinoma of unknown primary with gastrointestinal profile: immunohistochemistry and survival for this favorable subset. Int J CLIN Oncol 2013 June 28 (Epub ahead of print)

- All patients received colorectal site-specific chemotherapy regimens.
- Liver, peritoneum and nodes were common metastatic sites.
- Median survivals exceeded 21 months (37 and 21 months for two groups).
- CUP patients should have “optimal” IHC to diagnose a colorectal profile (colorectal tissue of origin) as these CUP patients benefit substantially from colorectal site-specific therapy.

Responses and survivals are similar to known advanced CRC and compares favorably to empiric chemotherapy for CUP patients.
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
Prospective Outcomes with 92-gene RT-PCR assay: Background and Study Objective

**Objective**

- To evaluate the ability of gene expression-based classification with the 92-gene assay (CancerTYPE ID) to render a tumor type diagnosis in patients with CUP
- To determine the efficacy of treatment regimens based on molecular assay-predicted site of origin

**Endpoints**

- Further evaluation of the accuracy of the molecular assay to identify responsive vs non-responsive tumor types, and determine outcomes.
- Improvement in overall survival of patients who received molecular assay-directed, site-specific therapy of at least 30% compared to previous trials from the same study group (9.1 months to at least 11.7 months). Overall survival compared to 396 patients from a compilation of 4 CUP trials with contemporary empiric chemotherapies performed by the same clinical trial network.
Study Design

- **Design**
  - Eligible patients had a diagnosis of CUP after diagnostic workup on initial presentation
  - Patients excluded if they had a treatable CUP syndrome
  - Patients were treated with standard first-line chemotherapeutic treatment regimens based on molecular results

### Table 1. Site-Specific Treatments

<table>
<thead>
<tr>
<th>Predicted Tissue of Origin</th>
<th>Treatment*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>Taxane/bevacizumab</td>
</tr>
<tr>
<td>Colorectal</td>
<td>FOLFOX (or variant) + bevacizumab, or FOLFIRI (or variant) + bevacizumab</td>
</tr>
<tr>
<td>Lung, non-small cell</td>
<td>Platinum-based doublet + bevacizumab</td>
</tr>
<tr>
<td>Ovary</td>
<td>Paclitaxel/carboplatin + bevacizumab</td>
</tr>
<tr>
<td>Pancreas</td>
<td>Gemcitabine/erlotinib</td>
</tr>
<tr>
<td>Prostate</td>
<td>Androgen ablation therapy</td>
</tr>
<tr>
<td>Renal</td>
<td>Sunitinib or bevacizumab ± interferon</td>
</tr>
<tr>
<td>Other diagnoses</td>
<td>Standard first-line treatment per guidelines</td>
</tr>
</tbody>
</table>

*Abbreviations: FOLFIRI, fluorouracil, leucovorin, and irinotecan; FOLFOX, infusional fluorouracil, leucovorin, and oxaliplatin.
*Bevacizumab was omitted from the treatment regimen for patients with contraindications.
Patients Enrolled
N= 289

Successful Assay
n= 252

Insufficient tissue for assay (n= 37)

Not a treatment candidate (n= 29)*
Received empiric CUP therapy (n= 29)**

Received site-specific therapy based on assay results
n= 194

Received site-specific therapy for less responsive tumor types
n= 79

Received site-specific therapy for more responsive tumor types
n= 115

* Declining performance status, brain metastasis, patient decision
**Unclassifiable result, physician chose to treat with CUP regimen, non-assay directed therapy

Tumor Classification Predicted by 92-gene RT-PCR Assay

- Molecular assay provided a primary site prediction in 98% of the cases
- 26 different tumor types predicted
  - Approximately 60% of patients had tumor types that are more likely to respond to site-directed chemotherapy (median survival >12 months)
  - 48% of identified tumors have indicated molecularly targeted therapies

Table 3. Tissue of Origin Predicted by Molecular Assay

<table>
<thead>
<tr>
<th>Predicted Tissue of Origin</th>
<th>No. of Patients (N = 282)</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biliary tract (gallbladder, bile ducts)</td>
<td>52</td>
<td>21</td>
</tr>
<tr>
<td>Urothelium</td>
<td>31</td>
<td>12</td>
</tr>
<tr>
<td>Colorectum</td>
<td>28</td>
<td>11</td>
</tr>
<tr>
<td>Non-small-cell lung</td>
<td>27</td>
<td>11</td>
</tr>
<tr>
<td>Pancreas</td>
<td>12</td>
<td>5</td>
</tr>
<tr>
<td>Breast</td>
<td>12</td>
<td>5</td>
</tr>
<tr>
<td>Ovary</td>
<td>11</td>
<td>4</td>
</tr>
<tr>
<td>Gastroesophageal</td>
<td>10</td>
<td>4</td>
</tr>
<tr>
<td>Kidney</td>
<td>9</td>
<td>4</td>
</tr>
<tr>
<td>Liver</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>Sarcoma</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Cervix</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Neuroendocrine</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Prostate</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Germ cell</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Skin, squamous</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Carcinoïd, intestine</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Mesothelioma</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Thyroid</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Endometrium</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Melanoma</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Skin, basal cell</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Lung, small cell</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Head and neck</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Adrenal</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>No prediction possible (unclassifiable)</td>
<td>5</td>
<td>2</td>
</tr>
</tbody>
</table>

Identification of Responsive Clinical Subsets

- Patients identified by the 92-gene RT-PCR assay to have responsive tumor types had a statistically significant increase in overall survival compared to those with less responsive tumor types (p=0.04)
- Provides evidence that when more effective therapies are available, this molecular assay has an even greater impact on patient outcome

Less Responsive Tumors*
- Biliary tract
- Pancreas
- Gastroesophageal
- Liver
- Sarcoma
- Cervix
- Carcinoid
- Endometrium
- Mesothelioma
- Melanoma
- Skin
- Thyroid
- Head and Neck
- Adrenal

Responsive Tumors**
- Colorectal
- NSCLC
- Urothelial
- Breast
- Ovary
- Kidney
- Prostate
- Germ cell
- Lymphoma
- SCLC
- Neuroendocrine

*Less Responsive (Median OS ≤12 mo with standard treatment)
**Responsive (Median OS ≥12 mo with standard treatment)
Assay Directed Treatment vs. Empiric Treatment Historical Control

• 37% increase in overall survival with assay-directed therapy

Summary

- First prospective trial in which molecular cancer classification has directed site-specific therapy.
- The molecular assay provided a primary site prediction in 98% of cases.
- Approximately 60% of patients were predicted to have responsive tumor types and as treatment options improve, molecular cancer classification may have an even greater impact on patient outcome.
- Even a correct diagnosis of a relatively unresponsive cancer type is now unlikely to provide much if any therapeutic benefit.
- In this study, there was a 37% increase in overall survival of the whole group receiving assay-directed therapy.
- Gene expression-based classification is recommended as part of the standard evaluation for selected patients with CUP.
CUP needs to be specifically diagnosed to offer the best therapy to patients

- Site of origin + Tumor subtype + Biomarker Profile =
  - Increasing ability to personalize cancer therapy with a combination of site-directed cytotoxic therapy and/or molecularly-targeted agents
**Future Studies**

- Future studies will concentrate on defining the genetic aberrations in CUP to explain the biology of these cancers and to test specific targeted drugs.
- For example, in this study:

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Molecular Biomarker</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>EGFR mutations, EGFR expression, ALK rearrangement, ALK mutations, KRAS mutations, ROS1 rearrangement, c-MET amplification, c-MET expression, RRM1 expression, ERCC1 expression, DDR2 mutations, BRAF mutation, PTEN deletion, PIK3CA mutations</td>
</tr>
<tr>
<td>Breast</td>
<td>HER-2 expression, HER-2 amplification, ER/PR, FGFR1 amplification, PTEN deletion, PIK3CA mutations</td>
</tr>
<tr>
<td>Colorectal</td>
<td>KRAS mutations, BRAF mutation, NRAS mutations, ERCC1 expression, PTEN deletion, PIK3CA mutations</td>
</tr>
<tr>
<td>Gastric</td>
<td>HER-2 expression, HER-2 amplification, c-MET amplification, ERCC1 expression, PTEN deletion, PIK3CA mutations</td>
</tr>
<tr>
<td>Melanoma</td>
<td>BRAF mutation, C-kit mutation</td>
</tr>
<tr>
<td>Basal cell carcinoma</td>
<td>SMO mutation</td>
</tr>
<tr>
<td>Medullary Thyroid</td>
<td>RET rearrangement</td>
</tr>
</tbody>
</table>
When should a molecular assay be ordered in CUP?

- Any patient without IHC patterns diagnostic of a single primary site or tissue of origin.
- In patients with small biopsy specimens when sufficient IHC evaluation will not be feasible (e.g., FNAs, pleural effusions, small needle biopsies).
- In patients with metastasis and a history of 1 or more previous cancers, when IHC is inconclusive.
- In patients with atypical presentation / clinical presentation does not match pathologic characterization.
- In any tumor that is very poorly differentiated and there is question of lineage and/or tissue of origin from IHC.
Impact of Molecular Cancer Classification in CUP

• The integration of a molecular assay into the evaluation of CUP patients complements appropriate IHC/clinical findings and leads to the diagnosis of the tissue of origin in the majority (90%+) of patients, even though the anatomical primary site remains undetectable.

• Site-specific therapy is critical to give many of these patients the best outcome possible.

• As therapy improves for solid tumors of many types these therapies may be administered to CUP patients provided their primary tumor sites or tissues of origin are recognized.
# Changing Clinical Landscape of CUP over the Decades

<table>
<thead>
<tr>
<th></th>
<th>CUP in 1976</th>
<th>CUP in 1996</th>
<th>CUP in 2013</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical Evaluation</strong></td>
<td>• Rudimentary</td>
<td>• CT scans</td>
<td>• Can be extensive</td>
</tr>
<tr>
<td></td>
<td>• CT not yet available</td>
<td>• Endoscopies</td>
<td>• CT, PET, MRI, endoscopy, ultrasound, etc</td>
</tr>
<tr>
<td><strong>Pathology</strong></td>
<td>• H&amp;E</td>
<td>• Limited IHC</td>
<td>• Evolving IHC, useful panels</td>
</tr>
<tr>
<td></td>
<td>• No IHC</td>
<td></td>
<td>• Molecular diagnosis very useful</td>
</tr>
<tr>
<td><strong>Favorable Subsets</strong></td>
<td>• NOT appreciated</td>
<td>• Multiple subsets appreciated with specific therapy (20% of all CUP)</td>
<td>• Specific IHC and molecular diagnosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Outcome improved with site-specific therapy</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td>• Symptomatic/supportive</td>
<td>• Treatment helpful in favorable subsets</td>
<td>• Site-specific therapy</td>
</tr>
<tr>
<td></td>
<td>• No effective therapies</td>
<td>• Empiric regimens</td>
<td>• Most CUP patients can have primary site diagnosed by molecular dx</td>
</tr>
<tr>
<td></td>
<td>• Empiric regimens</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Prognosis</strong></td>
<td>• Very poor</td>
<td>• Good for favorable subsets</td>
<td>• Improved with site-specific therapy based upon an accurate diagnosis of the primary site</td>
</tr>
<tr>
<td></td>
<td>• All patients lumped together</td>
<td>• Empiric regimens helpful for some tumors</td>
<td>• Poor for specific tumors with ineffective therapy</td>
</tr>
<tr>
<td></td>
<td>• Only a few known solid tumors had useful therapy</td>
<td></td>
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</tr>
</tbody>
</table>
Evaluation and Management of Possible CUP Patient

Clinical Presentation

Initial Clinical/Diagnostic Evaluation and Biopsy

Standard Pathology, Immunohistochemistry Stains

Anatomical Primary Site Not Identified

Favorable Subset CUP

Specific Treatment for Subset

Molecular profile Assay on Selected Tumors (When IHC not diagnostic of a single tissue of origin)

Single Tissue of Origin Diagnosed

Clinical Trial or Site Specific Therapy

Anatomical Primary Site Identified

Site Specific Therapy

Additional Directed Evaluation

Single Tissue of Origin Not Diagnosed

Clinical Trial or Empiric Therapy