Metastatic Carcinoma of Unknown Primary: A Diagnostic Dilemma

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Overview

- Definition
- Epidemiology
- Biology
- Diagnostic Work-up
  - Clinical
  - Radiology
  - Pathology
  - Specific Clinical Syndromes
- Treatment

Definition

- Metastatic Cancer of Unknown Primary
  - Biopsy confirmed malignancy
  - for which the site of origin cannot be identified by routine workup
- Primary lesion can be identified in only 30-80% of cases at autopsy
- Hypotheses
  - primary tumor has involuted and is not detectable
  - Malignant phenotype favors metastases over primary tumor growth

Epidemiology

- Accounts for 5-10% of cancer diagnoses
- Median survival of approximately 6-12 months despite therapy
- However, certain subgroups are potentially curable
- Factors relating to overall survival
  - age
  - sex
  - lymph node vs visceral mets

Biology

- Heterogeneous group of malignancies, but share common features
  - presence of early metastases
  - maybe useful model to understand early tumor invasion and distant spread
- 30% have 3 or more organs involved compared to only 15% of patients with known primary
- Unusual metastatic pattern involving kidneys, adrenal, skin and heart

Biology

- Aneuploidy
  - chromosome instability
  - found in 70-90% of tumors
  - usually implies worse prognosis
- Chromosomal Abnormalities
  - loss of short arm of chromosome 1
  - 13/30 patients studied
- Overexpress Oncogenes
  - c-myc
  - bcl-2
  - her 2 neu
- Inactivated tumor suppresser genes
  - p53
- Microvessel Density
  - marker of angiogenesis
  - worse survival

Clinical Work-Up

- Natural inclination is to perform extensive search for a primary
  - absence of primary generates anxiety
  - used to predicting tumor behavior and survival based on primary tumors
  - therapy usually based on primary tumor pathology
- Typical evaluation costs between $4500 and $18,000 per patient
- Total annual US costs roughly 1.5 billion dollars

H&P **** Important Step ****

History

- Complete ROS
- PMH
  - previous moles?
  - Biopsies?
- SH
  - smoking
  - asbestos
  - HIV
- FH -- clustering of cancers can lead to syndromes

- Physical
- Thorough skin evaluation
- Oral and nasal cavities
- Lymph nodes
- Breast
- Rectal
- Pelvic/Genital
- Prostate

Laboratory

- Basic CBC, CMP
- Recommended tumor markers
  - Men
    - PSA
    - *b*HCG
    - *a*FP
  - Women - none
- Other markers not recommended
  - poor sensitivity and specificity
  - all can be elevated in multiple tumor types

Radiology

- Recommended
  - CXR +/- Chest CT scan
  - Abdominal/Pelvic CT scan
  - Mammogram in women
- MD Anderson experience
  - Primary site identified in 20%
  - 1/3 of these based on unique histology
  - No difference in survival between patients in whom a primary site identified and those whose primary remained occult

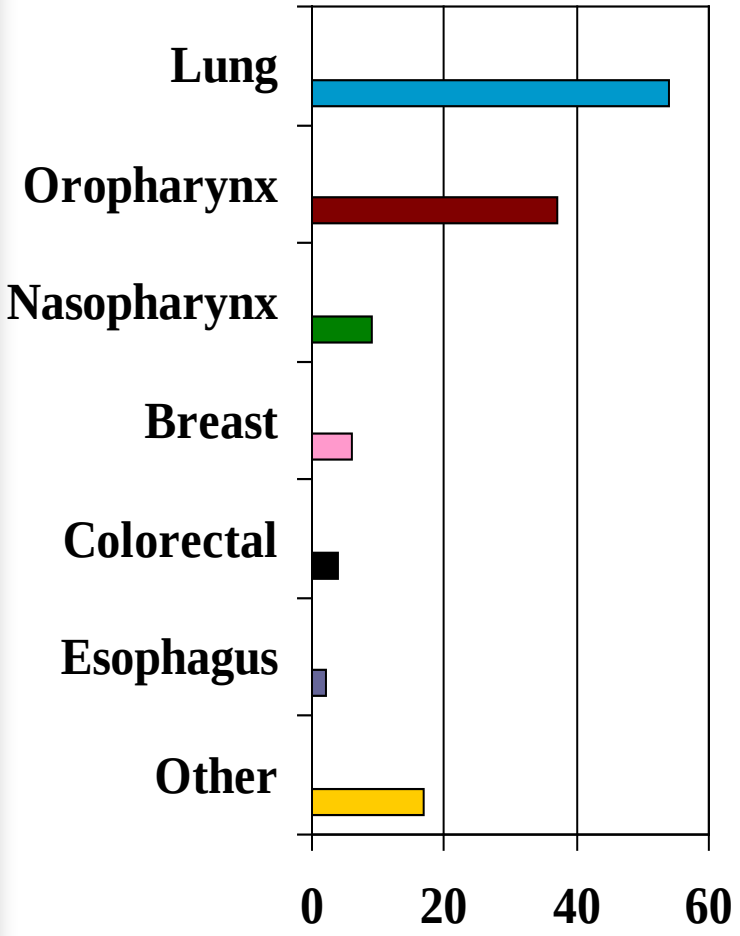
Pet Scans

- Positron Emission Tomography
  - Utilizes [18F] Fluorodeoxyglucose (FDG)
  - radio-isotope of glucose
  - Warburg effect -- neoplastic cells undergo accelerated glycolysis
  - FDG concentrates in neoplastic cells to localize tumors
- Theoretically could localize primary sites
- Limited studies available on this topic

PET

- Meta-analysis by Delgado-Bolton, et al published in The Journal of Nuclear Medicine 2003; 44:1301-1314
- 15 studies selected evaluating 302 patients
- Identified primary tumor site in 129 patients
- Sensitivity -- 0.87 (0.81-0.92)
- Specificity -- 0.71 (0.64-0.78)
- General use hindered by
  - lack of prospective studies
  - cost-effectiveness hasn't been assessed

Primary sites



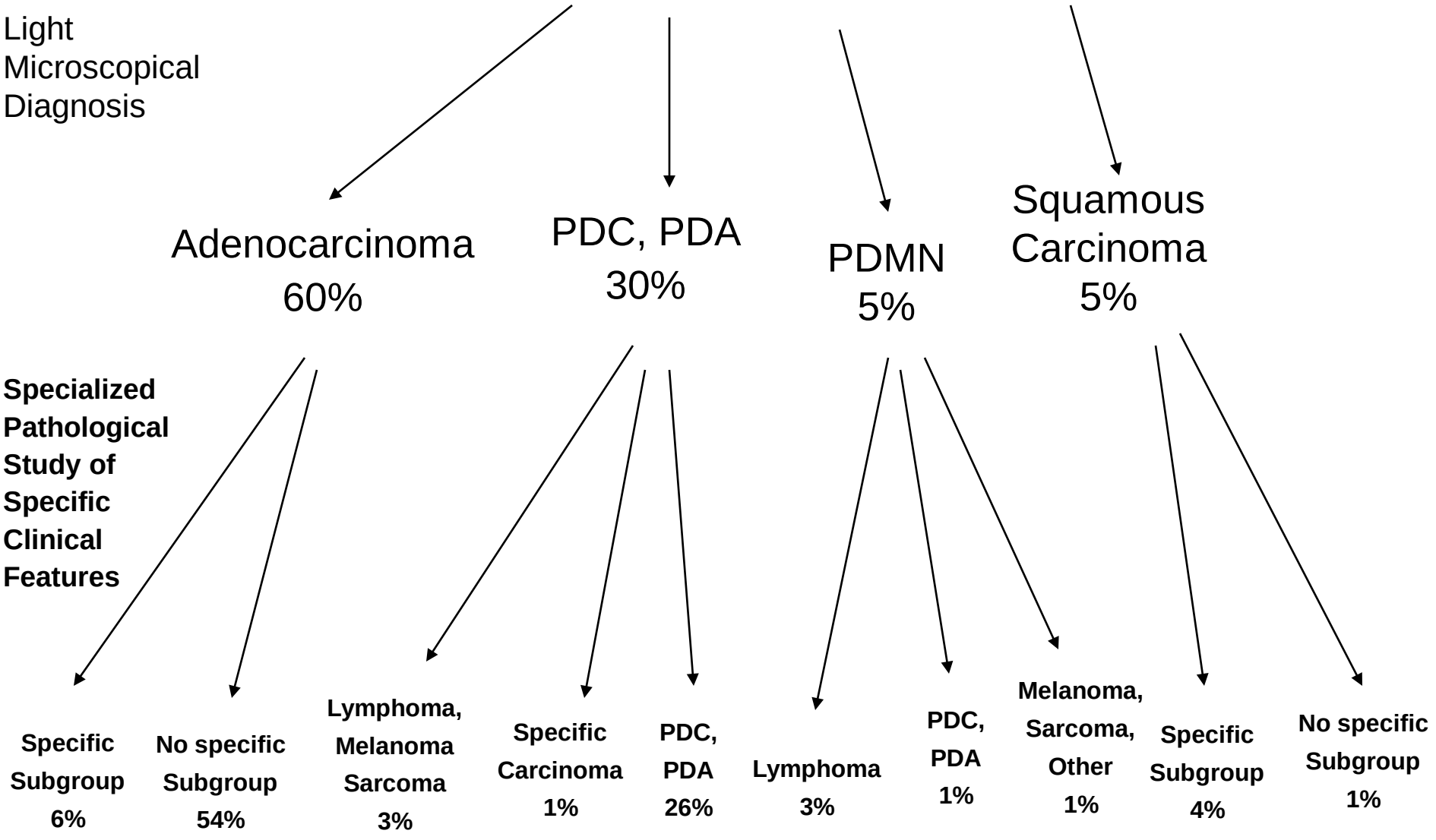
Localization of Tumor

Localization	Patients	
	Number	%
Cervical nodes	199	66
Axillary nodes	9	3
Other lymph nodes	6	2
Bone	11	3.6
Brain	42	14
Lung	6	2
Hepatic	4	1
Skin	5	1
Other	11	4
Several metastases	5	1
Total Number	298	

Pathology

- Heterogeneous collection of tumor types
- Includes
  - Carcinomas
  - Poorly differentiated malignancies
- Sophisticated pathologic evaluation
  - Identify certain histologies
  - Allow appropriate therapy
- Techniques
  - Light microscopy
  - Immunohistochemical staining
  - Electron microscopy
  - Molecular genetics

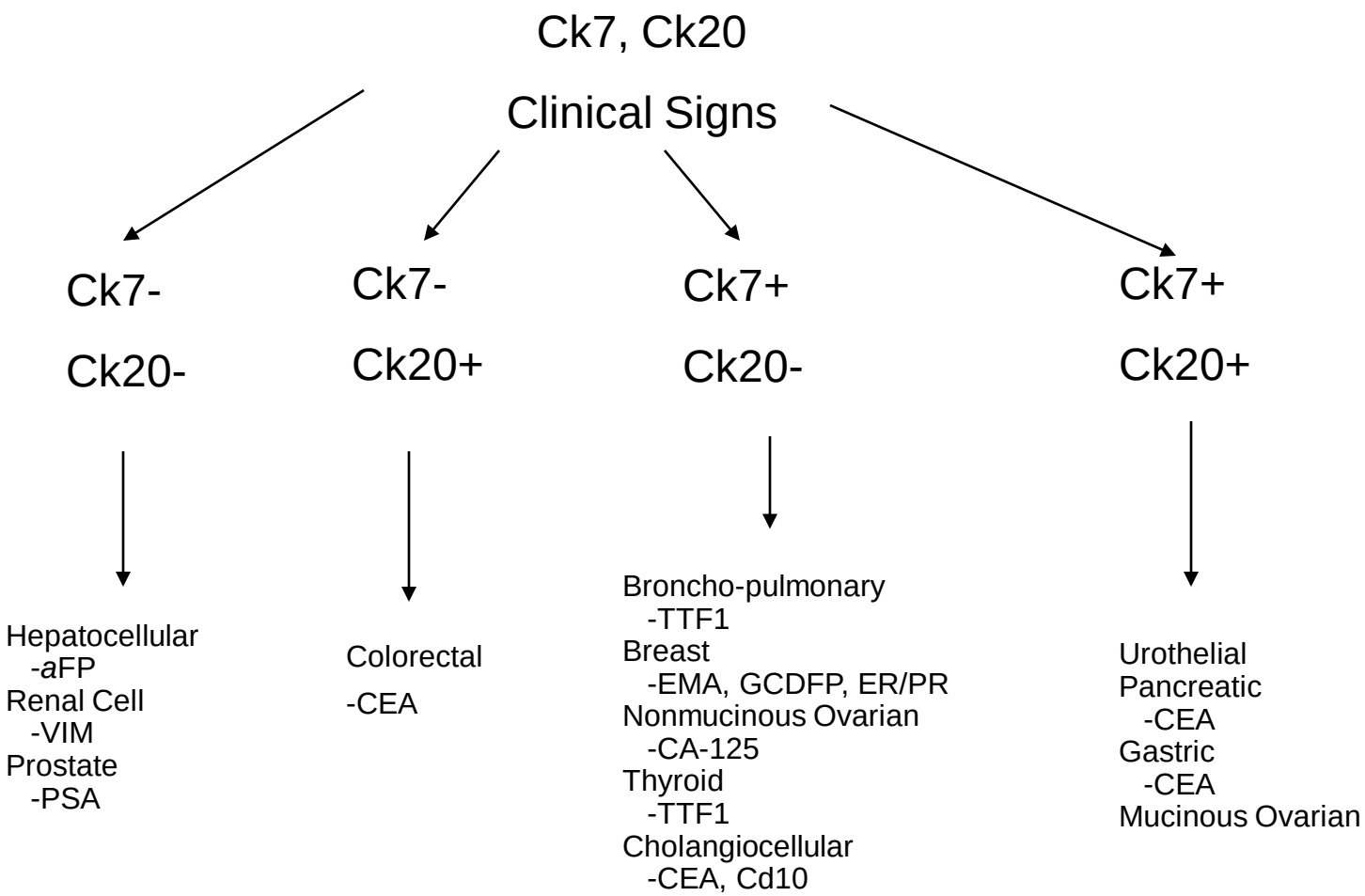
Cancer of an Unknown Primary



Immunohistochemistry

- Epithelial origin
  - cytokeratins
- Melanoma
  - PS100
  - HMB45
- Germ Cell Tumor
  - *a*FP
  - *b*HCG
  - PLAP
- Neuroendocrine
  - Chromogranin
  - synaptophysin
- Lymphoma
  - Cd45
  - Cd10
  - Cd3
- Thyroid
  - Thyroglobulin
- Prostate
  - PSA
- Sarcoma
  - AML
  - CD31
  - CD34

Adenocarcinoma



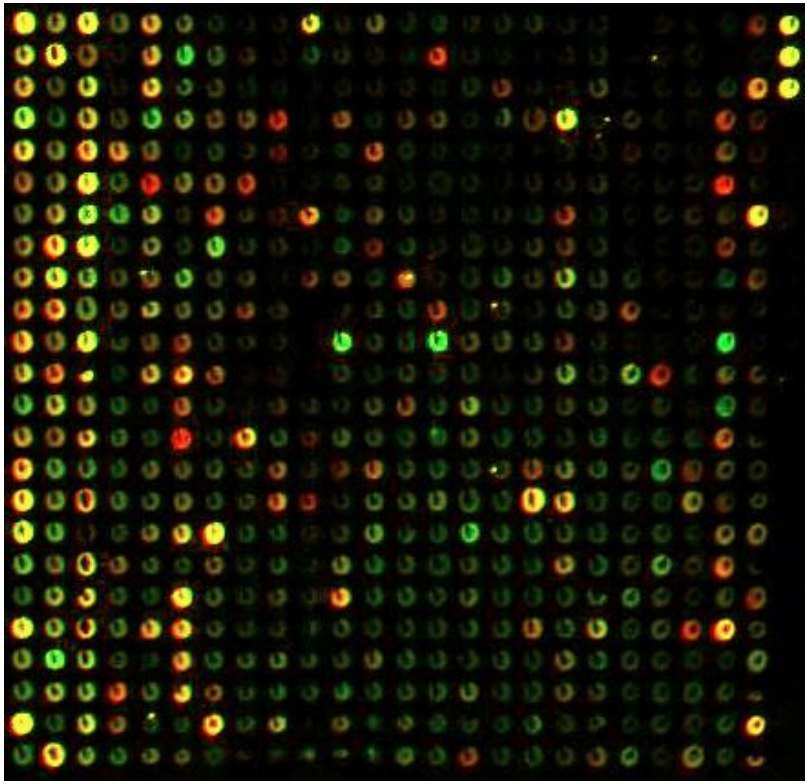
Molecular Genetics

- Chromosomal evaluation
- Well documented usefulness in hematologic malignancies
- Techniques
  - Classical
  - Southern blot
  - FISH
  - PCR

Tumor	Abnormality
Rhabdomyosarcoma	t(2/13)
Ewing's sarcoma	t(11;22)
Germ cell	i(12)p
Small –cell lung	del(3)
Neuroblastoma	del(1)
Uterine leiomyoma	t(12;14)
Retinoblastoma	del(11)

Microarray

- Uses cDNA technology
- Allows thousands of genes to be analyzed simultaneously
- Provides organ specific genetic profile
- Two investigators have correctly identified both
  - Primary site
  - Metastatic disease origin



Specific Clinical Syndromes

- After complete pathologic review evaluating
  - Treatable diagnoses such as lymphoma
  - Found primary sites
- Clinical syndromes can be identified
- Important to recognize these syndromes
- Can be potentially treatable or even curable
- Based on
  - Histology of tumor
  - Location
  - Gender

Peritoneal Carcinomatosis in Women

- Adenocarcinoma
  - Malignant ascites
  - Extensive peritoneal involvement
- Most characteristic of ovarian cancer
  - Used to be classified as MCUP
  - Now classified as ovarian
- Cell of origin unclear
  - Germinal epithelium of ovary and mesothelium of the peritoneum have the same embryologic origin
  - Retains multipotentiality

Peritoneal Carcinomatosis

- Histology is a serous carcinoma
- Ovarian primary not detectable
  - Can occur in women s/p oophorectomy
  - Small deposits of tumor can be seen on ovary surfaces
- Some women have BRCA 1 mutations
- Treatment similar to ovarian cancer
  - Surgical debulking
  - Followed by systemic chemotherapy
- Survival
  - Similar to ovarian cancer at equivalent stage
  - Median survival 11-24 months
  - Five-year survival of 15-20%

Metastatic Carcinoma in Axillary Lymph Nodes in Women

- Unilateral axillary lymph nodes
- Most suggestive of breast primary
- Careful breast evaluation
  - Breast exam
  - Mammogram
    - Detects primary in 25-50%
  - Ultrasound
  - MRI
    - One small study primary identified in 86% of 22 cases

Axillary Lymph Nodes -- Treatment

- Treated like node positive breast primary
- If breast primary not found on imaging
  - Local treatment is controversial
  - Historically mastectomy was done
    - Careful pathologic review failed to reveal a breast tumor in 33-47% of cases
  - Breast conservation therapy evaluated to limited extent
    - Axillary node dissection + breast radiation
    - Survival and local recurrence rates similar
- Chemotherapy
  - Treated like node positive breast tumors
  - No prospective studies validate this approach
- Hormonal therapy if ER+/PR+
- Prognosis based on number of positive nodes

Squamous Cell Cancer in Cervical Lymph Nodes

- Presentation accounts for 1-2% of all head and neck malignancies
- Lung and esophagus can present in similar fashion
  - Lymph nodes usually in low neck
- Work-up
  - CT of head and neck
  - Panendoscopy – laryngoscopy, bronchoscopy, and esophagoscopy
  - Also included blind biopsies of common primary sites
  - Ipsilateral tonsillectomy can harbor occult primary in 10-25% of cases
- Primary site still not identified in 2/3 of cases

Cervical Lymph Nodes -- Treatment

- Typical approach
  - Neck dissection
  - Followed by radiation therapy
- Controversy exists
  - Either treatment modality alone
  - Extent of radiation
    - Bilateral neck and total mucosal has high morbidity
    - Localized radiation to ipsilateral neck alone
    - Retrospective studies suggest more aggressive approach improves local control and survival
- Prognosis depends on extent on lymph node involvement
  - Long term local control 50-75% of patients
  - Five-year survival 40-60%

Squamous Cell Cancer in Inguinal Lymph Nodes

- Likely primary sites
  - Anus
  - Cervix, vulva or vagina in women
  - Lower extremities
- Work-up
  - Lower extremity exam
  - Anoscopy
  - Genital/pelvic exam
- Treatment if no primary found
  - Surgery +/- radiation therapy
  - Long term survival of 25%

Men with Possible Prostate Cancer

- Older men
- Predominant bony metastases – blastic
- Work-up
  - Serum PSA
  - IHC of tumor for PSA
- Treatment
  - Hormonal therapy
  - Some advocate even in setting of negative PSA in men with osteoblastic bone metastases

Neuroendocrine Carcinoma

- Heterogeneous Group
- Three identifiable subsets based on histology
  - Typical carcinoid or pancreatic islet cell tumors
  - Small cell carcinoma
  - Poorly differentiated carcinoma that has neuroendocrine features identified only by electron microscopy or IHC

Typical carcinoid

- Often have metastatic disease to the liver
- May or may not have clinical evidence of hormone production
- Typically indolent tumors and progress slowly
- Treatment
  - Chemotherapy has limited efficacy
  - Surgery if isolated metastases
  - Octreotide useful for symptomatic hormone production

Small Cell

- Natural history similar to lung primary
- Treated with platinum based chemotherapy
- Rare long term survival can be achieved
- Isolated metastasis have been reported
  - Only case reports published
  - Recommended treatment is similar to limited stage small cell
    - Radiation
    - chemotherapy

Poorly Differentiated Neuroendocrine Carcinoma

- One series published by Hainsworth, et al
- Represented a particularly chemosensitive group of patients
- Reported response rate to platinum based chemotherapy of over 60%
- Long term survival of 10%

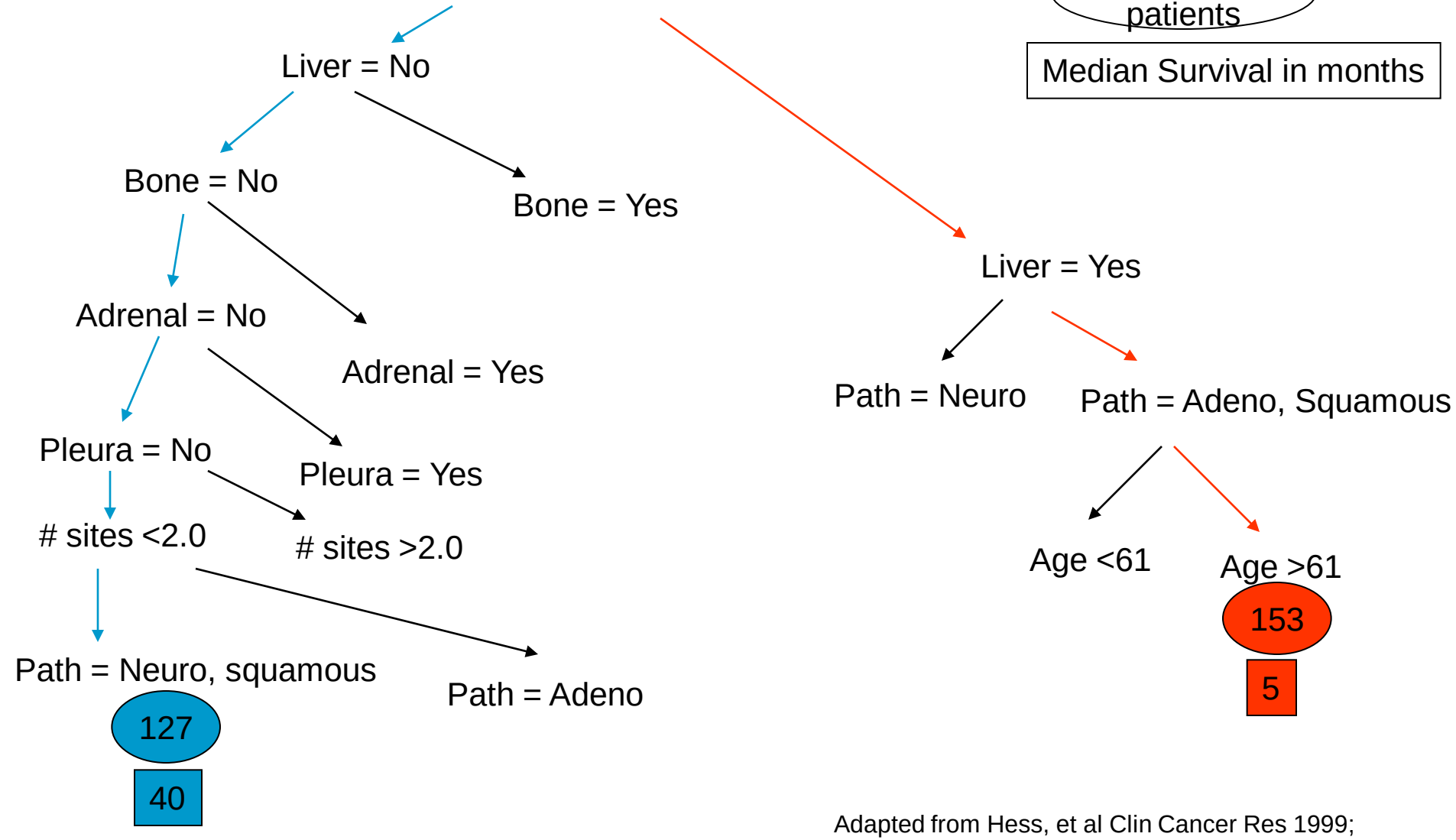
Extragonadal Germ Cell Tumor

- Clinical presentation consistent with metastatic germ cell tumor but lack definitive histology
  - Men <50
  - Midline tumors (retroperitoneum, mediastinum) and/or pulmonary nodules
  - Duration of symptoms short or rapid tumor growth
  - Elevated *a*FP, *b*HCG
- (i)12p on molecular genetics
- Usually respond well to platinum based chemotherapy
  - Survival similar to primary germ cell tumor based on tumor markers and location of disease

Prognosis of MCUP

- Prognosis
  - Median survival 6-12 months
  - 5-10% survival at 5 years
- Poor prognostic factors
  - Male gender
  - Liver mets
  - Increasing number of organs involved
  - Performance status

Regression Tree Analysis



Adapted from Hess, et al Clin Cancer Res 1999; 5:3403-10

Treatment

- Historically combination chemotherapy used
  - 5fu, cisplatin, adriamycin or mitomycin
  - Response rates 0-40%
  - Median survival 3-8 months
- Recent combinations included taxanes
  - Carboplatin, paclitaxel and oral etoposide
  - Hainsworth et al reported
    - Response rate of 47%
    - Median survival of 13 months
  - Other trials not as impressive results

Newer agents

- Gemcitabine and Docetaxel combination
  - Cisplatin refractory disease
  - Response rate 28%
  - Median survival 8 months
- Molecular agents
  - Herceptin for Her-2-*neu* positive disease
  - VEGF inhibitors
  - EGFR inhibitors
  - Proteosome inhibitors

Conclusions

- MCUP is a common heterogeneous disease
- Work-up
  - History and Physical
  - Limited radiographs
- Pathology
  - Light microscopy
  - IHC
  - Specialized techniques
- Identify specific clinical syndromes
- Treatment can be given