Primeri Bilinmeyen Kanserler

Dr. Deniz Tural

Primeri Bilinmeyen Kanserler

- PBC: Primer odağı tespit edilemeyen biyopsi ile tanı konan metastatik kanser

- ❑ Anamnez
- ❑ Fizik Muayene
- ❑ Laboratuvar
- ❑ Radyolojik değerlendirme
- ❑ Histolojik inceleme

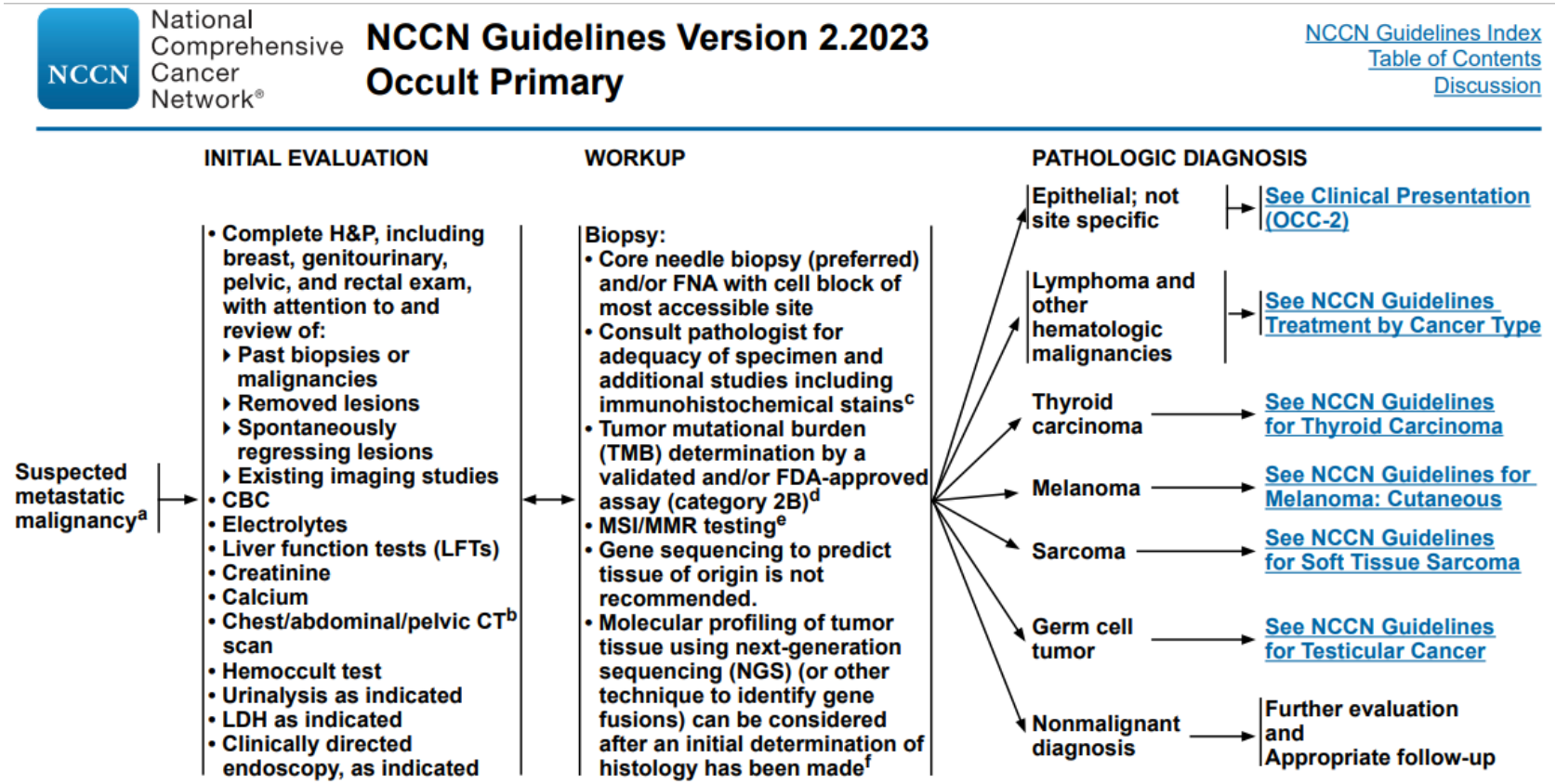
Pavlidis N, Pentheroudakis G. Cancer of unknown primary site. Lancet. 2012;1428-35.

Primeri Bilinmeyen Kanserler

- **Tüm kanserlerin % 3–5'i PBK**
- **USA 7–12/100000, Avustralya 18–19/100000, Hollanda 5–7/100000, İsveç 4–6 /100000**
- **En sık görülen Sekizinci –dokuzuncu sıklıkta ki kanserlerdir**
- **Ölüme sebebiyet veren dördüncü sıklıkta ki kanserlerdir**
- **Erkek cinsiyet , kadın cinsiyete göre hafif dominant**
- **Ortalama tanı yaşı 65**

Pavlidis N, Pentheroudakis G. Cancer of unknown primary site. Lancet. 2012;1428-35.

Primeri Bilinmeyen Kanserlere Yaklaşım



[a] For many patients the apparent uncertainties surrounding the diagnosis of an unknown primary cancer may result in significant psychosocial distress and increased difficulty in accepting treatment options. Empathetic discussion about the natural history of these types of cancer and their prognosis, and the provision of support and counseling both by the primary oncology team and specialized services may help to alleviate this distress. See NCCN Guidelines for Distress Management.

[b] CT/MRI should be performed with IV contrast unless contraindicated. PET/CT is an alternative in patients with a contraindication to contrast enhancement.

[c] See Immunohistochemistry Markers for Unknown Primary Cancers (OCC-A).

[d] Merino DM, et al. J Immunother Cancer 2020;8:e000147.

[e] The population of patients with microsatellite instability-high/mismatch repair-deficient (MSI-H/dMMR) occult primary tumors is low. Use immunohistochemisty (IHC) for MMR or polymerase chain reaction (PCR) for MSI, which are different assays measuring the same biological effect.

[f] Consider tumor/somatic molecular profiling for patients who are candidates for anti-cancer therapy to identifiy uncommon mutations (ie, *RET* fusions). Testing on tumor tissue is preferred; however, cell-free DNA testing can be considered if tumor tissue testing is not feasible.

Primeri Bilinmeyen Kanserlere Yaklaşım

TABLE 1: Immunohistochemical studies useful in the differential diagnosis of carcinoma vs another neoplasm

	Immunoperoxidase stains			
Tumor type	**Pan-keratin**	**CD45 and other markers**	**S-100 protein**	**Vimentin**
Carcinoma	+	–	–	–/+
Malignant lymphoma	–	+	–	–/+
Malignant melanoma	–	–	+	+
Sarcoma	–	–	–	+

Primeri Bilinmeyen Kanserlere Yaklaşım

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2023
Occult Primary

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POTENTIAL IMMUNOHISTOCHEMISTRY MARKERS FOR UNKNOWN PRIMARY CANCERS
Undifferentiated Panel: For Determining Most Likely Cell Lineage[3]

Markers*	Most Likely Cell Lineage
Pan-keratin (AE1/AE3 & CAM5.2)	Carcinoma
CK5/6, p63/p40	Squamous cell carcinoma
S100, SOX10	Melanoma
LCA± CD20± CD3±	Lymphoma
OCT3/4± SALL4±	Germ cell tumor
WT1, calretinin, mesothelin, D2-40	Mesothelial tumor

*These markers are not uniformly specific or sensitive and can be present on other tumors.

Primeri Bilinmeyen Kanserlere Yaklaşım

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COMMONLY USED IMMUNOHISTOCHEMISTRY MARKERS FOR UNKNOWN PRIMARY CANCERS[3]

Tumor Site or Type	Cytokeratin 7 (CK7) and Cytokeratin 20 (CK20)	Other Positive Markers	Other Useful Markers
Adrenocortical carcinoma	CK7-/CK20-	SF-1 Melan A Inhibin	
Breast carcinoma	CK7+/CK20-	GATA3 GCDFP-15 (BRST2)± Mammaglobin±	ER/PR±
Endocervical adenocarcinoma	CK7+/CK20-	p16+ (strong diffuse staining) PAX8±	Vimentin- ER/PR± Human papillomavirus in situ hybridization
Endometrial adenocarcinoma	CK7+/CK20-	Vimentin PAX8	ER/PR± p16- (to distinguish from endocervical and uterine serous carcinoma)
Hepatocellular carcinoma	CK7±/CK20± usually CK7-/CK20-	Arginase-1 HepPar-1 Glypican-3 CD10 and polyclonal CEA± (peri-canalicular pattern)	MOC31- (to distinguish from intrahepatic cholangiocarcinoma) Albumin in situ hybridization - (also for intrahepatic cholangiocarcinoma)
Lower gastrointestinal carcinoma, including small intestinal, appendiceal, and colorectal	CK7±/CK20+	CDX2 Villin SATB2	

Primeri Bilinmeyen Kanserlere Yaklaşım

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POTENTIAL IMMUNOHISTOCHEMISTRY MARKERS FOR UNKNOWN PRIMARY CANCERS

Immunohistochemistry markers for unknown primary cancers are provided as a resource to assist in localizing a primary but are not uniformly specific or sensitive. Avoid a large series of immunohistochemistry markers. Communication with the pathologist is essential to workup.

TUMOR-SPECIFIC MARKERS AND THEIR STAINING PATTERN[1,2]

Marker	Tumor	Staining Pattern
Arginase-1	Hepatocellular	Nuclear/cytoplasmic
Calretinin	Mesothelioma, sex cord–stromal, adrenocortical	Nuclear/cytoplasmic
CDX2	Colorectal, other gastrointestinal, pancreaticobiliary tract	Nuclear
D2-40	Mesothelioma, lymphatic endothelial cell marker	Membranous
EBV	Nasopharynx	Nuclear
ER/PR	Breast, ovary, endometrium	Nuclear
GATA3	Breast, urinary bladder, salivary gland	Nuclear
GCDFP-15	Breast	Cytoplasmic
Glypican-3	Hepatocellular	Cytoplasmic
HepPar-1	Hepatocellular	Cytoplasmic
HPV	Cervix, vulva, vagina, penis, anal, oropharynx	Nuclear (DNA ISH); nuclear/cytoplasmic (RNA ISH)
Inhibin	Sex cord–stromal, adrenocortical	Cytoplasmic
Mammaglobin	Breast	Cytoplasmic
Melan-A	Adrenocortical, melanoma	Nuclear
Napsin A	Lung	Cytoplasmic
NKX3-1	Prostate	Nuclear
P16	Cervix, vulva, vagina, penis, anal, oropharynx	Nuclear/cytoplasmic (if positive, perform HPV ISH)
PAP	Prostate	Membranous
PAX8	Thyroid, renal, ovary, endometrium, cervix, thymus	Nuclear
PSA	Prostate	Cytoplasmic
RCC marker	Renal	Membranous
SF-1	Adrenocortical, sex–cord stromal	Nuclear
SATB2	Colorectal, other gastrointestinal tract	Nuclear
Thyroglobulin	Thyroid	Cytoplasmic
TTF-1	Lung, thyroid	Nuclear
Uroplakin III	Urothelial	Membranous
Villin	Gastrointestinal (epithelia with brush border)	Apical
WT1	Ovarian serous, mesothelioma, Wilms	Nuclear

[1] ER/PR, estrogen receptor/progesterone receptor; GCDFP-15, gross cystic disease fluid protein 15; HepPar-1, hepatocyte paraffin 1; RCC, renal cell carcinoma; PAP, prostatic acid phosphatase; PSA, prostate-specific antigen; SF-1, steroidogenic factor-1; TTF-1, thyroid transcription factor 1. Reprinted from Bahrami A, Truong LD, Ro JY. Undifferentiated tumor: true identity by immunohistochemistry. Arch Pathol Lab Med 2008;132:326-348 with permission from Archives of Pathology & Laboratory Medicine. Copyright 2008 College of American Pathologists.

[2] Per physician discretion, TRK protein testing can be considered as part of broad immunohistochemistry testing (a positive test should then be confirmed with NGS). Drilon A, Laetsch TW, Kummar S, et al. Efficacy of larotrectinib in TRK fusion-positive cancers in adults and children. N Engl J Med 2018;378:731-739; Doebele RC, Drilon A, Paz-Ares L, et al. Entrectinib in patients with advanced or metastatic NTRK fusion-positive solid tumours: integrated analysis of three phase 1-2 trials. Lancet Oncol 2020;21:271-282.

Cancer. 2007 Jan 15;109(2):292-9.

The role of 2-deoxy-2-[F-18]fluoro-D-glucose positron emission tomography in disseminated carcinoma of unknown primary site.

Sève P, Billotey C, Broussolle C, Dumontet C, Mackey JR.

Department of Internal Medicine, Hôtel Dieu, Hospices Civils de Lyon, Lyon, France. pascal.seve@chu-lyon.fr

Abstract

BACKGROUND: The authors conducted a comprehensive review of the efficacy of 2-deoxy-2-[F-18]fluoro-D-glucose positron emission tomography (FDG-PET) in the detection of primary tumors in patients with disseminated carcinoma of unknown primary site.

METHODS: Ten studies (involving a total of 221 patients) tat were published between 1998 and 2006 were reviewed. Each study evaluated the role of FDG-PET in the detection of unknown primary tumors after a conventional diagnostic workup. Although 94% of patients had a single site of metastases, the studies otherwise were very heterogeneous in the studied population, study design, and additional diagnostic workup.

RESULTS: In 41% of patients, FDG-PET detected primary tumors that were not apparent after conventional workup. In this group of patients, the overall sensitivity, specificity, and accuracy rates of FDG-PET in detecting unknown primary tumors were 91.9%, 81.9%, and 80.5%, respectively. FDG-PET imaging also led to the detection of previously unrecognized metastases in 37% of patients. Lung cancers represented 59% of the detected tumors. FDG-PET had a notably high false-positive rate (58.3%) in tumors of the lower digestive tract. FDG-PET altered the clinical management in 34.7% of patients. Most of those patients (53%) received specific chemotherapy for lung and pancreatic cancers; whereas 12% received specific therapy for breast, ovarian, and prostate cancers; and 14% underwent surgery with curative intent.

CONCLUSIONS: FDG-PET was an efficient method for detecting primary tumors that were undetected by other modalities and was sensitive for the detection of previously unrecognized metastases. FDG-PET significantly changed clinical management in approximately one-third of the patients studied.

Radiol Med. 2006 Dec;111(8):1146-55. Epub 2006 Dec 20.

18F-FDG PET/CT in the assessment of carcinoma of unknown primary origin.

[Article in English, Italian]

Ambrosini V, Nanni C, Rubello D, Moretti A, Battista G, Castellucci P, Farsad M, Rampin L, Fiorentini G, Franchi R, Canini R, Fanti S.

Unità Operativa di Medicina Nucleare, Padiglione 30, Policlinico S. Orsola-Malpighi, Via Massarenti 9, I-40138, Bologna, Italy.

Abstract

PURPOSE: Metastatic cancers of unknown primary origin are characterised by a poor prognosis, with a survival rate from diagnosis of approximately 12 months. Conventional radiological imaging allows detection of 20%-27% of primary cancers, whereas the detection rate with positron emission tomography (PET) is 24%-40%. The aim of this study was to assess the role of 18F-fluorodeoxyglucose (FDG) PET/computed tomography (CT) in the identification of occult primary cancers.

MATERIALS AND METHODS: The study population consisted of 38 consecutive patients with histologically proven metastatic disease and negative or nonconclusive conventional diagnostic procedures. All patients were studied by 18F-FDG PET performed according to the standard procedure (6 h of fasting, intravenous injection of 370 MBq 18F-FDG, and image acquisition with a PET/CT scanner for 4 min per bed position).

RESULTS: 18F-FDG-PET/CT detected the occult primary cancer in 20 cases (53%), showing higher sensitivity than that reported for any other imaging modality, including PET.

CONCLUSIONS: The encouraging results, if validated by larger series, support the use of PET/CT in patients with carcinoma of unknown primary origin and negative conventional imaging results.

Serum Tümör Belirteçleri

- **PBK'de; CEA, CA-125, CA19-9, aFP, ßHCG yüksekliğinin tek başına tanısal ,prognostik, predictive değeri yoktur[1]**
- **Orta hat kötü diferansiye karsinomlar da aFP,ßHCG yüksekliği[2]**
- **Kemik metastastazı erkek hastada PSA yüksekliği[2]**
- **Primer seröz peritoneal adeno kanserlerde CA-125 yüksekliği[2]**
- **İzloe aksiler adeno kanser kadın hastada CA 15-3 yüksekliği[2]**

Pavlidis N, Briasoulis E, Hainsworth J, Greco FA. Diagnostic and therapeutic management of cancer of an unknown primary. *Eur J Cancer* 2003; 39: 1990–2005[1].

Pentheroudakis G. Pavlidis N. Serum tumor markers. In Wick MR, ed. Metastatic carcinomas of unknown origin. New York, NY: Demos Medical Publishing, 2008: 165–75[2].

PBK'de; Kolonoskopi, Bronkoskopi

- **Kolon benzeri histolojiye sahip metastazlarda(CK20+/CK7-)**
- **Semptomatik hastada**
- **Malign asitli hastalarda kolon obstrüksiyonu ile ilişkili semptom yok, gaitada gizli kan testi negatif ise tanısal değer %5<**
- **TTF-1 positive hastada bronkoskopi düşünülebilinir**

Pavlidis N, Pentheroudakis G. Cancer of unknown primary site. Lancet. 2012;1428-35.

Primeri Bilinmeyen Kanserlere Yaklaşım

J Clin Oncol. 2011 Feb 1;29(4):435-40. Epub 2010 Dec 28.

Familial risks in cancer of unknown primary: tracking the primary sites.

Hemminki K, Ji J, Sundquist J, Shu X.

German Cancer Research Centre, Heidelberg, Germany.

Abstract

PURPOSE: Cancer of unknown primary (CUP) is diagnosed at the metastatic stage, and despite extensive diagnostic work-up, the primary tumor often remains unidentified. No data are available on familial clustering of CUP. We hypothesize that familial clustering of CUP with other cancers may be informative of the primary sites.

PATIENTS AND METHODS: A total of 35,168 patients with CUP were identified in the Swedish Family-Cancer Database, and risks between family members were calculated for concordant (CUP-CUP) and discordant (CUP-any other cancer) cancers using standardized incidence ratio (SIR).

RESULTS: Familial cases of CUP accounted for 2.8% of all CUP cases in the offspring generation. Familial SIR for CUP was 1.69 when a sibling was diagnosed with CUP. As to discordant associations between siblings, CUP was associated with lung (SIR, 1.87), kidney (SIR, 1.82), liver (SIR, 1.67), ovarian (SIR, 1.45), colorectal (SIR, 1.26), and breast (SIR, 1.15) cancers and melanoma (SIR, 1.26). Upper aerodigestive tract, bladder, pancreatic, and prostate cancers were additionally associated with CUP. Notably, CUP was associated with families of kidney, lung, and colorectal cancers.

CONCLUSION: The present data show that CUP is not a disease of random metastatic cancers but, instead, a disease of a defined set of cancers. The association of CUP with families of kidney, lung, and colorectal cancers suggests a marked genetic basis and shared metastatic mechanisms by many cancer types. Familial sites shared by CUP generally match those arising in tissue-of-origin determinations and, hence, suggest sites of origin for CUP. Mechanistic exploration of CUP may provide insight into defense against primary tumors and the metastatic process.

Primeri Bilinmeyen Kanserlere Yaklaşım

- Swedish Family–Cancer Databese

  PBC'in % 2.8 ailesel geçiş (Birinci derece)

- Ayrıca aile öyküsünde Akciğer, böbrek, kolorektal kanser olanlarla ilişkili

Patoloji

- Ras
- HER-2
- *P53*
- *BCL-2*

  p53 ; %53 +, BCL-2; %40 +
- *Çocuk ve erişkin erken dönemlerinde, orta hat PBK*

  Kromosal translokasion t(15-19)

  BRD4-NUT oncogeni +

van de Wouw AJ, Jansen RL, Speel EJ, Hillen HF. The unknown biology of the unknown primary tumour: a literature review. Ann Oncol. 2003 ;14:191-6.

Pavlidis N, Fizazi K. Cancer of unknown primary (CUP). Crit Rev Oncol Hematol. 2005 ;54:243-50.

Greco FA, Hainsworth JD. Cancer of unknown primary site. In: DeVita VT, Lawrence TS, Rosenberg SA, eds. *DeVita, Hellman, and Rosenberg's Cancer: Principles and Practice of Oncology*. 8th ed. Philadelphia, Pa: Lippincott Williams & Wilkins; 2008:2363-2387.

HİSTOPATOLOJİ, IŞIK MİKROSKOPİ (H+E)

İYYİ DİFERANSİYE ADENO CA; %60

KÖTÜ DİFERANSİYE KARSİNOM, ADENOKARSİNOM; % 29

SKUAMÖZ HÜCRELİ KARSİNOM; % 5

İNDİFERANSİYE KARSİNOM %5

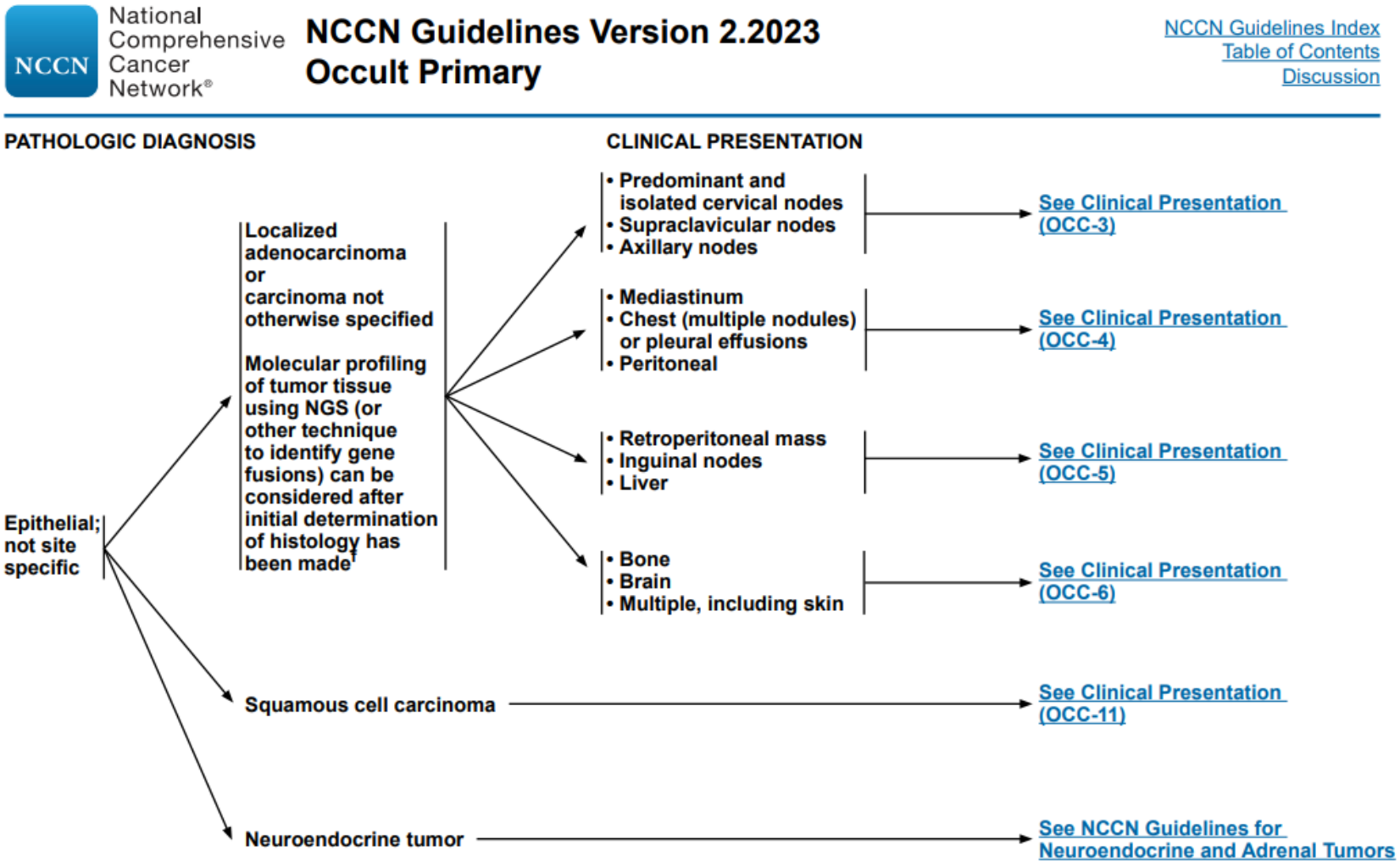
NEUROENDOKRİNE KARSİNOM;%1

TANA ANINDA PRİMERİ BİLİNMEYEN KANSERLERİN % 30'DA PRİMER TESPİT EDİLEBİLİNMEKTEDİR.

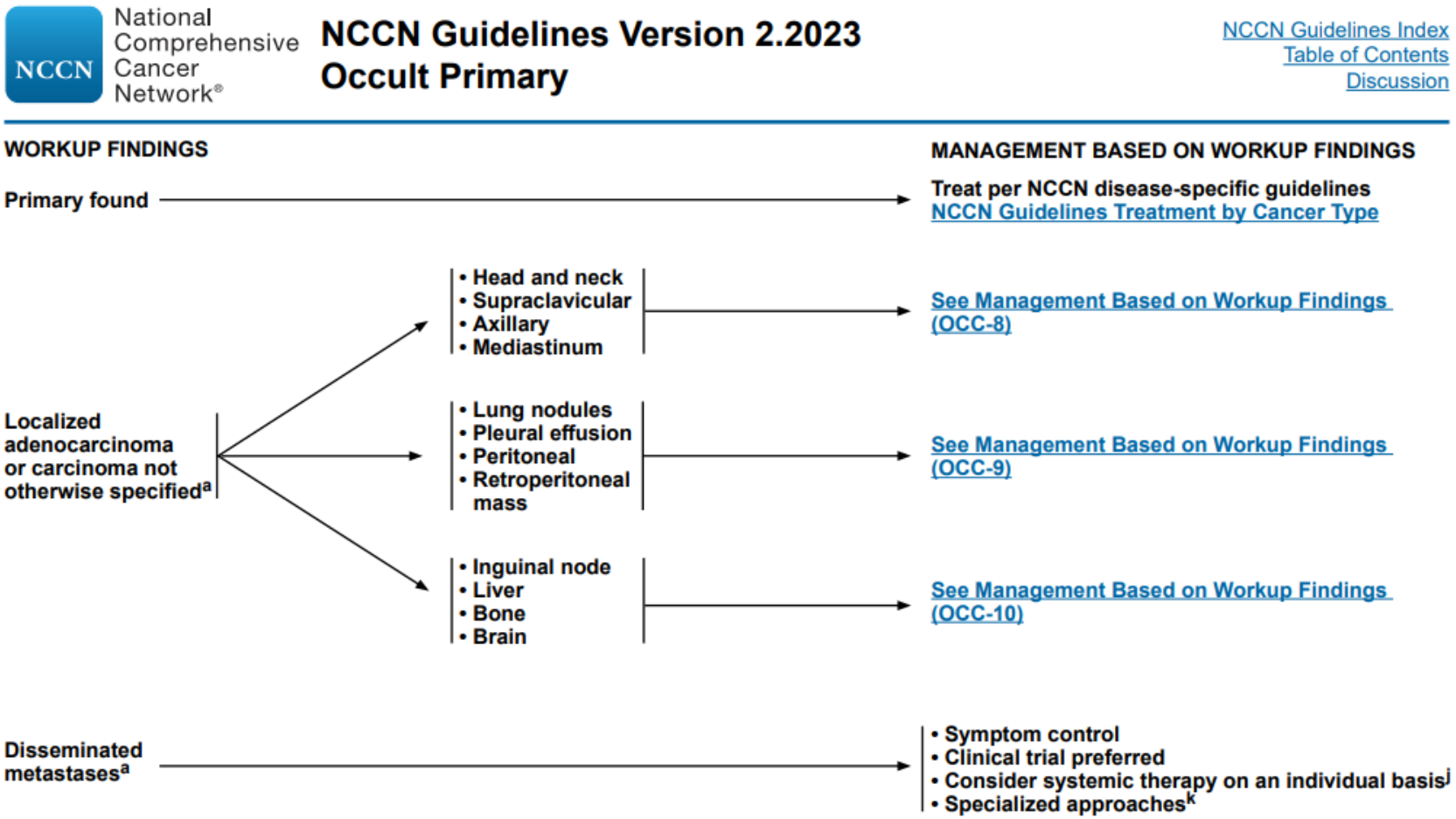
POSTMORTEM OTOPSİ YAPILANLARDA %25-30 PRİMER TESSPİT EDİLEMEMEKTEDİR.

PAVLİDİS N, PENTHEROUDAKİS G. CANCER OF UNKNOWN PRIMARY SITE. LANCET. 2012;1428-35.

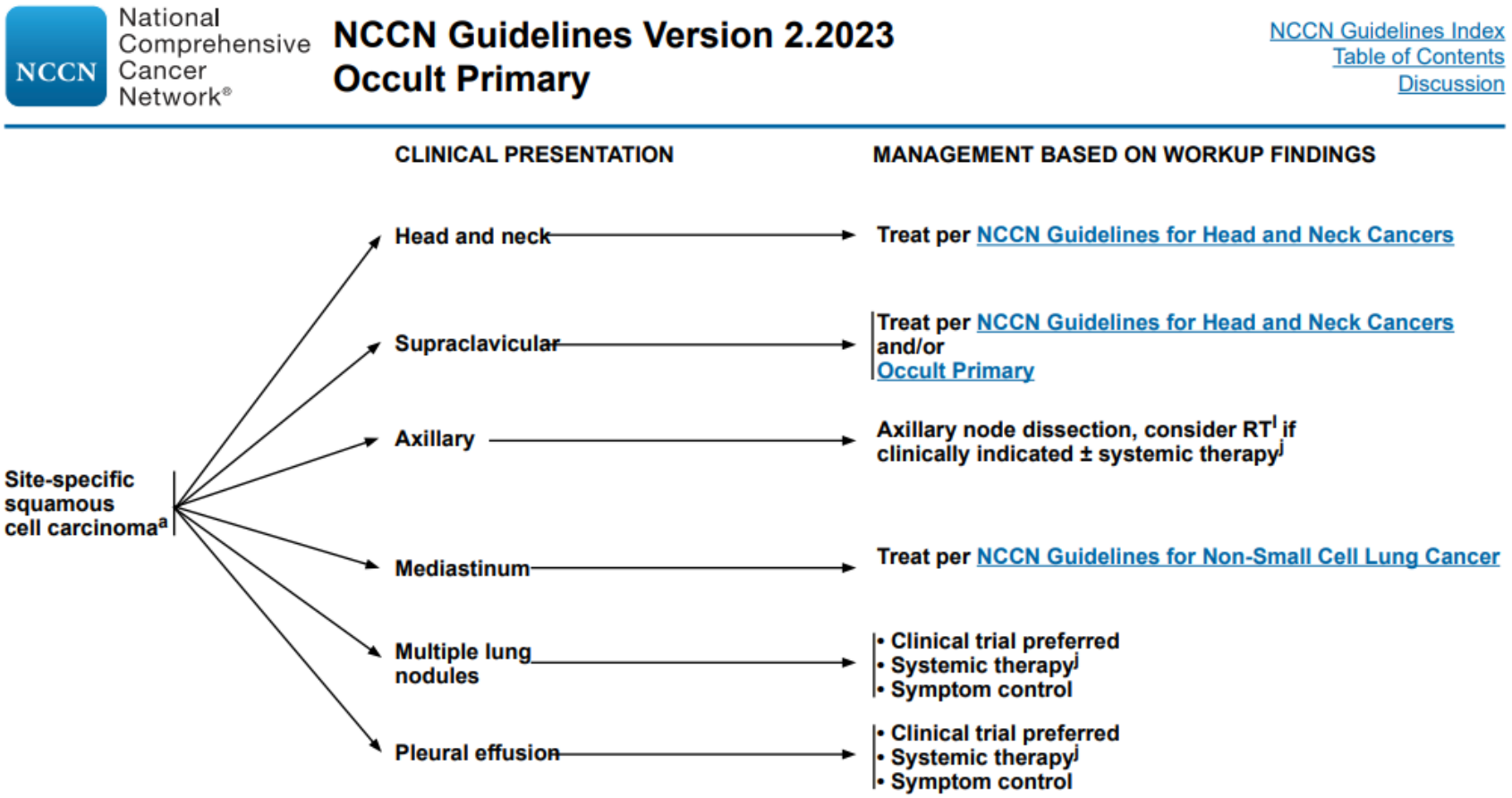
Primeri Bilinmeyen Kanserlere Yaklaşım



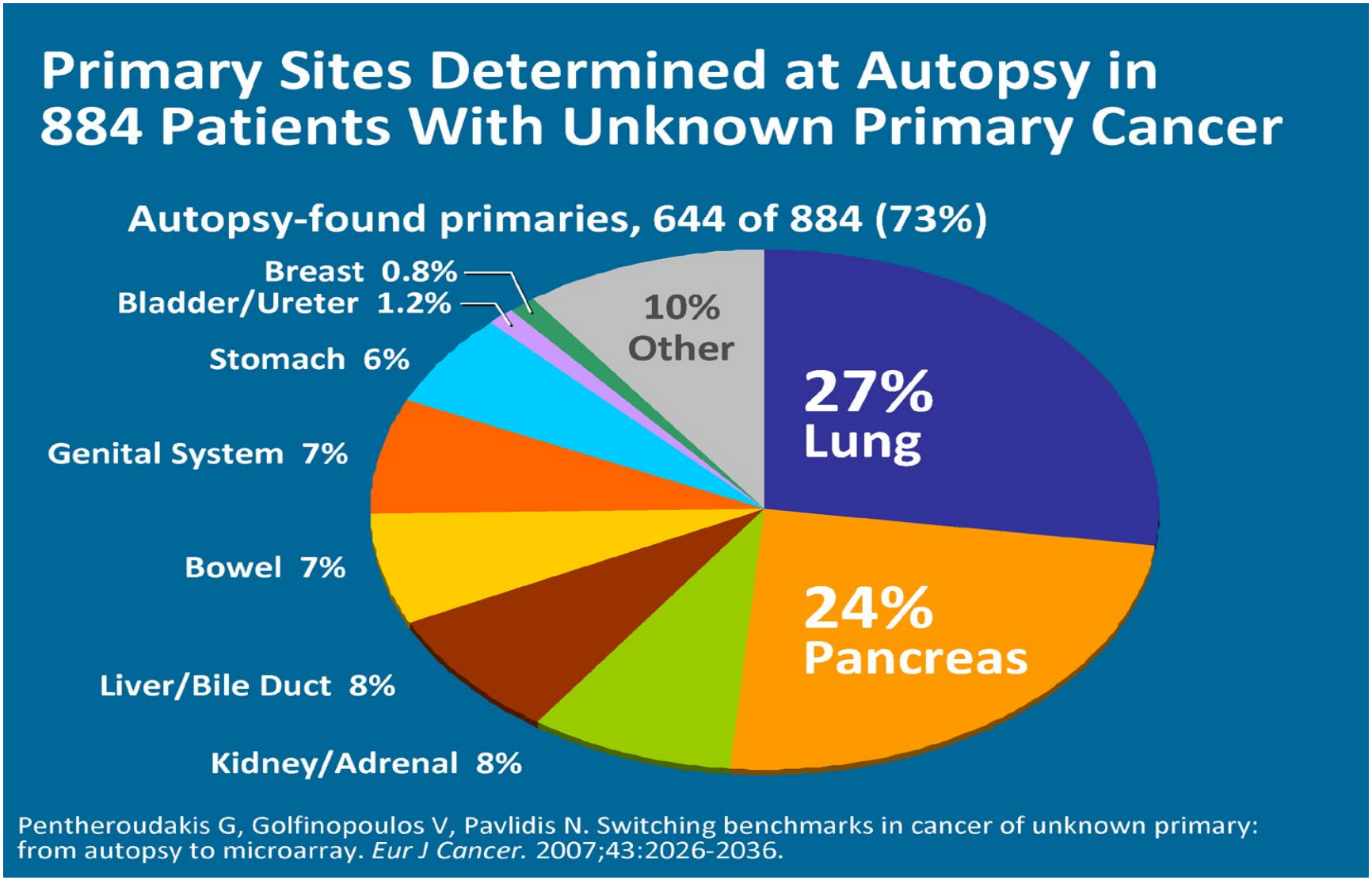
Primeri Bilinmeyen Kanserlere Yaklaşım



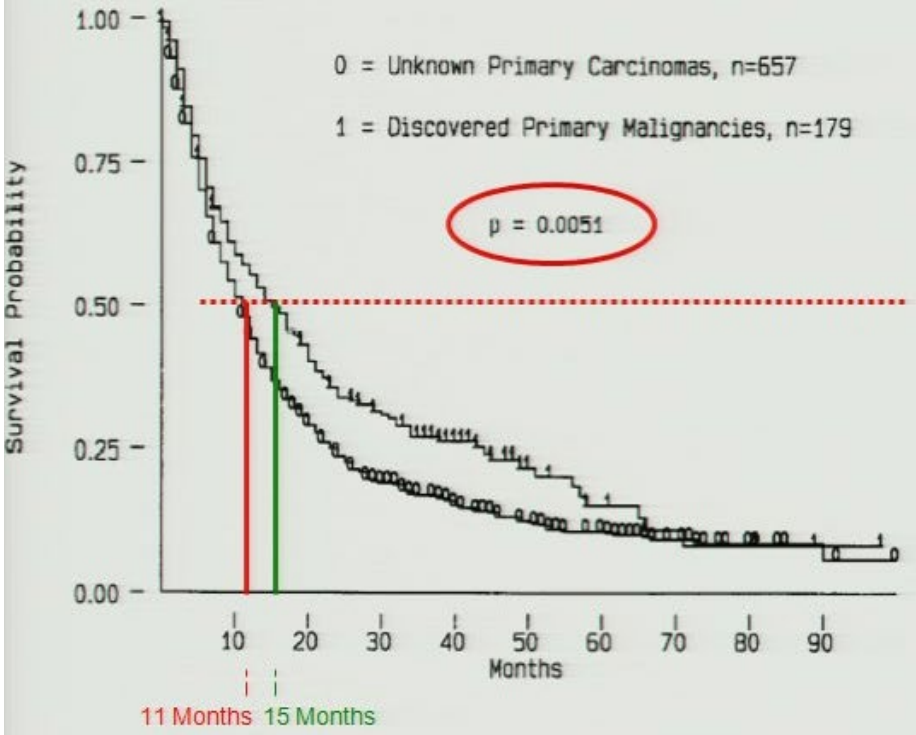
Primeri Bilinmeyen Kanserlere Yaklaşım



USA ve Avrupa 1944–2000 ,12 post-mortem çalışma



PBK tanıya ulaşmanın sağkalıma faydası?

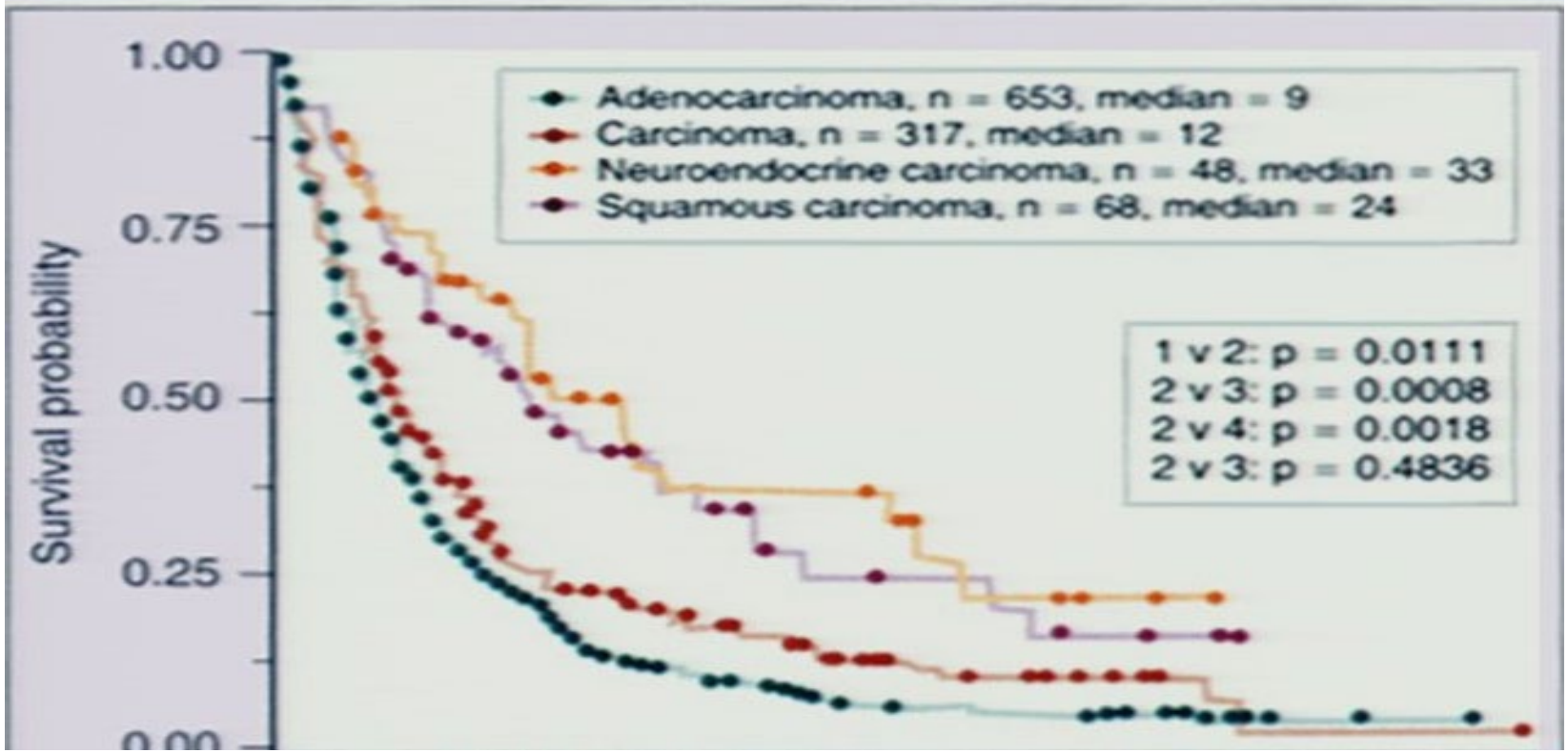


Tedaviye iyi CEVAP veren kanserler[2]:

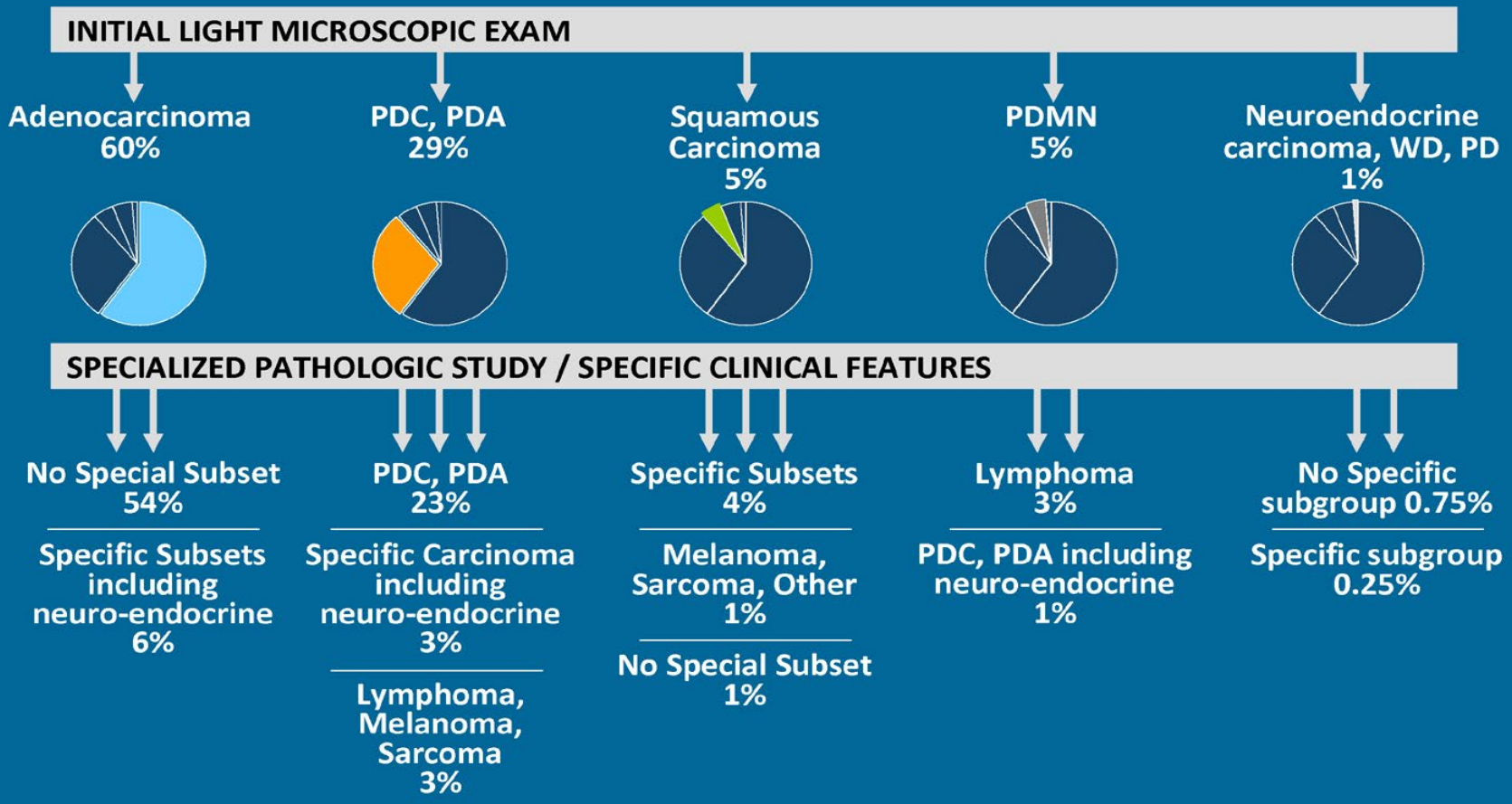
- Germ hücreli kanserler
- Over kanseri
- Meme kanseri
- Lenfomalar
- Nöroendokrin kanserler
- Prostat kanseri

[1] *Abbruzzese et al, JCO, Vol 13, No 8, 1995*
[2] Pavlidis et al, Eur. J. Cancer, 39, 1990-2005, 2003

Histolojiye göre prognoz
n=1109



Cancer, Unknown Primary Site



Greco FA, Hainsworth JD. Cancer of unknown primary site. In: DeVita VT Jr, Hellman S, Rosenberg SA, eds. *Cancer: Principles and Practice of Oncology*. 8th ed. Philadelphia: Lippincott; 2008:2363-2387.

Prognoz ve Tedaviye yanıt

- **İyi prognostik gurup ;%20**
- **Kötü prognostik grup;%80**

Non-papiler maling karekterde asit

Multiple akciğer ve plevra metastazı

Karaciğer /diğer organ metastazı gösteren adenokarsinom

Multiple serebla metastaz

Multiple litik kemik metaztazı

Abdominal kaviteye metastaz yapan SCC

Pavlidis N, Pentheroudakis G. Cancer of unknown primary site. Lancet. 2012;1428-35.

Greco FA, Hainsworth JD. Cancer of unknown primary site. In: DeVita VT, Lawrence TS, Rosenberg SA, eds. *DeVita, Hellman, and Rosenberg's Cancer: Principles and Practice of Oncology*. 8th ed. Philadelphia, Pa: Lippincott Williams & Wilkins; 2008:2363-2387.

İyi prognostik grup

- İzole aksiler lenf nodu metastazı olan kadın
- Papiler seröz adenokarsinomlu asiti olan kadın hasta
- Servikal lenf nodlarında SCC metastazı
- İzole ingunal lenf nodlarında SCC metastazı
- Kemik metastazı erkek, yüksek serum PSA veya dokuda PSA +

İyi prognostik grup

- Orta hat az diferansiye karsinom
- Az diferansiye NET
- Rezektable soliter metastazlar
- Kolon profilinde metastatik karsinom(CK20+,CK7 – CDX2+)

Pavlidis N, Pentheroudakis G. Cancer of unknown primary site. Lancet. 2012;1428-35.

Panel 2: Prognostic classification of patients with CUP

Favourable subset

- Women with papillary adenocarcinoma of the peritoneal cavity
- Women with adenocarcinoma involving the axillary lymph nodes
- Poorly differentiated carcinoma with midline distribution
- Poorly differentiated neuroendocrine carcinoma
- Squamous-cell carcinoma involving cervical lymph nodes
- Adenocarcinoma with a colon-cancer profile (CK20+, CK7–, CDX2+)
- Men with blastic bone metastases and elevated prostate-specific antigen (adenocarcinoma)
- Isolated inguinal adenopathy (squamous carcinoma)
- Patients with one small, potentially resectable tumour

Unfavourable subset

- Adenocarcinoma metastatic to the liver or other organs
- Non-papillary malignant ascites (adenocarcinoma)
- Multiple cerebral metastases (adenocarcinoma or squamous carcinoma)
- Several lung or pleural metastases (adenocarcinoma)
- Multiple metastatic lytic bone disease (adenocarcinoma)
- Squamous-cell carcinoma of the abdominopelvic cavity

Pavlidis N, Pentheroudakis G. Cancer of unknown primary site. Lancet. 2012;1428-35.

İzole Aksiler Lenf Nodu Metastazı Olan Kadın

- Evre II meme kanserine benzer biyolojik ve tedaviye yanıt özelikleri gösterir
- Tüm kanserlerin 0.12%–0.67%
- Tanı yaşı ortalama 52
- %66 post menopoz

1-Pavlidis N, Fizazi K. Cancer of unknown primary. Crit Rev Oncol Hematol 2009; 69: 271–80.

2- Pavlidis N, Briasoulis E, Hainsworth J, Greco FA. Diagnostic and therapeutic management of cancer of an unknown primary. Eur J Cancer 2003; 39: 1990–2005. Pentheroudakis G, Lazaridis G, Pavlidis N.

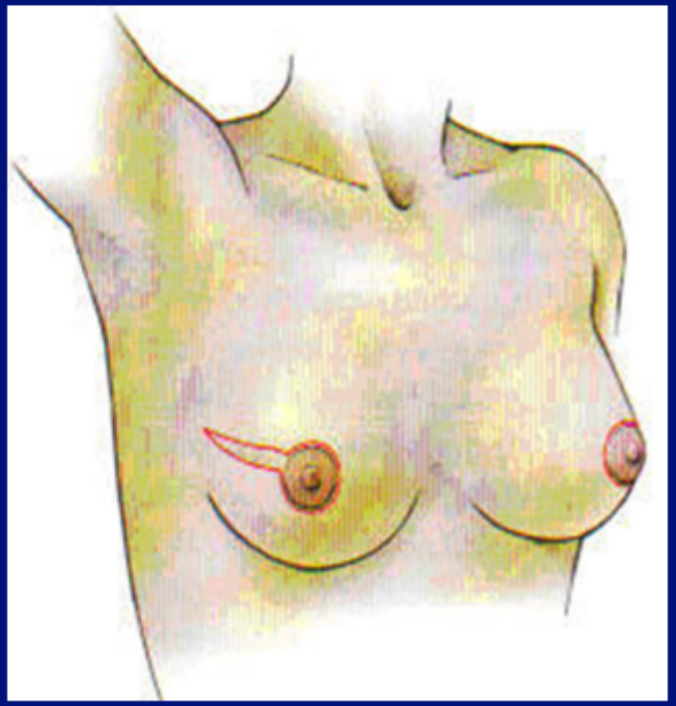
3-Axillary nodal metastases from carcinoma of unknown primary (CUPAX): a systematic review of published evidence. Breast Cancer Res Treat 2010; 119: 1–11.

İzole Aksiler Lenf Nodu Metastazı Olan Kadın

Aksillanın tedavi

Feigenberg aksiller Rt ile rekurens oranı % 50

Lokal kontrol için ALND tavsiye



Feigenberg Z, Zer M, DintsmanM(1976) Axillary metastases from an unknown primary source. Israel. J Med Sci 12:1153–1158

Tedavi

- **Tüm hastalarda Aksiler diseksiyon**
- **Standart Yaklaşım MRM**
- **Hasta isteğine bağlı Olarak tüm meme ışınlaması düşünülebilir**
- **Karşılaştırmalı çalışma yoktur.**

İzole Aksiler Lenf Nodu Metastazı Olan Kadın

Hasta LN+ meme kanseri gibi tedavi edilir

Prognoz meme kanserine benzerdir

Mobil LN varlığında mastektomi+LN diseksiyonu+adjuvant meme kanser tedavisi

Fixe LN varlığında neoadjuvan kemoterapi uygundur

İzole Aksiler Lenf Nodu Metastazı Olan Kadın

Ann Surg Oncol. 2005 Dec;12(12):1045-53. Epub 2005 Oct 25.

Utility of breast magnetic resonance imaging in patients with occult primary breast cancer.

Buchanan CL, Morris EA, Dorn PL, Borgen PI, Van Zee KJ.

Department of Surgery, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10021, USA.

Abstract

BACKGROUND: Although carcinoma presenting as axillary metastases is assumed to be due to breast cancer, identification of the primary lesion may prove problematic. We investigated the ability of breast magnetic resonance imaging (MRI) to identify the primary tumor, thereby confirming the diagnosis and broadening treatment options.

METHODS: From 1995 to 2001, 69 patients at our institution presented with occult primary breast cancer. All patients had negative breast examinations and mammograms and underwent breast MRI.

RESULTS: Of 69 patients, 55 had axillary adenopathy without evidence of distant disease (stage II); 14 had stage IV disease. In patients with stage II disease, MRI revealed suspicious lesions in 76% (42 of 55). In 62% (26 of 42), the MRI finding proved to be the occult primary tumor. Of these, 58% (15 of 26) were candidates for breast conservation. MRI did not identify the primary tumor in 25 women; 12 underwent mastectomy. Cancer was found in 33% (4 of 12) of these. Thirteen patients were treated with primary breast irradiation; three were lost to follow-up, one developed distant disease, and nine were without evidence of disease with a median follow-up of 4.5 years. In women with stage IV disease, MRI identified the primary tumor in 5 of 9 patients with regional adenopathy and 2 of 5 patients with distant disease (overall 50%; 7 of 14). MRI identified the primary tumor in women with both mammographically dense (19 of 44; 43%) and less dense (10 of 20; 50%) breasts.

CONCLUSIONS: Breast MRI detects mammographically occult cancer in half of women with axillary metastases, regardless of breast density. MRI is a powerful tool for stage II and stage IV patients with occult primary breast cancer.

PMID: 16244803 [PubMed - indexed for MEDLINE]

İzole Aksiler Lenf Nodu Metastazı Olan Kadın

Breast Cancer Res Treat. 2010 Jan;119(1):1-11.

Axillary nodal metastases from carcinoma of unknown primary (CUPAx): a systematic review of published evidence.

Pentheroudakis G, Lazaridis G, Pavlidis N.

Department of Medical Oncology, Ioannina University Hospital, Ioannina, Greece. gpenther@otenet.gr

Abstract

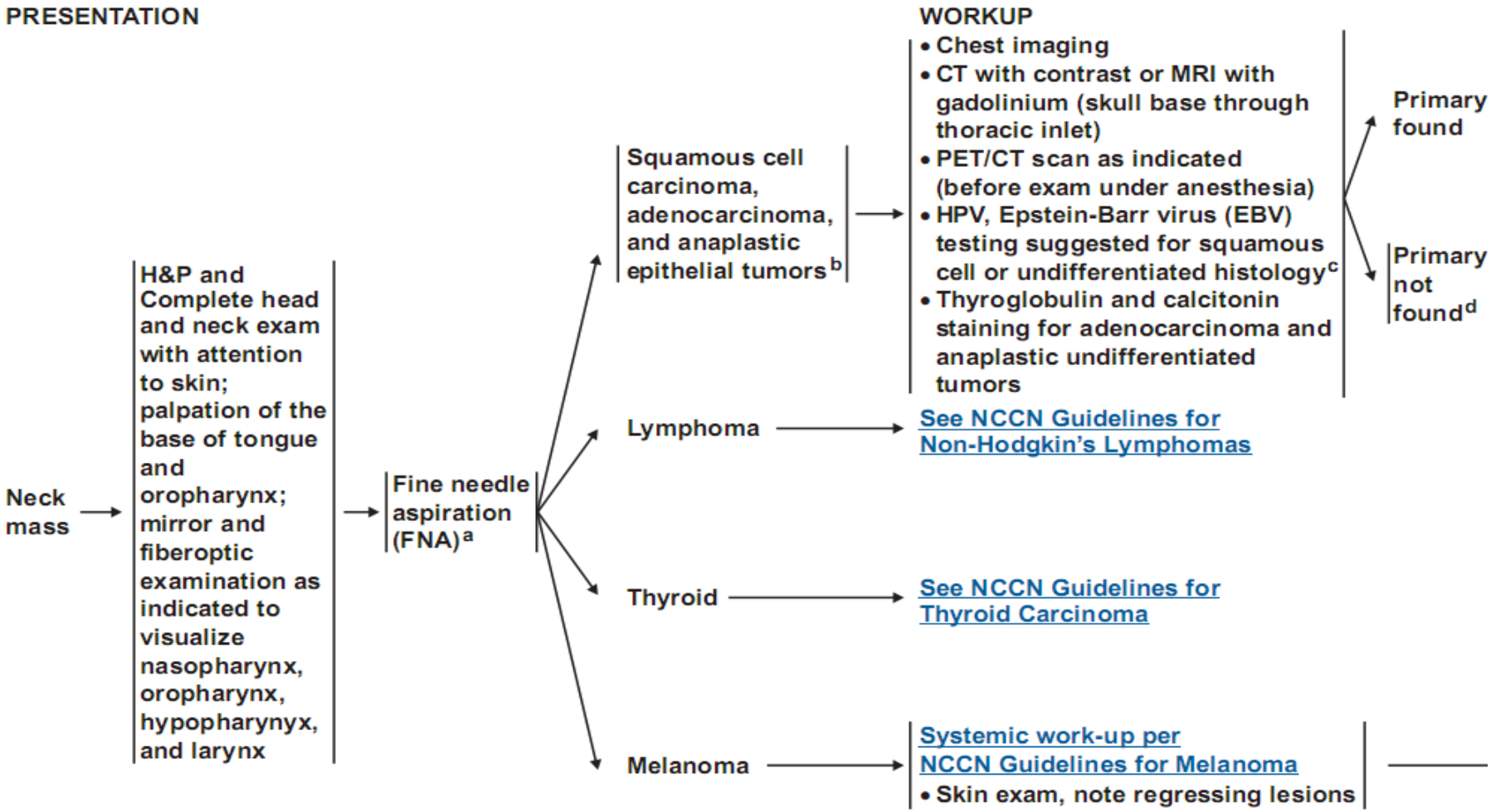
Axillary lymph node metastases from adeno carcinoma or poorly differentiated carcinoma of unknown primary (CUPAx) represent a rare clinical entity without consensus on its biology, management and outcome. We systematically reviewed published CUPAx series and identified 24 retrospective studies enrolling 689 patients from 1975 till 2006. CUPAx affected women at a mean age of 52 years, 66% of whom post-menopausal harbouring low-volume (N1, 48%) or high-volume (52%) nodal disease from ductal adenocarcinoma (83%). Among a total of 446 patients managed with mastectomy, a small breast primary was identified histologically in 321 (72% of cases). Hormone receptor protein expression was observed in 40-50% of cases, while HER2 overexpression in 31%. CUPAx patients were managed with axillary lymph node dissection coupled to mastectomy (59%), primary breast irradiation (26%) or observation (15%). Observation was associated with high locoregional relapse rates (42%) and risk of metastatic spread. Mastectomy or radiotherapy provided locoregional disease control in 75-85% of cases, while adjuvant systemic therapy was associated with a nonsignificant trend for improved survival in few series. Five-year survival ranged from 59.4 to 88% at a median follow-up of 62 months (mean 5-year survival 72%), with axillary tumour burden being the pivotal prognostic factor. CUPAx is associated with similar presentation, biology and outcome to resected node-positive overt breast cancer and should be treated accordingly.

Papiler seröz adenokarsinom asiti olan kadın hasta

- Evre III Over ca benzer prognoz ve tedaviye yanıt özelikleri
- Debulking cerrahi sonrası kemoterapi
- Bulky hastalığı olanda neoadjuvan sonrası kemoterapi

Hainsworth JD, Fizazi K.Treatment for patients with unknown primary cancer and favorable prognostic factors. Semin Oncol. 2009 ;36:44-51.

Servikal lenf nodlarında Skuamöz hc Karsinom



Servikal lenf nodlarında Skuamöz hc Karsinom

Figure 1

Anatomic sites and subsites of the head and neck

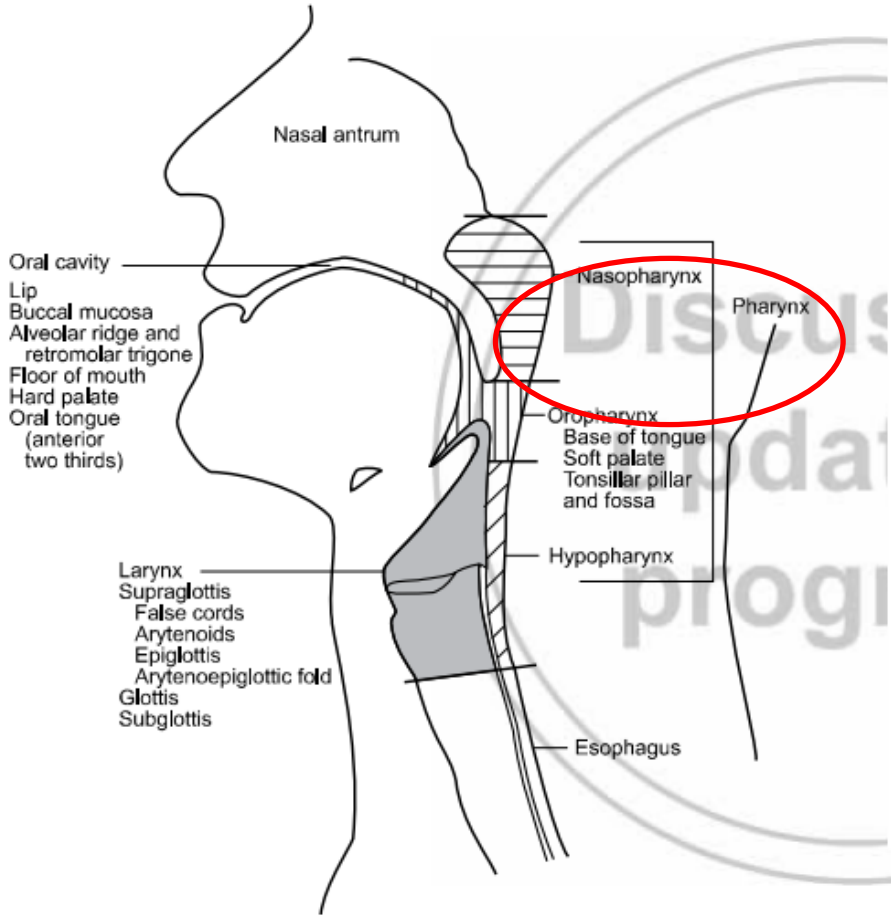
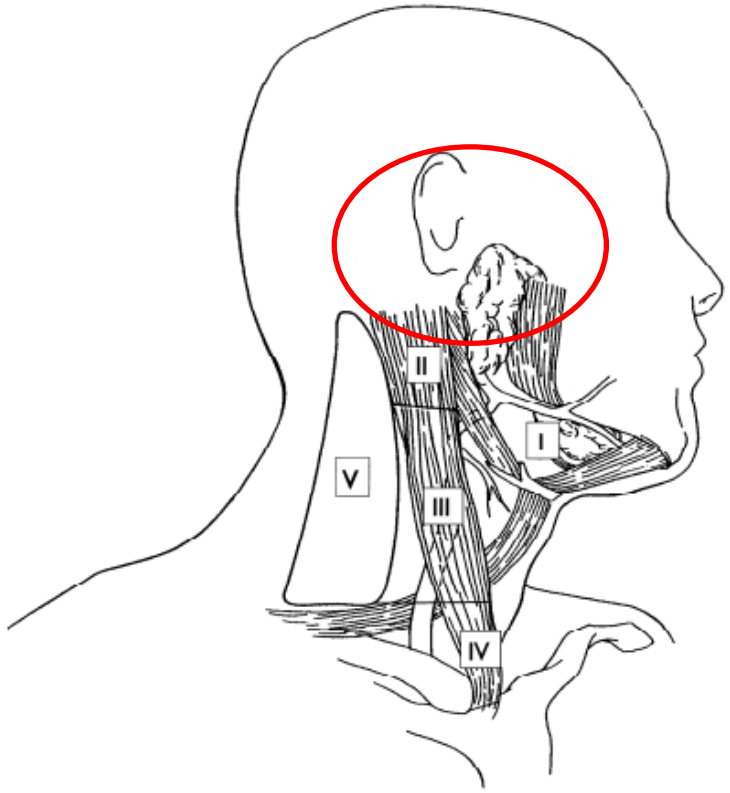


Figure 2

Level designation for cervical lymphatics in the right neck



Servikal lenf nodlarında Skuamöz hc Karsinom

- İnce iğne bx %95 tanı koyar
- Flexible nasofarenkgoskopi ile direk bx
- BT %22 tanı koyar
- MR %36
- PET-CT %28-57
- Level II, Jugulodigastrik ve üst servikal bölgeye en sık metastaz görülür

Pavlidis N, Pentheroudakis G. Cancer of unknown primary site. Lancet. 2012;1428-35.

Servikal lenf nodlarında Skuamöz hc Karsinom

- Tüm baş-boyun kanserlerin %5
- İpsilateral tonsilektomi ile odak %10-15 bulunur
- PET/CT primer odağın bulunmasında yardımcı olabilir
- [1]Boyun d
- seksiyonu + RT+/- KRT(kategori 2A)
- [2]KRT(kategori 2B)
- [3]Yalnızca RT(kategori 3)
- [4]İndüksiyon CT sonrası CRT(kategori 3)

İzole inguinal lenf nodlarında Skuamöz metastazı

- Tümör genellikle anorektal veya genital bölgede lokalizedir

- Primer odak bulunmadığı zaman

  İnguinal lenf nodu diseksiyonu *+* RT tedavi

  seçeneği tedavi olarak düşünüle bilinir

- İlave kemoterapi ?

Kemik metastazı, yüksek serum PSA veya dokuda *PSA* +,Erkek cinsiyet

- **Metastatik prostat ca gibi tedavi edilir**
- **Tedavide antihormonal tedavi,**
  bisfosfanatlar,
  kemoterapi ,
  ve endikasiyon olanlarda palyatife RT

Orta hat kötü diferansiyeli karsinom/adenokarsinom

- Tümör lokalizasyonu genelde mediasten ya da retroperiton
  Multiple akciğer, lenf nodu metastazı
- 50 yaş<, Erkek cinsiyet
- Artmış serum aFP ve ßHCG seviyesi
- İzokromozom 12p varlığı

Ekstragonodal germ hücreli *tümörü düşündürmeli*
Bu hastalar ***kötü prognozlu germ hücreli*** *tümör gibi tedavi edilmelidir*

Kötü differansiye NET

- Agresif seyirlidir
- Genellikle multiple karaciğer ve kemik metastazı ile prezente olur
- Platin bazlı KT iyi yanıt verir

Primeri Bilinmeyen Kanserlere Yaklaşım

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2023
Occult Primary

NCCN Guidelines Index
Table of Contents
Discussion

SELECTED SYSTEMIC THERAPY REGIMENS FOR OCCULT PRIMARIES
ADENOCARCINOMA

Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
• Paclitaxel and carboplatin[1,2] • Gemcitabine and cisplatin[3] • CapeOX[4] • mFOLFOX6[4,5] • FOLFIRI[6-10]	• Docetaxel and carboplatin[11] • Gemcitabine and docetaxel[12] • Docetaxel and cisplatin[13] • Irinotecan and carboplatin[14] • Capecitabine[a,15,16] • Fluorouracil[a,17-20]	• Paclitaxel, carboplatin, and etoposide[b,21] • Irinotecan and gemcitabine[c,22] • FOLFIRINOX[b,d,23] • mFOLFIRINOX[b,d,24,25] • Pembrolizumab[e,26,27] (only in tumors that are dMMR/MSI-H[28] or have TMB-H [≥10 mut/Mb])[29] • Dostarlimab-gxly[e,f,30] (only in tumors that are dMMR/MSI-H) • Selpercatinib (only in *RET* gene fusion-positive tumors)[g,31]

For Squamous Cell see OCC-B 6 of 11

Kötü prognostik grupta tedavi

Minnie Pearl Research Network Studies
First 6 Phase 2 Sequential Studies (N=451) and 1 Phase 3 Study (N=198)

- Paclitaxel, carboplatin, etoposide (N=71)
- Docetaxel, cisplatin (N=26)
- Docetaxel, carboplatin (N=47)
- Paclitaxel, carboplatin, gemcitabine (N=120)
- Paclitaxel, carboplatin, etoposide followed by gemcitabine, irinotecan (N=132)
- Paclitaxel, carboplatin, bevacizumab, erlotinib (N=55)
- Paclitaxel, carboplatin, etoposide vs gemcitabine, irinotecan both followed by gefitinib (N=198)

Greco FA, Hainsworth JD. Cancer of unknown primary site. In: DeVita VT Jr, Lawrence TS, Rosenberg SA, eds. *Cancer: Principles and Practice of Oncology*. 8th ed. Philadelphia: Lippincott; 2008:2363-2387.
Burris HA III, Spigel DR, Thompson DM. Paclitaxel/carboplatin plus bevacizumab/erlotinib as first-line treatment for patients with carcinoma of unknown primary site. Program and abstracts of the American Society of Clinical Oncology 2008 Annual Meeting; May 30-June 3, 2008; Chicago, Illinois [Poster #4607].
Hainsworth JD, Lane C, Spigel D, et al. Randomized phase III comparison of paclitaxel/carboplatin/etoposide vs gemcitabine/irinotecan, both followed by gefitinib, in patients with carcinoma of unknown primary site. Program and abstracts of the American Society of Clinical Oncology 2009 Annual Meeting; May 29-June 2, 2009; Orlando, Florida [Poster #4631].

Long-term Survival of 396 Patients in First 5 Sequential MPCRN Phase 2 Trials

Greco FA, Hainsworth JD. Cancer of unknown primary site. In: DeVita VT Jr, Lawrence TS, Rosenberg SA, eds. *Cancer: Principles and Practice of Oncology*. 8th ed. Philadelphia: Lippincott; 2008:2363-2387.

Long-term Survival in Patients With Unknown Primary Carcinoma and Unfavorable Prognostic Factors

Author and Year of Publication	Number of Patients	Regimen	Median Survival (Months)	1-Year Survival (%)	2-Year Survival (%)	3-Year Survival (%)
Briasoulis et al 2000	33	PCb	10.0	25.0	5.0	NR
Dowell et al 2001	34	P5FUL (17) CbE (17)	8.3 6.4	26.0	NR	NR
Balaña et al 2003	30	GCE	7.2	36.0	14.0	NR
Park et al 2004	37	PC	11.0	38.0	11.0	NR
Piga et al 2004	102	CbDoxE	9.0	35.3	18.0	11.0
Pouessel et al 2004	35	GD	10.0	43.0	7.0	NR
El-Rayes et al 2005	22	PCb	6.5	27.0	NR	NR

5FUL = 5-fluorouracil/leucovorin; C = cisplatin; Ca = capecitabine; Cb = carboplatin; D = docetaxel; Dox = doxorubicin; E = etoposide; G = gemcitabine; Ir = irinotecan; NR = not reported; Ox = oxaliplatin; P = paclitaxil; V = vinorelbine

*Mean survivals of all studies

Greco FA. Therapy of adenocarcinoma of unknown primary: are we making progress? *J Natl Compr Canc Netw*. 2008;6:1061-1067.

Long-term Survival in Patients With Unknown Primary Carcinoma and Unfavorable Prognostic Factors

Author and Year of Publication	Number of Patients	Regimen	Median Survival (Months)	1-Year Survival (%)	2-Year Survival (%)	3-Year Survival (%)
Pittman et al 2006	51	GCb	7.8	26.0	12.0	NR
Palmieri et al 2006	66	GPC (33) GVC (33)	9.6 13.6	30.0 52.0	NR NR	NR
Berry et al 2007	42	PCb	8.5	33.0	17.0	NR
Briasoulis et al2007	47	OxIr	9.5	40.0	NR	NR
Schneider et al2007	33	GCaCb	7.6	35.6	14.2	11.0
MPCRN Trials (5) 1997-2008	396	Multiple Regimens	9.1	38.0	19.0	NR
Total	928		8.9*	34.6*	13.0*	12.0*

5FUL = 5-fluorouracil/leucovorin; C = cisplatin; Ca = capecitabine; Cb = carboplatin; D = docetaxel; Dox = doxorubicin; E = etoposide; G = gemcitabine; Ir = irinotecan; NR = not reported; Ox = oxaliplatin; P = paclitaxil; V = vinorelbine

*Mean survivals of all studies

Greco FA. Therapy of adenocarcinoma of unknown primary: are we making progress? *J Natl Compr Canc Netw*. 2008;6:1061-1067.

Cancer J. 2010 Jan-Feb;16(1):70-5.

Paclitaxel/carboplatin/etoposide versus gemcitabine/irinotecan in the first-line treatment of patients with carcinoma of unknown primary site: a randomized, phase III Sarah Cannon Oncology Research Consortium Trial.

Hainsworth JD, Spigel DR, Clark BL, Shipley D, Thompson DS, Farley C, West-Osterfield K, Lane CM, Cescon T, Bury MJ, Greco FA.

Sarah Cannon Research Institute, Nashville, TN, USA. jhainsworth@tnonc.com

Abstract

PURPOSE: To compare the results of empiric first-line therapy with paclitaxel/carboplatin/etoposide (PCE) versus gemcitabine/irinotecan, both followed by single-agent gefitinib, in patients with carcinoma of unknown primary site.

PATIENTS AND METHODS: Patients with previously untreated carcinoma of unknown primary site were randomized to receive either PCE or gemcitabine/irinotecan. Responding and stable patients continued treatment for 4 to 6 cycles. Patients with no evidence of tumor progression at that time received single-agent gefitinib until tumor progression. The trial was designed to detect an improvement in the 2-year survival rate from 20% to 30%.

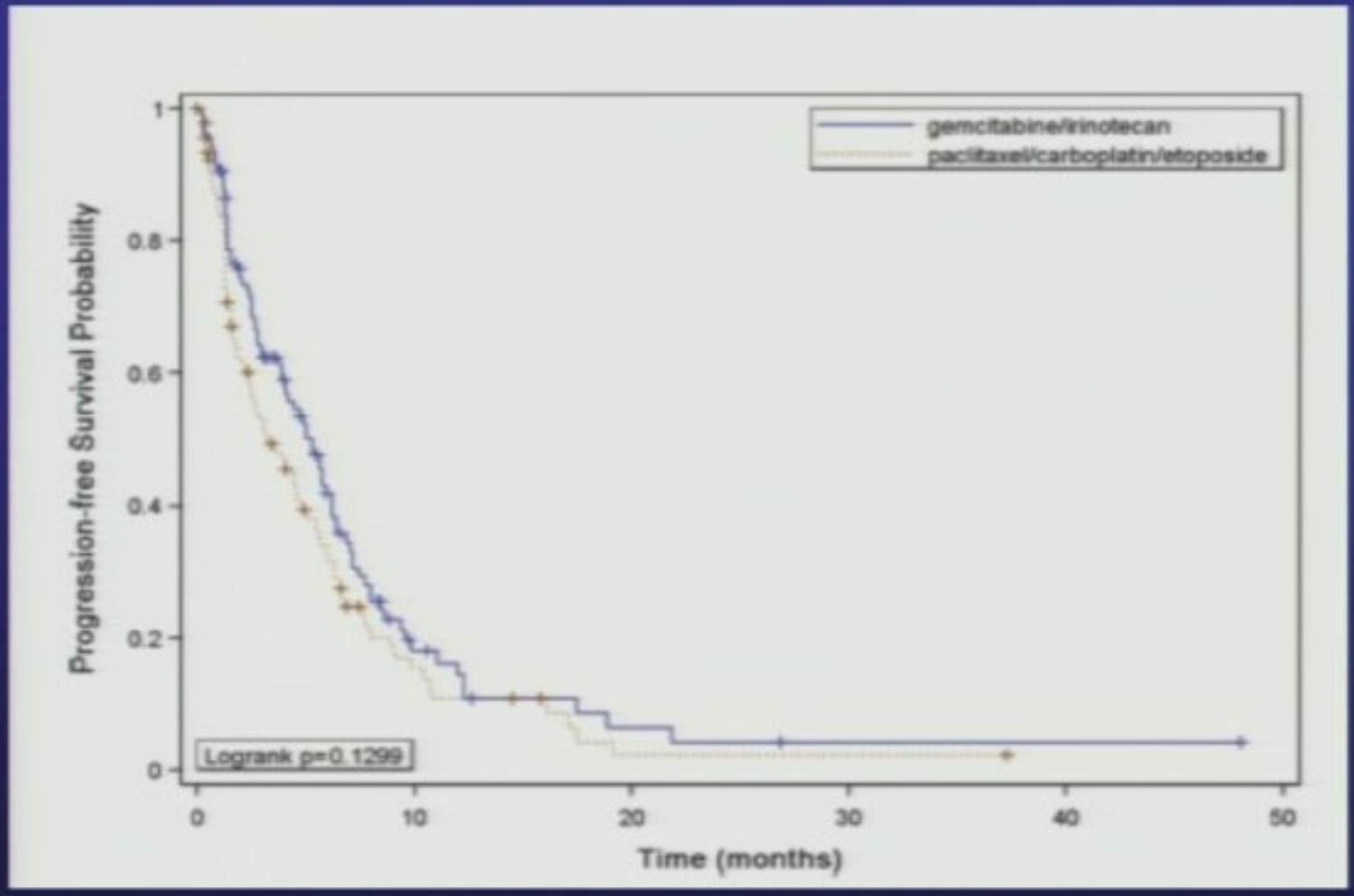
RESULTS: Between September 2003 and July 2008, 198 patients entered this multicenter, community-based trial. Because of slow accrual, the trial was stopped short of its target accrual of 320 patients. Clinical characteristics were comparable for patients receiving PCE (N = 93) and gemcitabine/irinotecan (N = 105). PCE and gemcitabine/irinotecan produced similar 2-year survival (15% vs. 18%), median survival (7.4 months vs. 8.5 months), median progression-free survival (3.3 months vs. 5.3 months), and response rate (18% vs. 18%). Grade 3/4 neutropenia, thrombocytopenia, anemia, febrile neutropenia, and red blood cells transfusions were more common with PCE; diarrhea was more common with gemcitabine/irinotecan. The median duration of gefitinib maintenance was 3 months, suggesting no role as a maintenance therapy in this setting.

DISCUSSION: The PCE and gemcitabine/irinotecan regimens have comparable efficacy in the first-line treatment of patients with carcinoma of unknown primary site. Gemcitabine/irinotecan is the preferable regimen, due to its favorable toxicity profile. However, the moderate efficacy of both regimens underscores the need for novel treatment approaches in this patient population.

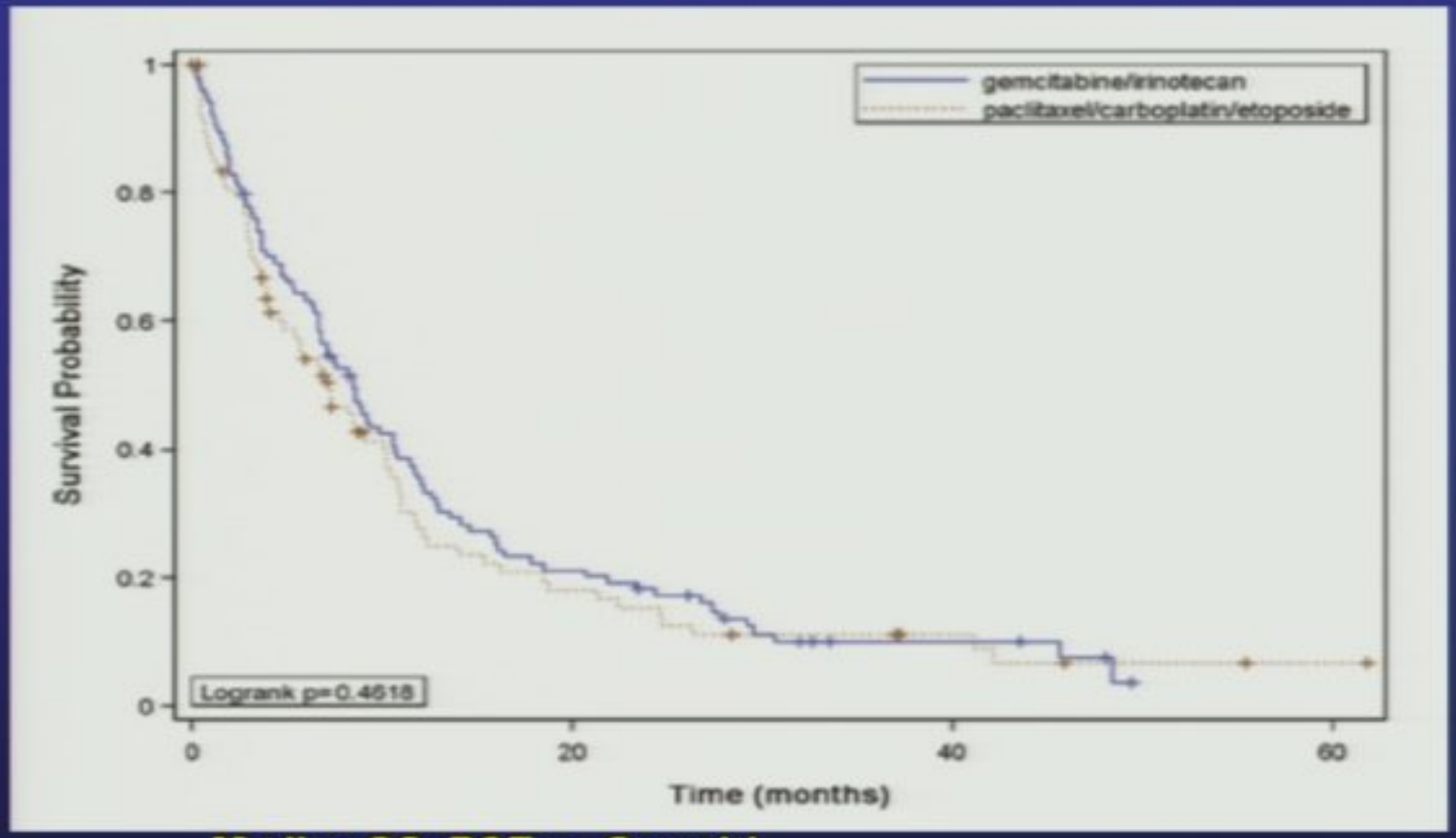
Phase 3 PCE vs Gemcitabine/Irinotecan
Comparison of Overall Survival

- Paclitaxel/carboplatin/etoposide vs gemcitabine/irinotecan (both followed by gefitinib):
  - Overall survival 7.4 months for PCE, vs
  - Overall survival 8.6 months for GI
  - *P* = .34

Hainsworth JD, Lane C, Spigel D, et al. Randomized phase III comparison of paclitaxel/carboplatin/etoposide vs gemcitabine/irinotecan, both followed by gefitinib, in patients with carcinoma of unknown primary site. Program and abstracts of the American Society of Clinical Oncology 2009 Annual Meeting; May 29-June 2, 2009; Orlando, Florida [Poster #4607].



Median PFS: PCE vs Gem+iri
3.3 ay vs 5.3 ay



Median OS: PCE vs Gem+iri

7.4 ay vs 8.5 ay

Molecular Diagnostics for Cancer of Uncertain Origin

*Overview of Commercial Tests**

Test Providers	bioTheranostics: THEROS CancerTYPE Id[b]	Rosetta Genomics: miRview mets[c]	Pathwork Diagnostics: Tissue of Origin Test[f]
Number of Cancer Types	39 Types[a] and 64 Subtypes	25 types	15 types
Sample Requirement	FFPE	FFPE	Frozen; FFPE available**
Platform	RT-PCR mRNA	RT PCR miRNA	Microarray mRNA
Sensitivity	Overall = 86%	90%	88%
Specificity	>99%[a,b]	99%	>99%[e]
Regulatory Aspect/Clearance	CLIA	CLIA	FDA on frozen sample CLIA for FFPE

[a]Ma, et al. *Arch Pathol Lab Med.* 2006. [b]bioTheranostics Website. [c]Rosetta Genomics Website. [d]Rosenfeld, et al. *Nat Biotechnol.* 2008. [e]Monzon, et al. *J Clin Oncol*. 2009. [f]Pathwork Diagnostics Website.
*Available in the United States. **Accuracy not reported.