Primeri Bilinmeyen Kanserler

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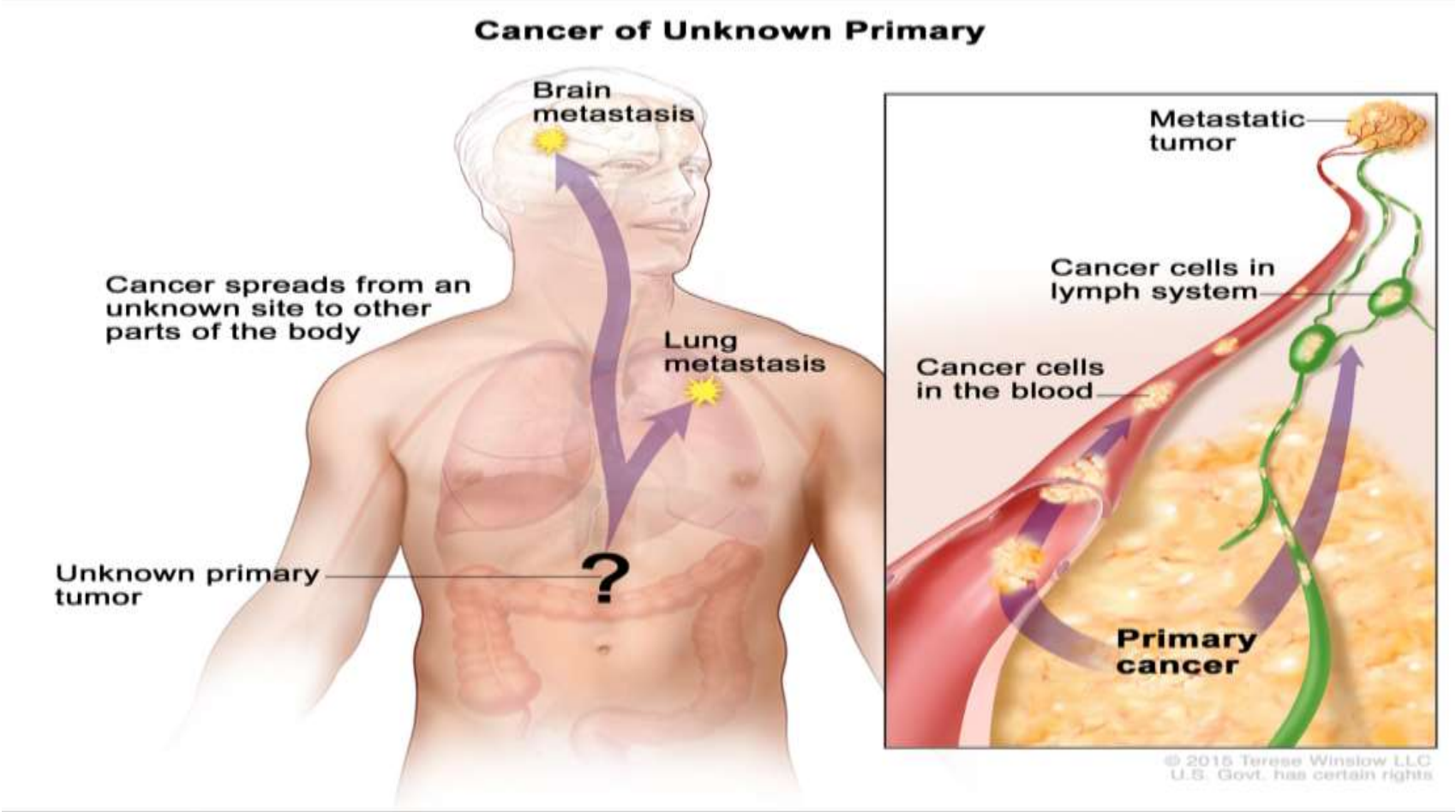
Koç Üniversitesi Hastanesi Medikal Onkoloji

Ders planı

- Primeri Bilinmeyen Kanser(PBC) tanımı
- İnsidans ve mortalite
- İyi/kötü prognostik özelik gösteren PBC
- Tedavi seçenekleri
- Tümör agnostik mutasyonlar gen alterasyonları
- Sonuç

Primeri Bilinmeyen Kanser(PBC) tanımı

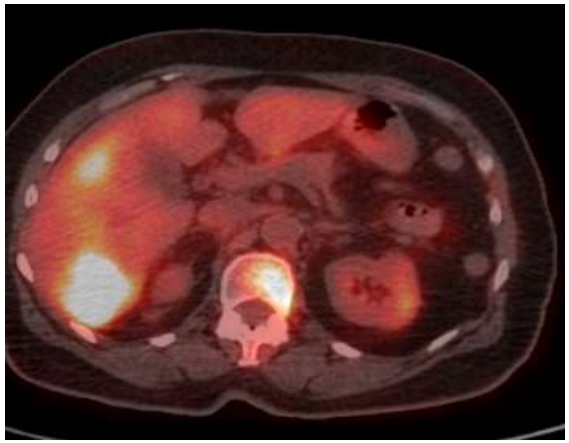


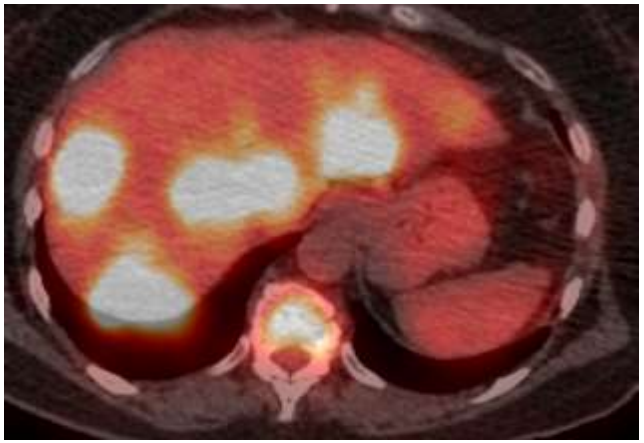
Carcinoma of unknown primary, NCI 2025.

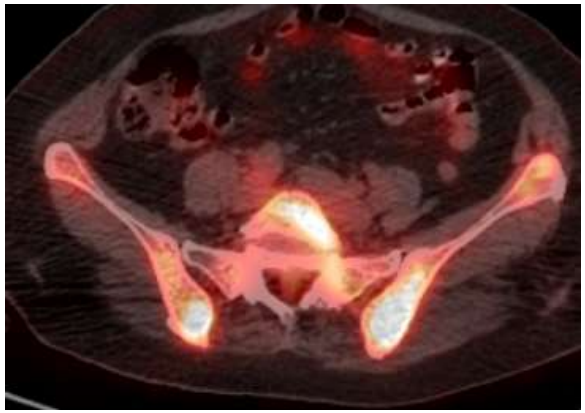
Vaka Sunumu 1

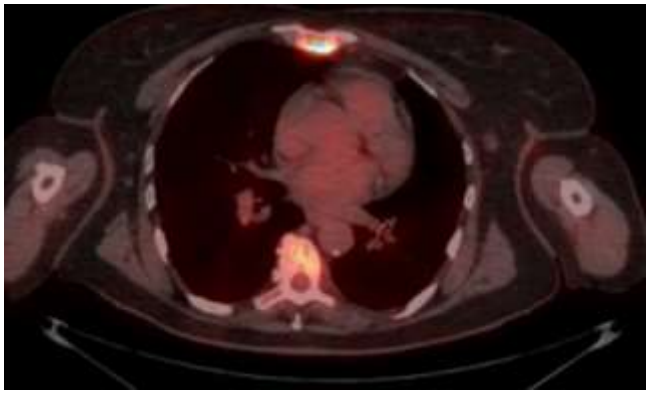
- 68 Yaşında kadın hasta
- Üç ay önce başlayan bel ve sırt ağrısı
- Bilinen hastalıkları; HT ve DM
- Dış ülkede görüntülemede KC ve Kemik metastazı
- Primeri bilinmeyen malignite

Vaka Sunumu 1









- **Karaciğer her iki lobda bazılarının santrali ametabolik (kistik/nekrotik?) olmak üzere hipermetabolik lezyonlar; ön planda primer / sekonder malignite lehine değerlendirildi.**
- **Aksiyal ve apendiküler iskelette yaygın kemik metastazları.**
- **Bilateral servikal, sol retropektoral-aksiller lenf nodları; ön planda metastaz lehine değerlendirildi**

Mamografi

- Sol meme üst iç kadranda malignite kuşkulu kitle dışı lezyon. Mamografi asimetrik dansite karşılığıdır.

- Sol aksiller patolojik görünümde multipl lenf nodları. Sol supraklavikuler ve sol alt servikal kuşkulu lenf nodları mevcuttur. Sol retropektoral yumuşak doku kitlesi izlenmiştir. Patolojik lenf noduna ait olabilir.

- ACR BI-RADS Kategori 5: Malignite açısından yüksek kuşkulu bulgular

Öneri: Sol meme bulgularının yaygınlığının meme MRG ile değerlendirilmesi, sol meme ve sol aksilla bulgularının histopatolojik verifikasyonu önerilir

Patoloji

- Karaciger; Tru-cut Biyopsi:

- KARSINOM METASTAZI, MEME KARSINOM METASTAZI ILE UYUMLU.

- ✓ ER : NEGATIF
- ✓ PR : NEGATIF
- ✓ HER2/NEU : POZITIF (SKOR 3+).
- ✓ -KI-67 : %40

Tümör markeri

Primeri Bilinmeyen Kanserler

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

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

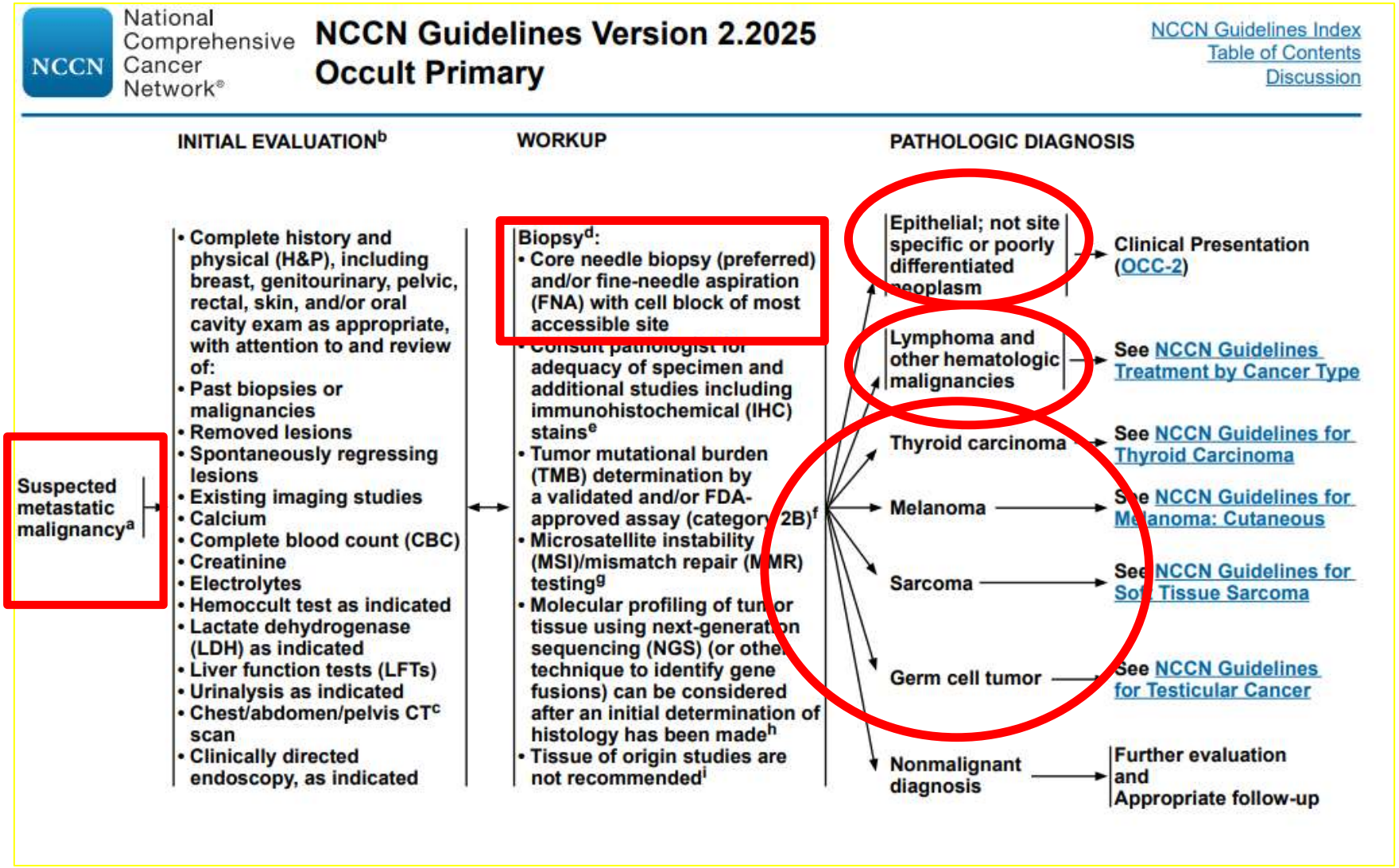
Pavlidis N, Pentheroudakis G. Cancer of unknown primary site. Lancet. 2012;1428-35.

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 kanserlerdir
- Ölüme sebebiyet veren dördüncü sıklıkta kanserlerdir
- Erkek cinsiyet , kadın cinsiyete göre hafif dominant
- Ortalama tanı yaşı 65
- Kötü prognostik grupta ortalama yaşam beklentisi 8-12 ay
- İyi prognostik grupta ortalama yaşam beklentisi 12-36 ay

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

Primeri Bilinmeyen Kanserlere Yaklaşım



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

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COMMONLY USED IMMUNOHISTOCHEMISTRY/IN SITU HYBRIDIZATION 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-	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	

[3] Conner JR, Hornick JL. Metastatic carcinoma of unknown primary: diagnostic approach using immunohistochemistry. Adv Anat Pathol 2015;22:149-167.

Primeri Bilinmeyen Kanserlere Yaklaşım

National Comprehensive Cancer Network®

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POTENTIAL IMMUNOHISTOCHEMISTRY/IN SITU HYBRIDIZATION MARKERS FOR UNKNOWN PRIMARY CANCERS

Communication between the clinician and the pathologist is essential for the workup to direct the staining pattern to the clinical differential diagnosis. The pathologist should select a focused panel of IHC or ISH markers, and avoid a large series of markers. IHC and ISH markers for unknown primary cancers are provided as a resource to assist in localizing a primary but are not uniformly specific or sensitive.

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
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
Melan-A	Adrenocortical, melanoma	Nuclear
Napsin A	Lung	Cytoplasmic
NKX3-1	Prostate	Nuclear
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, osteosarcoma, and 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; gross cystic disease fluid protein 15; HepPar-1, hepatocyte paraffin 1; PAP, prostatic acid phosphatase; PSA, prostate-specific antigen; RCC, renal cell carcinoma; 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.

Note: All recommendations are category 2A unless otherwise indicated.

PET/CT primer saptamada kanserde ek bilgi sağlar

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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.

PET/CT , lolal-regional hastalıkta yada tedavi seçeneğini değiştireceği düşünülüyorsa ek olarak istenebilir

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

HİSTOPATOLOJİ, IŞIK MİKROSKOPİ (H+E)

İYYİ DİFERANSİYE ADENO CA; %60

KÖTÜ DİFERANSİYE KARSİNOM, ADENOKARSİNOM; % 29

SKUAMÖZ HÜCRELİ KARSİNOM; % 5

İNDİFERANSİYE KARSİNOM %5

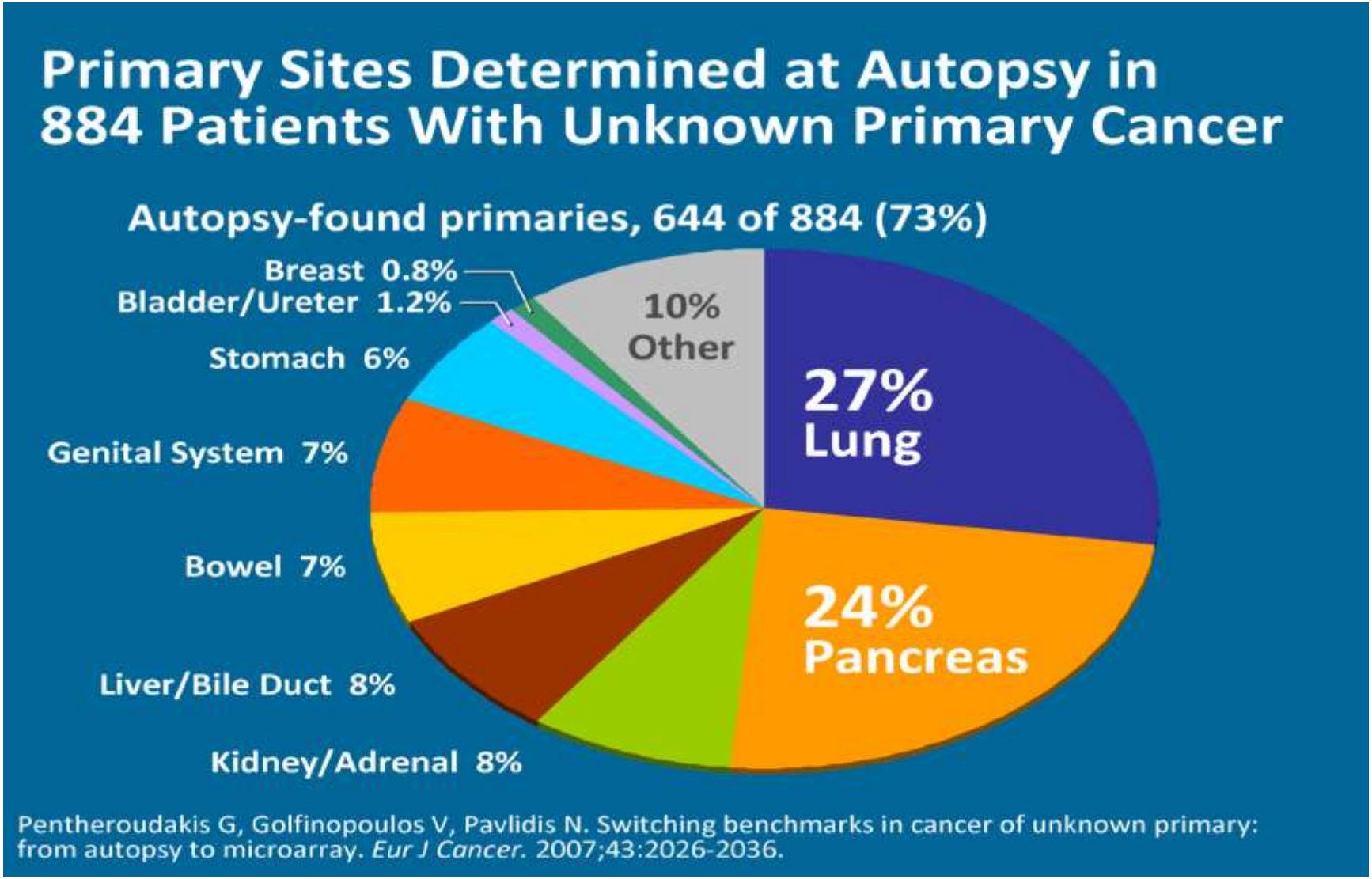
NEUROENDOKRİNE KARSİNOM;%1

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.

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



Gene expression profiling (GEP)

Molecular Diagnostics for Cancer of Uncertain Origin

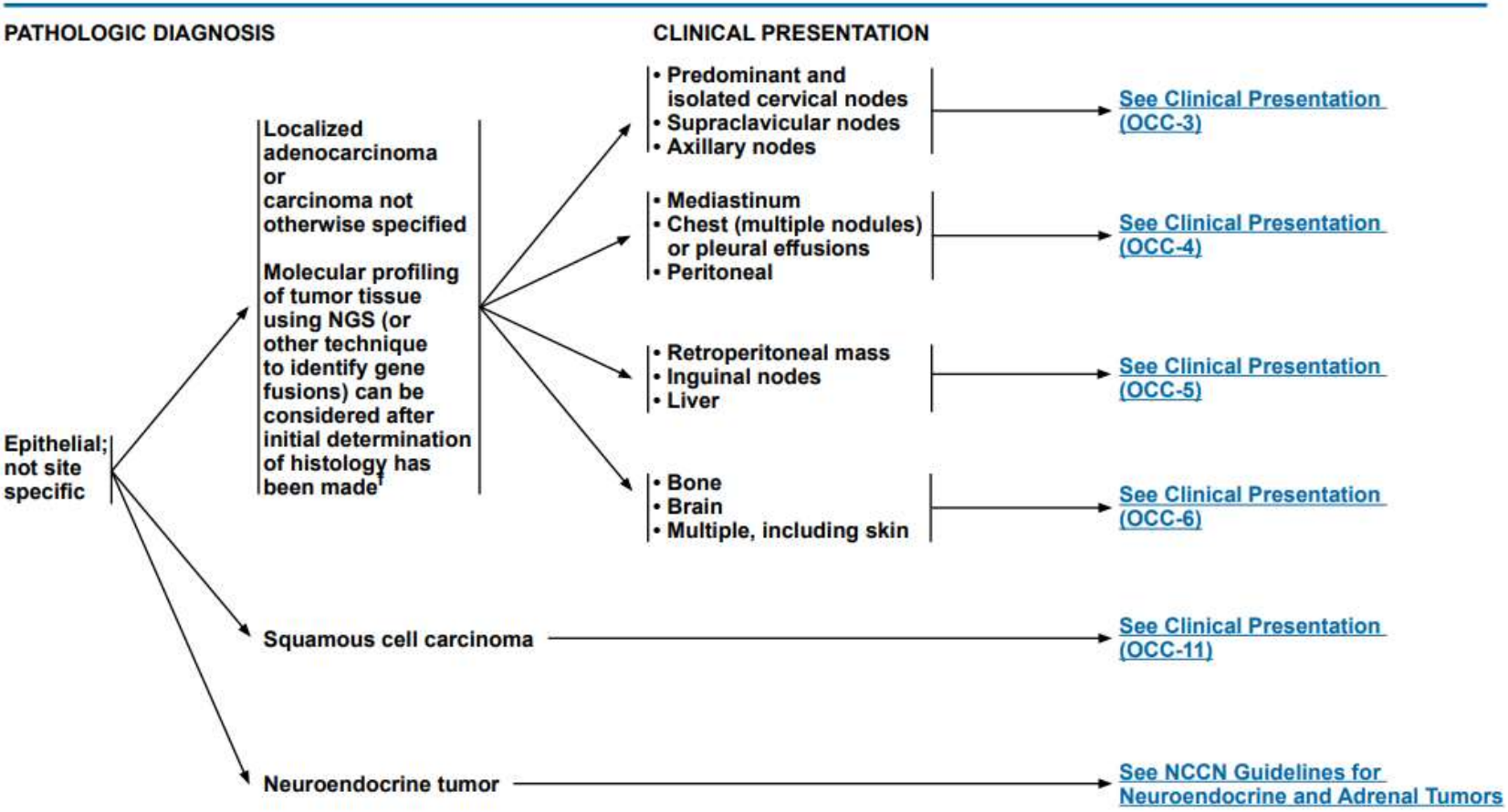
*Overview of Commercial Tests**

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

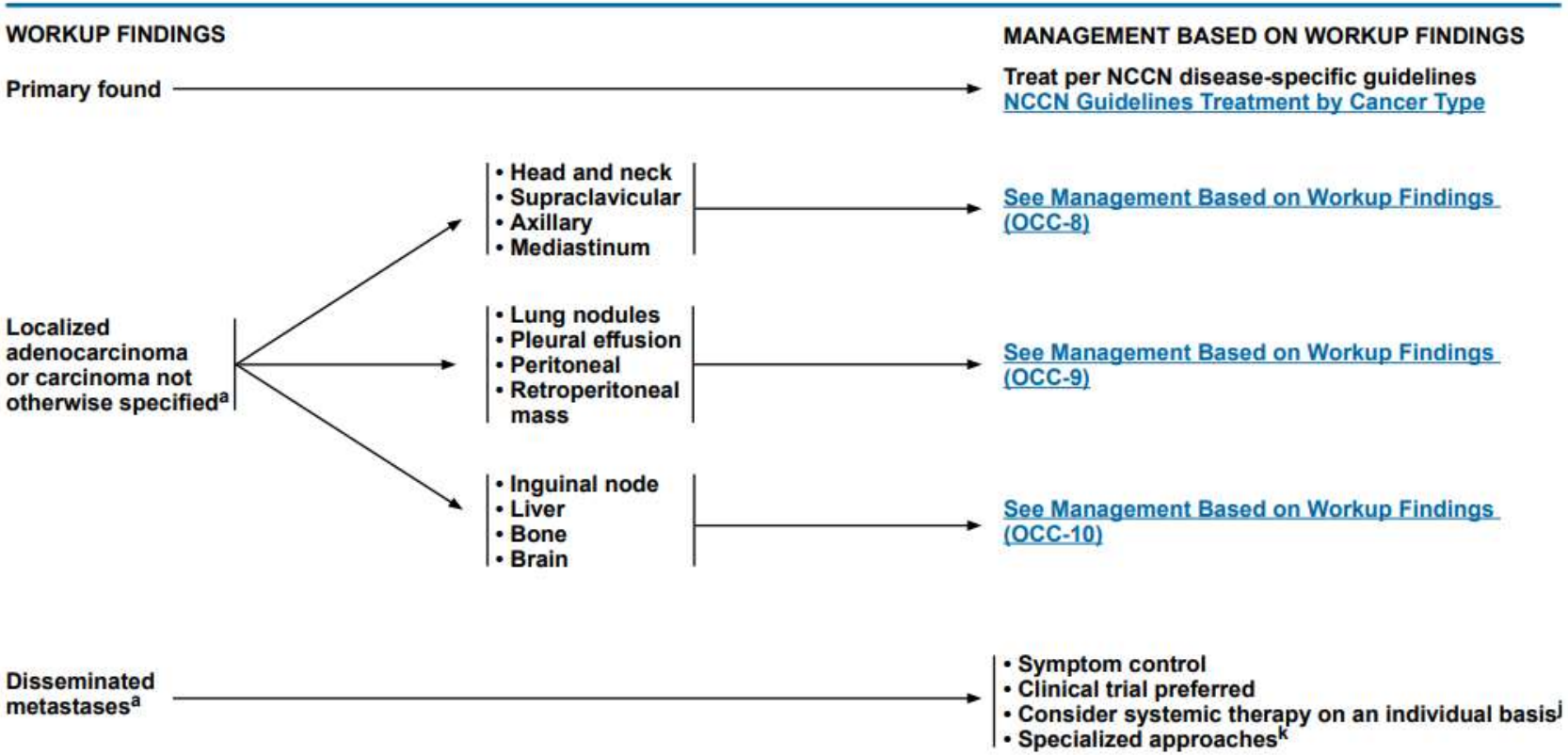
[a]Ma, et al. *Arch Pathol Lab Med*. 2006. [b]bioTheranostics Website. [c]Rosetta Genomics Website. [d]Rosenfeld, et al. *Nat Biotechnol*. 2008. [e]Monzon, et al. *J Clin Oncol*. 2009. [f]Pathwork Diagnostics Website.
*Available in the United States. **Accuracy not reported.

GEP primerin tespitinden çok, tümör sınıflandırmasında yardımcı olabilir. Örneğin akciğer adeno, meme triple negatif, kolon adeno ca özeliğinde benzeri yorumlar. Fakat IHK belirgin bit üstünlüğü gösterilmemiştir.

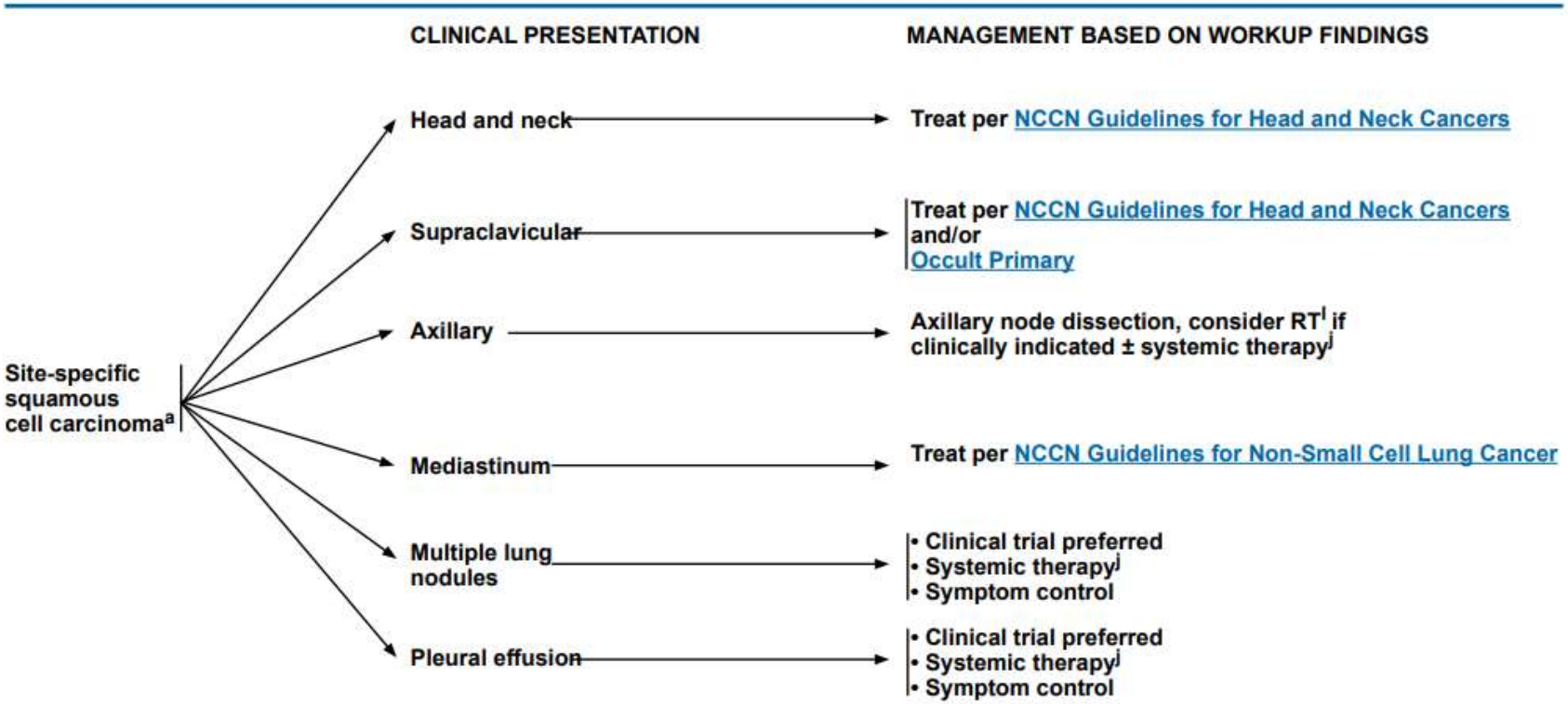
Primeri Bilinmeyen Kanserlere Yaklaşım



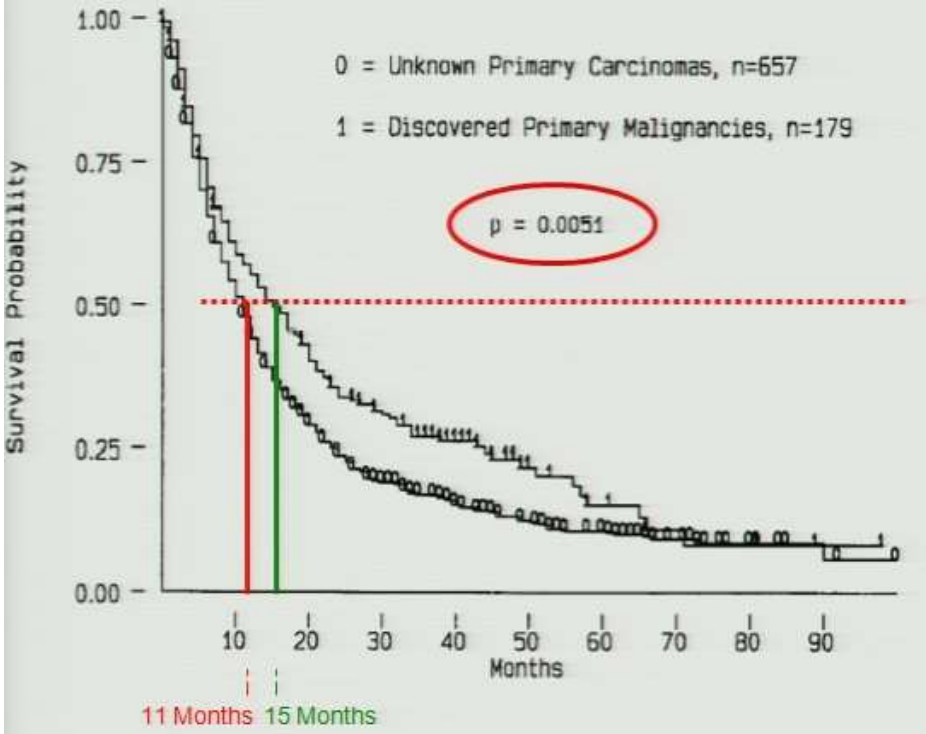
Primeri Bilinmeyen Kanserlere Yaklaşım



Primeri Bilinmeyen Kanserlere Yaklaşım



PBK tanıya ulaşmanın sağkalıma faydası?

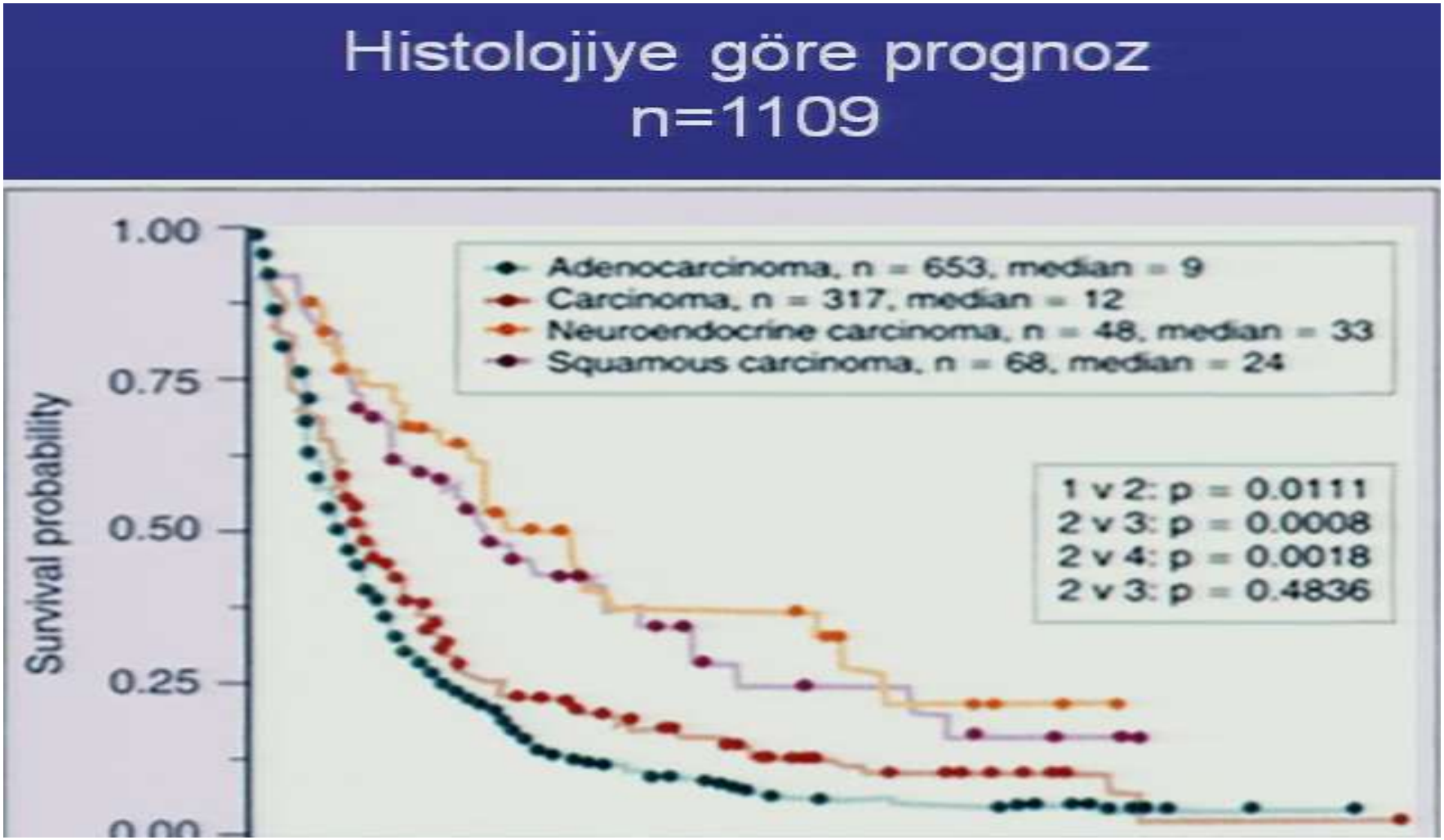


Tedaviye iyi CEVAP veren kanserler[2]:

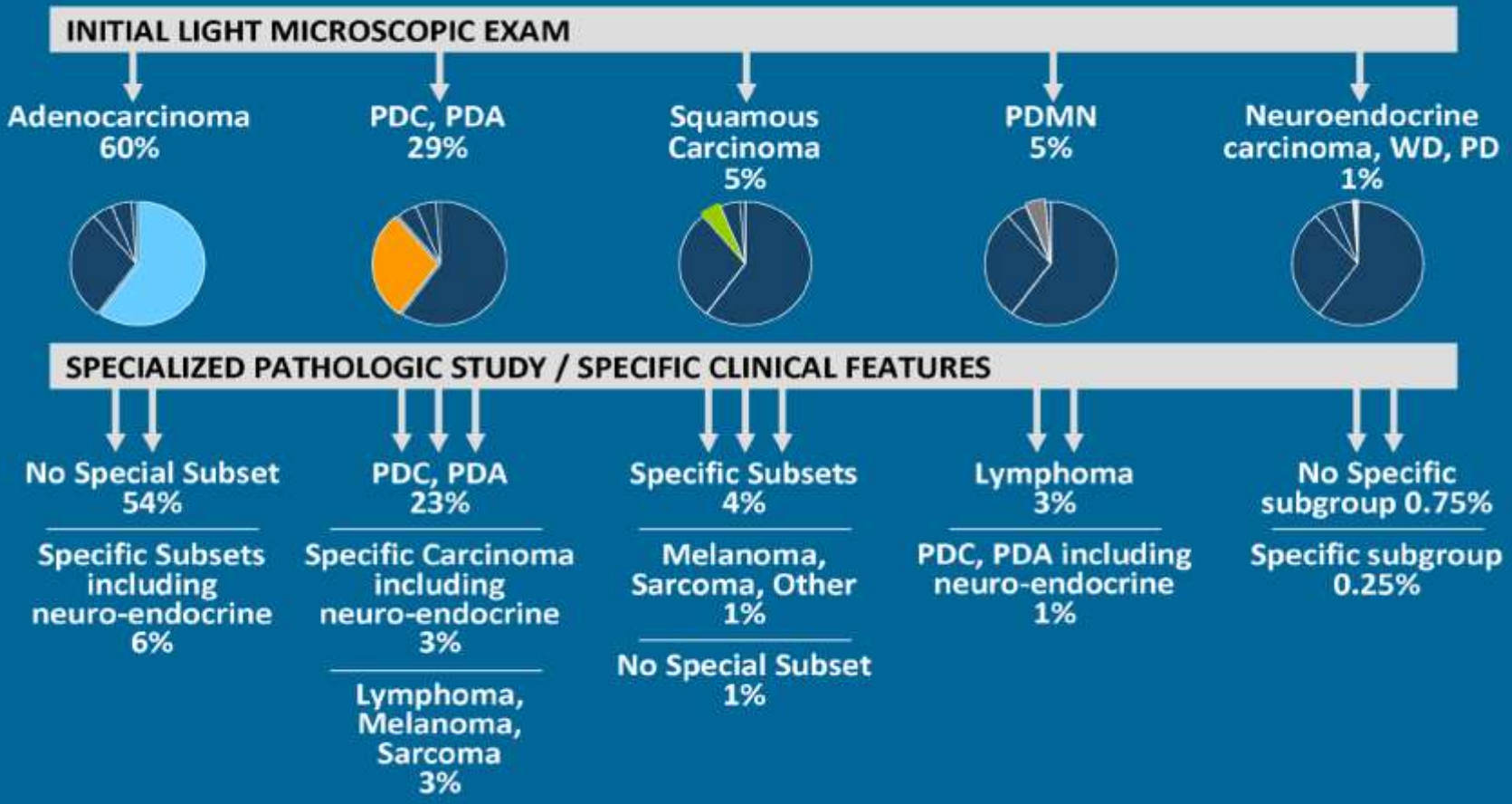
- Germ hücreli kanserler
- Over kanseri
- Meme kanseri
- Lenfomalar
- Nöroendokrin kanserler
- Prostat kanseri

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

PBK tanıya ulaşmanın sağkalıma faydası?



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.

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.

Tedavi

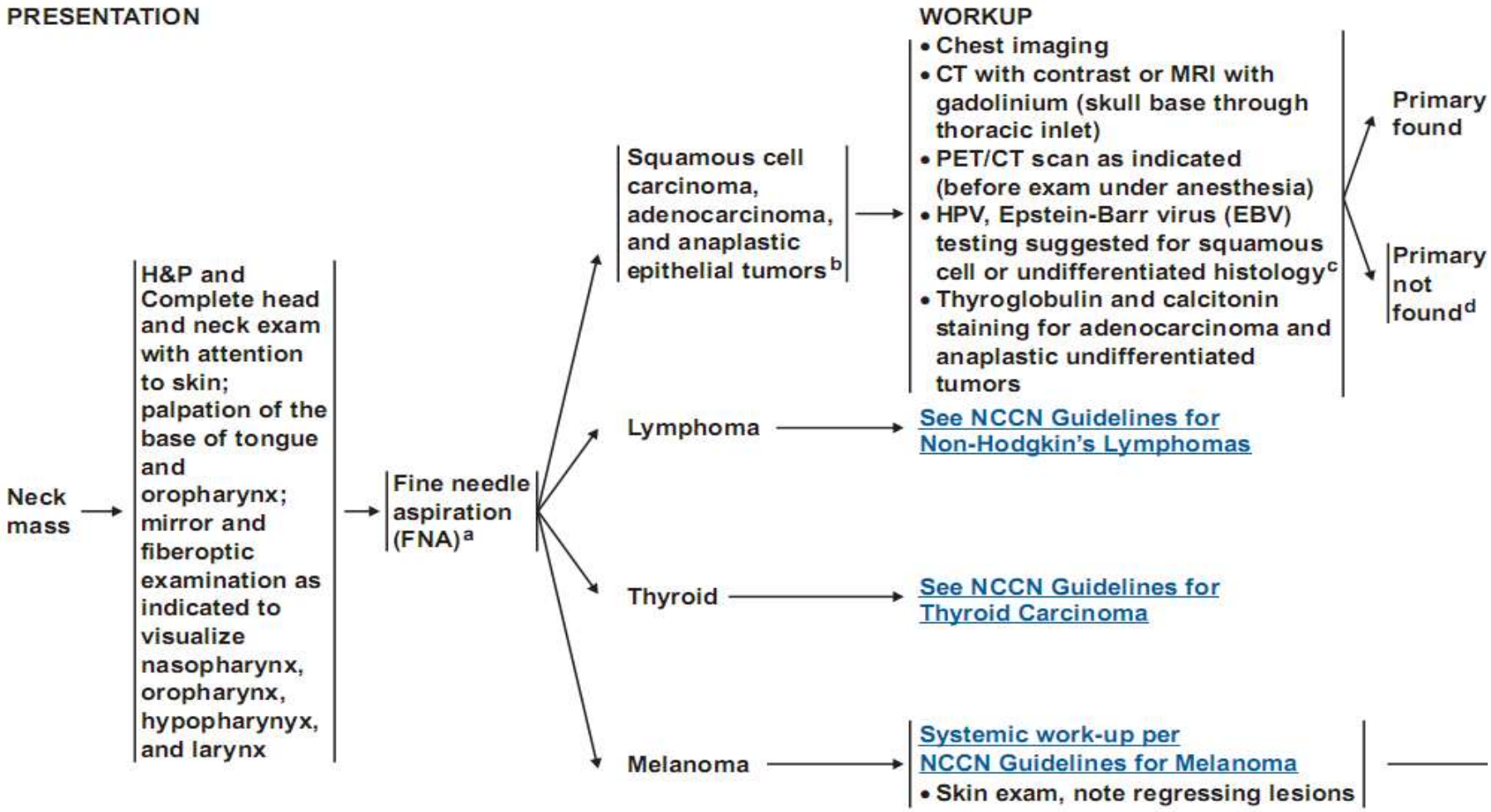
- Tüm hastalarda Aksiler diseksiyon
- Standart Yaklaşım MRM
- Hasta isteğine bağlı Olarak tüm meme ışınlaması düşünülebilir
- Karşılaştırmalı çalışma yoktur.

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

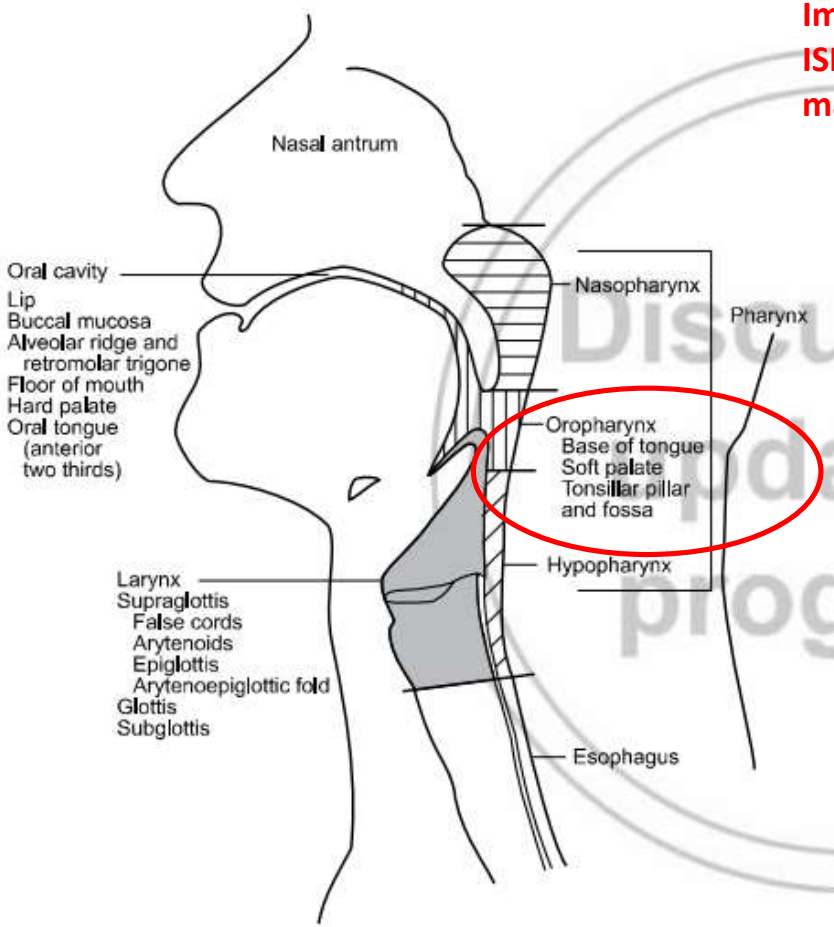
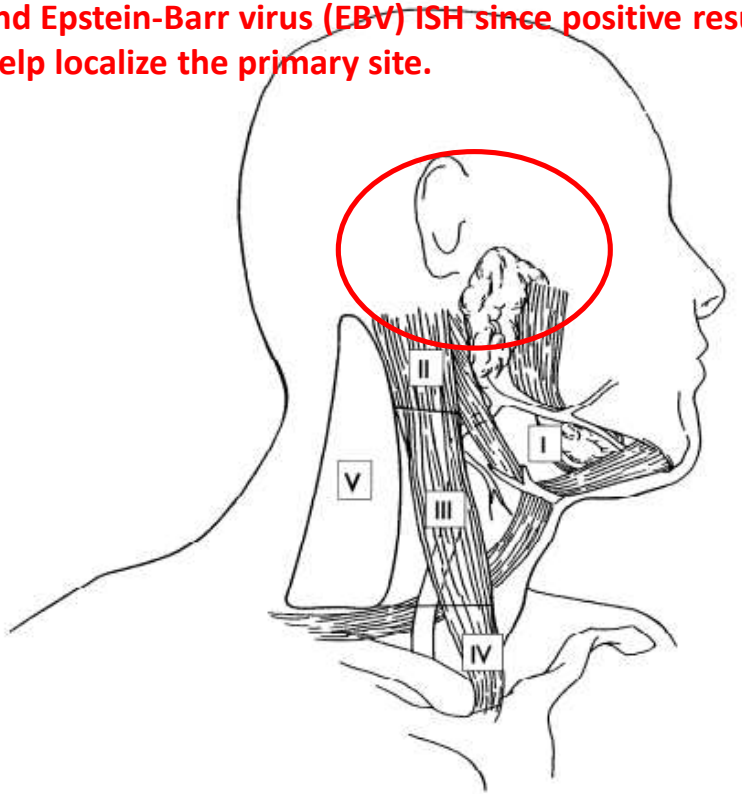


Figure 2

Level designation for cervical lymphatics in the right neck

Importantly, clinicians should check results of p16 IHC, HPV ISH, and Epstein-Barr virus (EBV) ISH since positive results may help localize the primary site.



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 diseksiyonu + 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 ?

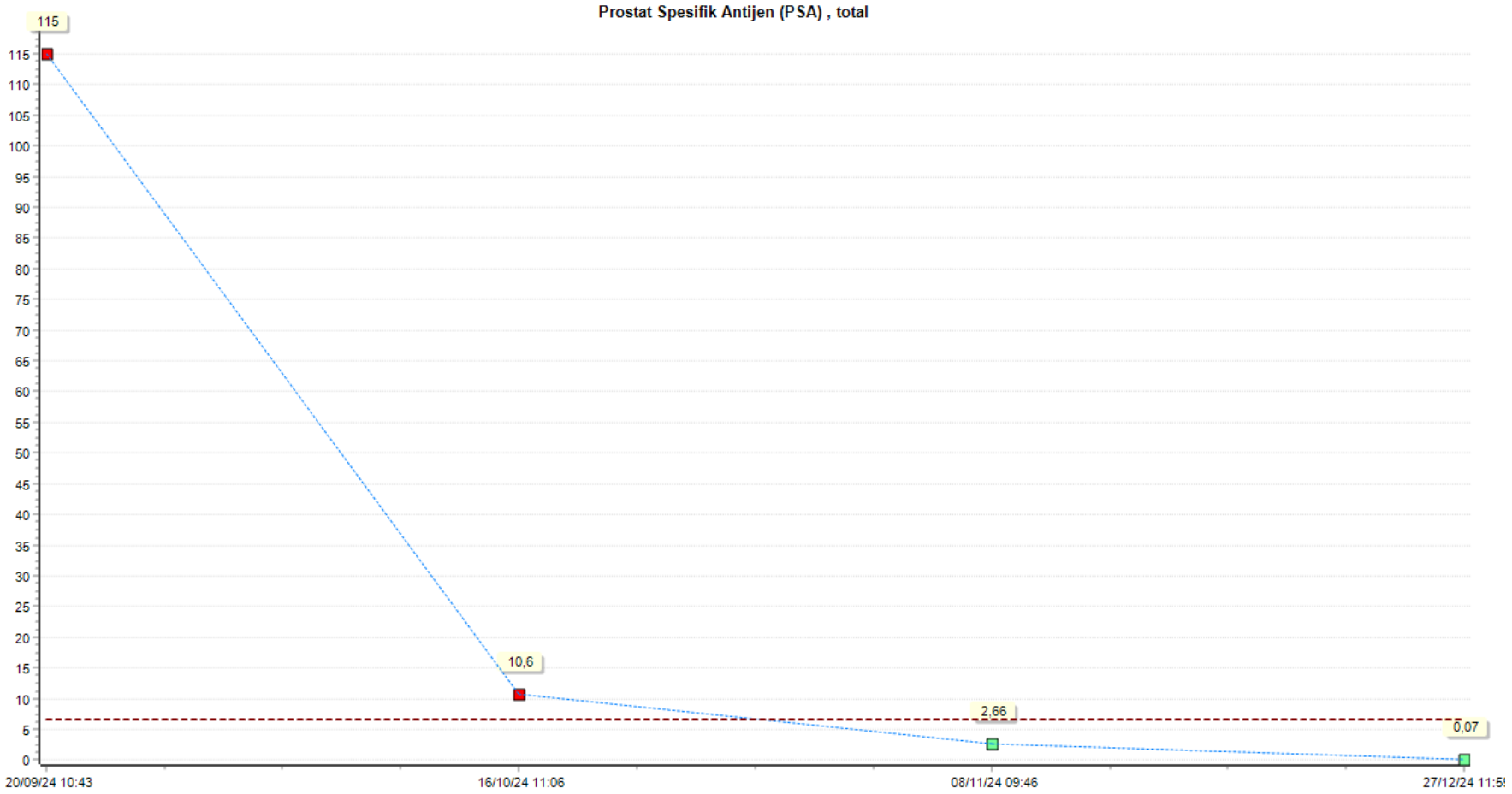
Kemik metastazı, yüksek serum PSA veya dokuda *PSA* +,Erkek cinsiyet

- Metastatik prostat ca gibi tedavi edilir
- Tedavide antihormonal tedavi,
- Bifosfonatlar
- Kemoterapi
- Endikasyona olanlarda palyatife RT

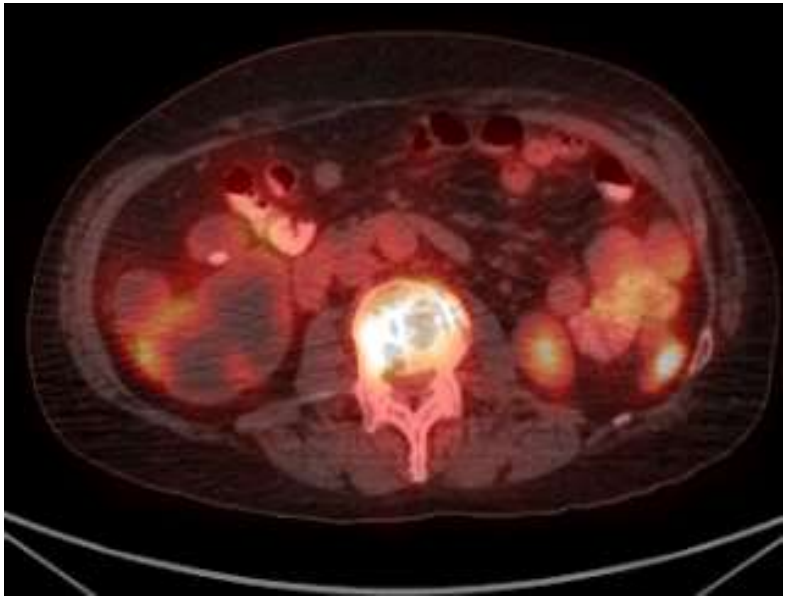
Vaka sunumu 2

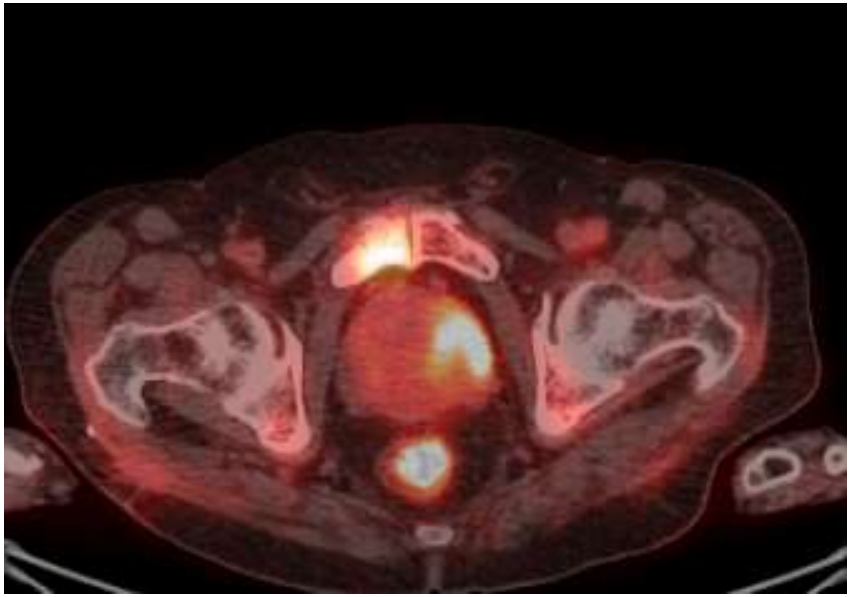
- 80 yaşında erkek hasta
- 1 ay önce başlayan şiddetli bel ağrısı
- Hastalık öyküsü : KOAH ve Migren
- Dış merkez vertebra MR; Metastaz şüphesi
- Tanı ve tedavi için başvurdu

Tümör Markeri



PSMA PET/CT





- Mesane indentasyonu oluşturmuş hiperplazik prostat glandında, sol ağırlıklı ve sol seminal vezikülün tamamı ile sağ seminal vezikülün medialini kaplayan yüksek grad'lı lokal invaze primer malignite ile uyumlu PSMA ekspresyonları.
- İskelet sisteminde, FDG PET çalışmasına göre daha fazla sayıdaki odakta, çoğunluğunun karşılığında sklerotik alanların olduğu yaygın metastaz ile uyumlu PSMA ekspresyonları.
- Bilateral inguinal ve eksternal iliak, sol kommon iliak ve sol obturator, PSMA ve FDG tutulum paternleri ile metastaz olasılığının kesin olarak ekarte edilemediği lenf nodları.

Patoloji

- KLİNİK BULGULAR:

- RT: Sağ baz sertlik (Medial ve lateralde sertlik). PSA: 110 ng/mL. MpMR: PIRADS 5 lezyon.

TANI:
Prostat, Sag bazal medial (Transrektal Igne Biyopsisi):
PROSTATIK ADENOKARSINOM, GLEASON SKOR-9 (9=5+4) (GRADE GRUP 5).

Prostat, Sag mid gland medial (Transrektal Igne Biyopsisi):
HER IKI KORDA PROSTATIK ADENOKARSINOM, GLEASON SKOR-9 (9=5+4) (GRADE GRUP 5).
TOPLAM DOKU UZUNLUGUNUN %70INI TUTAN.

- INTRADUKTAL KARSINOM ODAGI IZLENDI.

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 diferansiye NET

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

Tümör-agnostic tedavi

Tumor-agnostic therapy

A type of therapy that uses drugs or other substances to treat cancer based on the cancer's genetic and molecular features without regard to the cancer type or where the cancer started in the body. Tumor-agnostic therapy uses the same drug to treat all cancer types that have the genetic mutation (change) or biomarker that is targeted by the drug. It is a type of targeted therapy. Also called tissue-agnosticc therapy.

- ❑ **RET (NGS:next-generation sequencing)**
- ❑ **BRAF (NGS)**
- ❑ **Microsatellite instabilite(MSI)(IHK)**
- ❑ **HER2 +3 pozitifliği (IHK)**
- ❑ **Nörotrofik tirozin reseptör kinaz (NTRK) gen füzyonu(RNA NGS)**
- ❑ **Tumor mutation burden(TMB)(NGS)**

Doebele RC, Lancet Oncol 2020., Administration USFD. FDA grants accelerated approval to dabrafenib in combination with trametinib for unresectable or metastatic solid tumors with BRAF V600E mutation. , Meric-Bernstam F, DESTINY-PanTumor02 phase II trial. J Clin Oncol 2024

Tümör-agnostic tedavi

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2025
Occult Primary

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PRINCIPLES OF SYSTEMIC THERAPY

DOSING SCHEDULES FOR OCCULT PRIMARIES: ADENOCARCINOMA

Useful in Certain Circumstances: Biomarker-Driven Therapy

***BRAF* V600E Mutation-Positive Tumors**
Dabrafenib + trametinib[e]
Dabrafenib 150 mg PO twice daily
Trametinib 2 mg PO daily
Repeat every 4 weeks[22]

dMMR/MSI-H Tumors
Dostarlimab-gxly[f,g]
500 mg IV Day 1
Repeat every 3 weeks for 4 doses followed by 1000 mg IV Day 1
Repeat every 6 weeks[23]

Pembrolizumab[f]
200 mg IV Day 1
Repeat every 3 weeks[24-26]
OR
400 mg IV Day 1
Repeat every 6 weeks[24-26]

***NTRK* Gene Fusion-Positive Tumors**
Entrectinib[h]
600 mg PO daily
Repeat every 4 weeks[27]

Larotrectinib[h]
100 mg PO twice daily
Repeat every 4 weeks[28]

Repotrectinib[h]
160 mg PO once daily for 14 days,
then increase to 160 mg PO twice daily[29]

TMB-H (≥10 mut/Mb) Tumors
Pembrolizumab[f]
200 mg IV Day 1
Repeat every 3 weeks[24-26,30]
OR
400 mg IV Day 1
Repeat every 6 weeks[24-26,30]

***RET* Gene Fusion-Positive Tumors**
Selpercatinib[j]
<50 kg: 120 mg PO twice daily[32]
≥50 kg: 160 mg PO twice daily[32]

HER2-Positive (IHC 3+) Tumors
Fam-trastuzumab deruxtecan-nxki[i]
5.4 mg/kg IV Day 1
Repeat every 21 days[31]

Footnotes on OCC-B 7A of 14

Primeri Bilinmeyen Kanserlere Yaklaşım

National Comprehensive Cancer Network®

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Occult Primary

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PRINCIPLES OF SYSTEMIC THERAPY

Selected Systemic Therapy for Occult Primaries: Adenocarcinoma[a]

Regimens are listed in alphabetical order by category of preference.

Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
• Carboplatin and paclitaxel[1,2] • Cisplatin and gemcitabine[3] **Preferred Regimens for Presumed GI Primary Site** • CapeOX[4] • FOLFIRI[b,5-9] • mFOLFOX6[b,4,10]	• Capecitabine[c,d,11,12] • Docetaxel and carboplatin[13] • Docetaxel and cisplatin[14] • Fluorouracil[b,c,d,15-18] • Gemcitabine and carboplatin[19] • Gemcitabine and docetaxel[20] • Irinotecan and carboplatin[21]	**Biomarker-Driven Therapy** ***BRAF* V600E mutation-positive tumors** • Dabrafenib + trametinib[e,22] **dMMR/MSI-H tumors** • Dostarlimab-gxly[f,g,23] • Pembrolizumab[f,24-26] ***NTRK* gene fusion-positive tumors** • Entrectinib[h,27] • Larotrectinib[h,28] • Repotrectinib[h,29] **TMB-high (TMB-H) (≥10 mut/Mb) tumors** • Pembrolizumab[f,24-26,30] **HER2-positive (IHC 3+) tumors** • Fam-trastuzumab deruxtecan-nxki[i,31] ***RET* gene fusion-positive tumors** • Selpercatinib[j,32] **Cytotoxic Chemotherapy** • FOLFIRINOX [b,c,k,33] • Irinotecan and gemcitabine[l,34] • mFOLFIRINOX[b,c,k,35,36] • Paclitaxel, carboplatin, and etoposide[k,37]

[a] Consider programmed death ligand 1 (PD-L1) testing for patients with recurrent, progressive, or metastatic disease.
[b] Leucovorin is indicated with certain fluorouracil-based regimens. Depending on availability, these regimens may be used with or without leucovorin.
[c] For patients with presumed gastrointestinal (GI) primary site.
[d] These regimens can be given with concurrent radiation.
[e] For patients with *BRAF* V600E mutation-positive unresectable or metastatic solid tumors that have progressed following prior treatment and have no satisfactory alternative treatment options.
[f] NCCN Guidelines for Management of Immunotherapy-Related Toxicities.
[g] For patients with recurrent or advanced tumors that have progressed on or following prior treatment and who have no satisfactory alternative treatment options. Note, patients who had received prior immune checkpoint inhibitor therapy were excluded from the dostarlimab-gxly clinical trial.
[h] For patients with *NTRK* gene fusion-positive tumors without a known acquired resistance mutation, that are metastatic or where surgical resection is likely to result in severe morbidity, and that have no satisfactory alternative treatments or that have progressed following treatment.
[i] For patients with advanced or metastatic solid tumors that progressed on or following prior systemic treatment and who have no satisfactory alternative treatment options.
[j] For patients with advanced or metastatic solid tumors that progressed on or following prior systemic treatment or who have no satisfactory alternative treatment options.
[k] Only for patients with PS ECOG 0–1.
[l] For patients ineligible to receive platinum-based chemotherapy.

For Squamous Cell Carcinoma see OCC-B 8 of 14

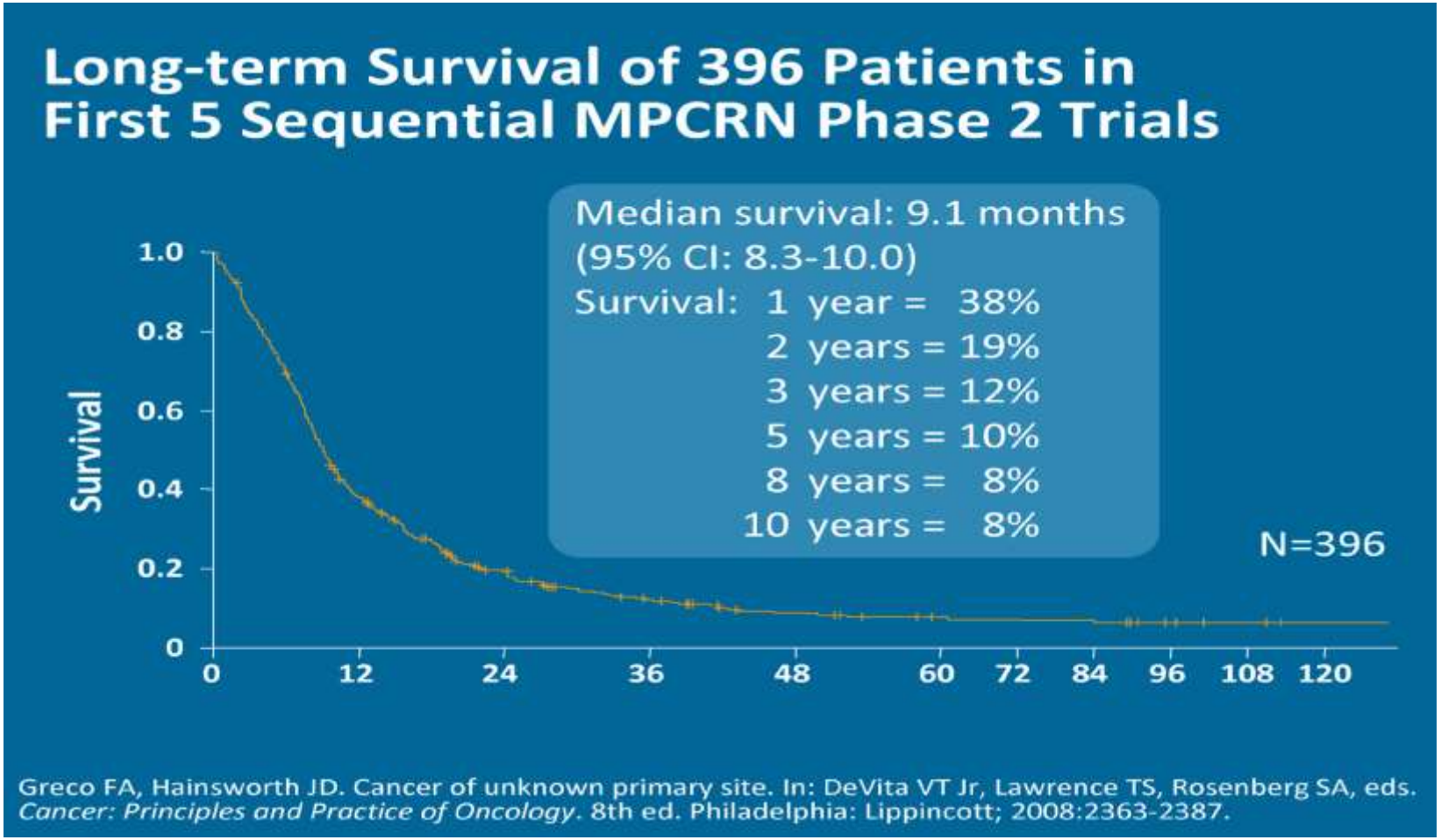
Kötü prognostik grupta tedavi

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].

Kötü prognostik grupta tedavi



Kötü prognostik grupta tedavi

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.

Kötü prognostik grupta tedavi

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

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

Kötü prognostik grupta tedavi
Üçlü kombinasyon= İkili kombinasyon

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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.

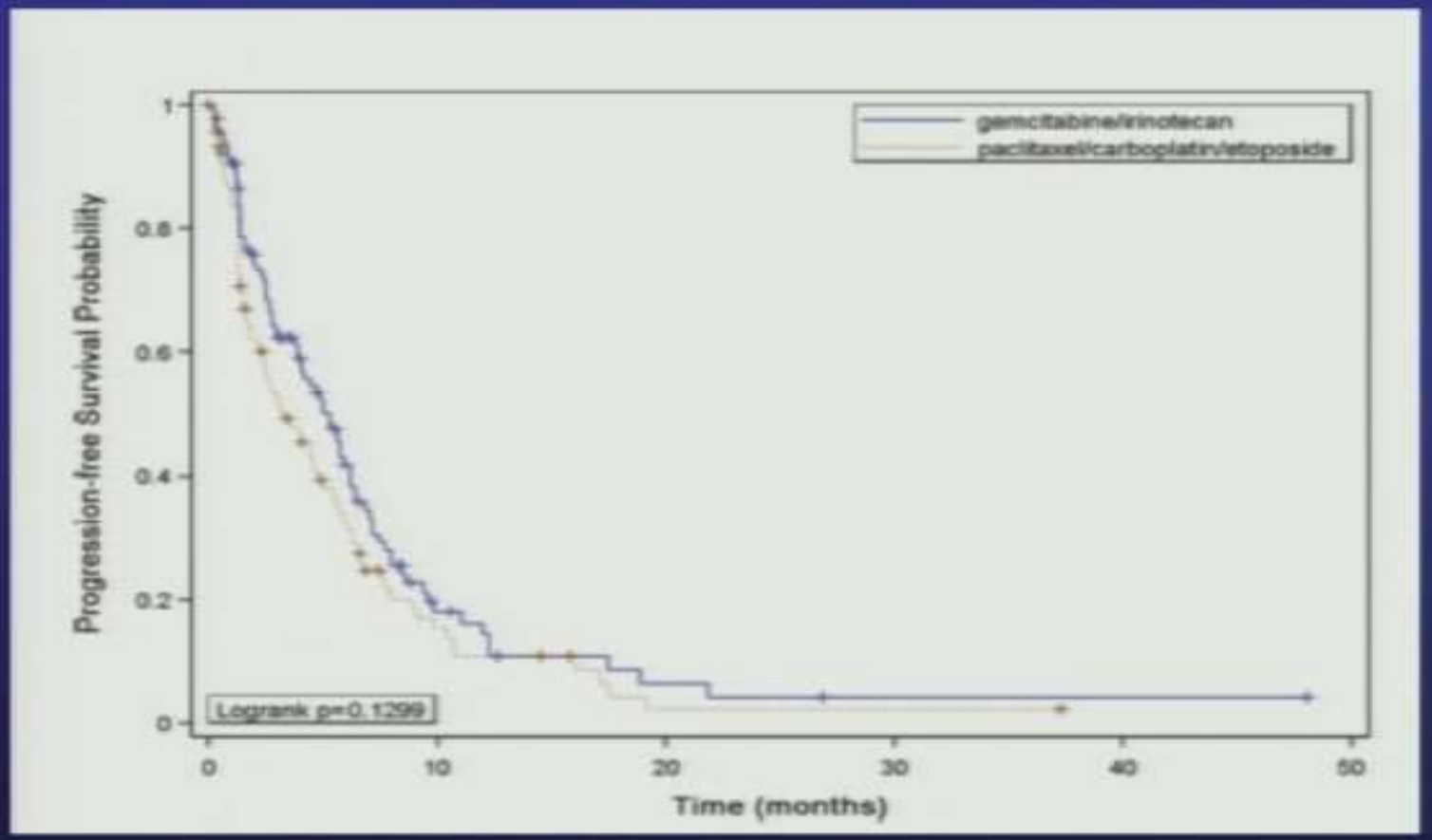
Kötü prognostik grupta tedavi
Üçlü kombinasyon=İkili kombinasyon

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
  - $P = .34$

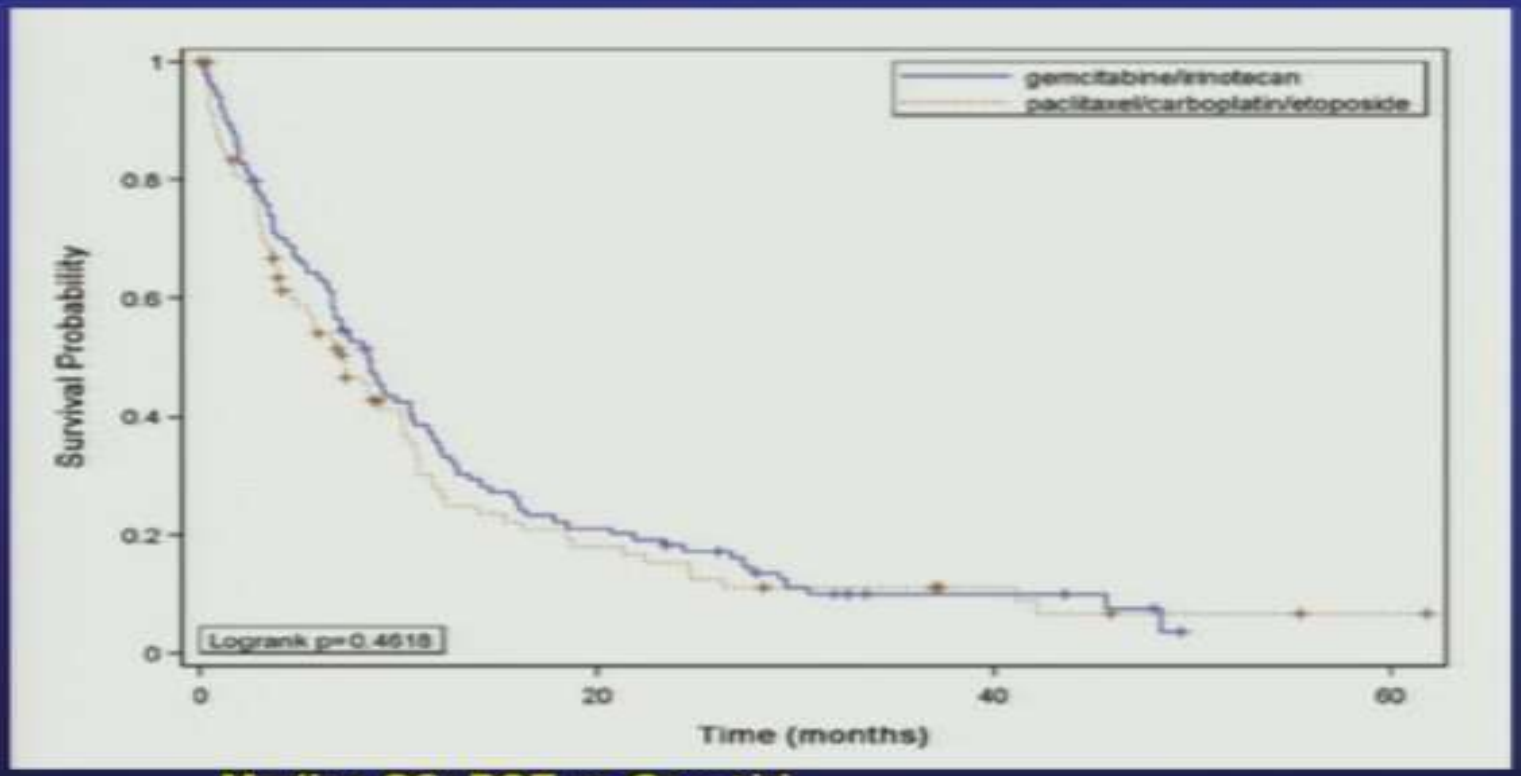
Hainsworth JD, Lane C, Spigel D, et al. Randomized phase III comparison of paclitaxel/carboplatin/etoposide vs gemcitabine/irinotecan, both followed by gefitinib, in patients with carcinoma of unknown primary site. Program and abstracts of the American Society of Clinical Oncology 2009 Annual Meeting;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

Kötü prognostik grupta tedavi
Üçlü kombinasyon=İkili kombinasyon



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

Kötü prognostik grupta tedavi
Üçlü kombinasyon= İkili kombinasyon



Median OS: PCE vs Gem+iri
7.4 ay vs 8.5 ay

Sonuç

- İyi prognostik grup hastaların erken tedaviye erişimi
- İyi prognostik grup histolojik alt gruba tedavi edilmeli
- Kötü prognostik grup hastalarda gereksiz tetkik ve girişimlerden sakınılması
- Kötü prognostik grup ikili kombinasyon olarak karboplatin+paklitaksel, karboplatin+gemsitabin benzeri tedavi seçenekleri
- Tümör agnostik markerların istenmesi; RET, BRAF, MSI, HER2 +3 pozitifliği, NTRK füzyonu, TMB