Primeri Bilinmeyen Kanserler

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Tıbbi Onkoloji

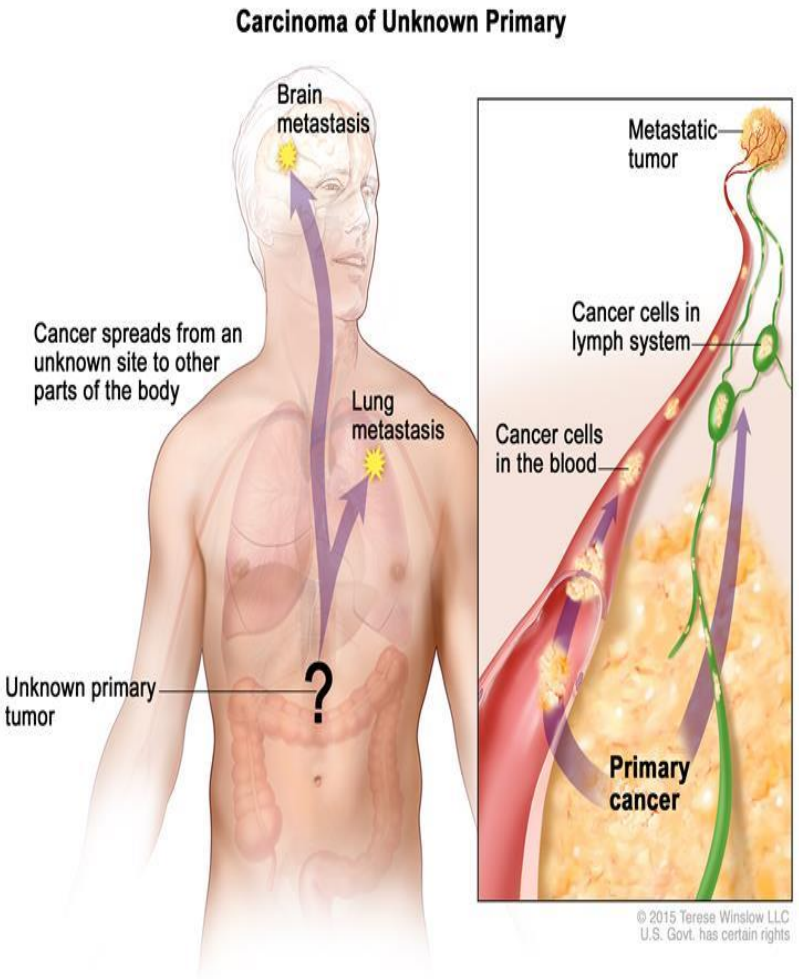
Sunum Akışı

- **Epidemiyoloji, Tanım**
- **Patoloji, Tanı**
- **Vakalar eşliğinde hastalığa yaklaşım**
  İyi Prognostik Grup
  izole aksila, karaciğer metastazı, asitli hasta
  mediastinal, servikal metastazlar…

  Kötü Prognostik Grup
- **Tedavi**
- **Soru ve tartışma**

Primeri Bilinmeyen Kanserler

- PBC: Primer odağı tespit edilemeyen biyopsi ile tanı konan metastatik kanser
- Anamnez
- Fizik Muayene
- Laboratuar
- Radyolojik değerlendirme
- Histolojik inceleme



I.SORU

40 y, kadın, premenopozal, sigara içmemiş. USG'de incidental olarak karaciğerde 3 cm lezyon saptanmış. Biyopsi; adeno ca ile uyumlu gelmiş. IHC; CK7 -, CA19.9 -, CK20+, CDX2 +, TTF-1 -, ER -, HER2-, CT ve PET-CT karaciğer dışında ek patoloji saptanmamış. Bundan sonraki aşamada hangi test yapılmalı?

A. Pankreas protokolünde CT
B. Meme MR
C. Bronkoskopi
D. Kolonoskopi

Primeri Bilinmeyen Kanserler İnsidans

- 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 sıklıktaki 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.

Kanser Tarihçesi

- Mısır papirüslerinde elde edilen bilgiler MÖ 2500 yılında, Mısırda kanser hakkında zamanın doktorlarının bilgisi olduğu ve zaman koşularına göre mücadele ettiği bilinmektedir. Bu dönem hakkındaki bilgilere papirüsler ile ulaşıyoruz. 1862 yılında Edwin Smith adlı bir antikacının ve Mısır dil bilimcisinin Mısır Luksor kentinde aldığı bir papirüste, meşhur hekimi olan İmhotep ve onun öğretilerinden bahsedilmektedir. Bu öğretilerde kanserden bahsedilmektedir.

- Herodot MÖ Pers kraçilesi Atossadan ve onun yakalandığı meme kanserinden bahseder. Atossa kanserli memesini Yunanlı bir kölesinin aldırdığını buradan öğreniyoruz.

- Hipokrat MÖ 400 yıllarda bu hastalığı yengece benzetip Karkinos adını vermiş.

- MS 160 yıllarda, Galen dört sıvı kavramıyla, kanseri siyah safra olarak adlandırır. Galene göre kanser siyah safranın hapsolmuş haliydi.

- 1500 Yıllarından sonra Vesalius insan anatomisini incelemesiyle Galen teorisini yerine, insan anatomisi ve onu istila eden kanserle karşı karşı olduğunu anlıyoruz.

- 19 yüzyılın ortalarında Lister antiseptiği cerrahi girişimlere sokarak, Cerrahide yeni çığır açıyor.

- Bilroth gastrointestinal tümörlerin cerrahisinde başarılı operasyonlar yapıyor. Kansere karşı mücadele kökten alıp çıkarma şiarıyla tam hız bu yılarda sürüyor.

- 19 yüzyılın sonlarına doğru efsane cerrah William Halsted, meme kanserinde radikal mastektomiyi uyguluyordu. Bay Halsted'da kökten alıp çıkarma şiarına uyarak çıkarabildiği kadar daha çok doku ve lenf nodu çıkarıyordu.

Kanser Tarihçesi

We Have Been at War Against Cancer Throughout Human History

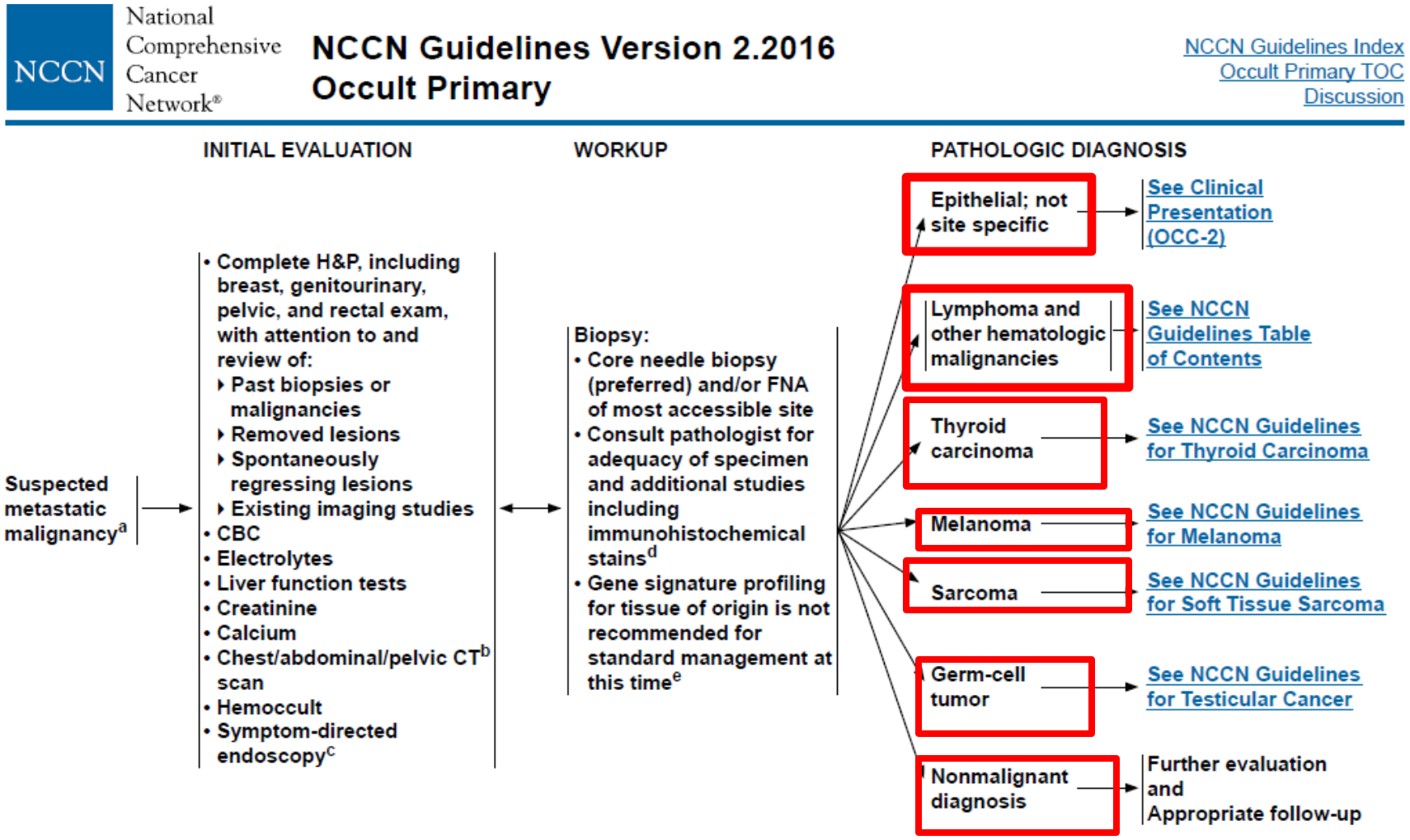
President Nixon declares a "War on Cancer" in 1971

Medieval Saxon man with a large tumor of the left femur

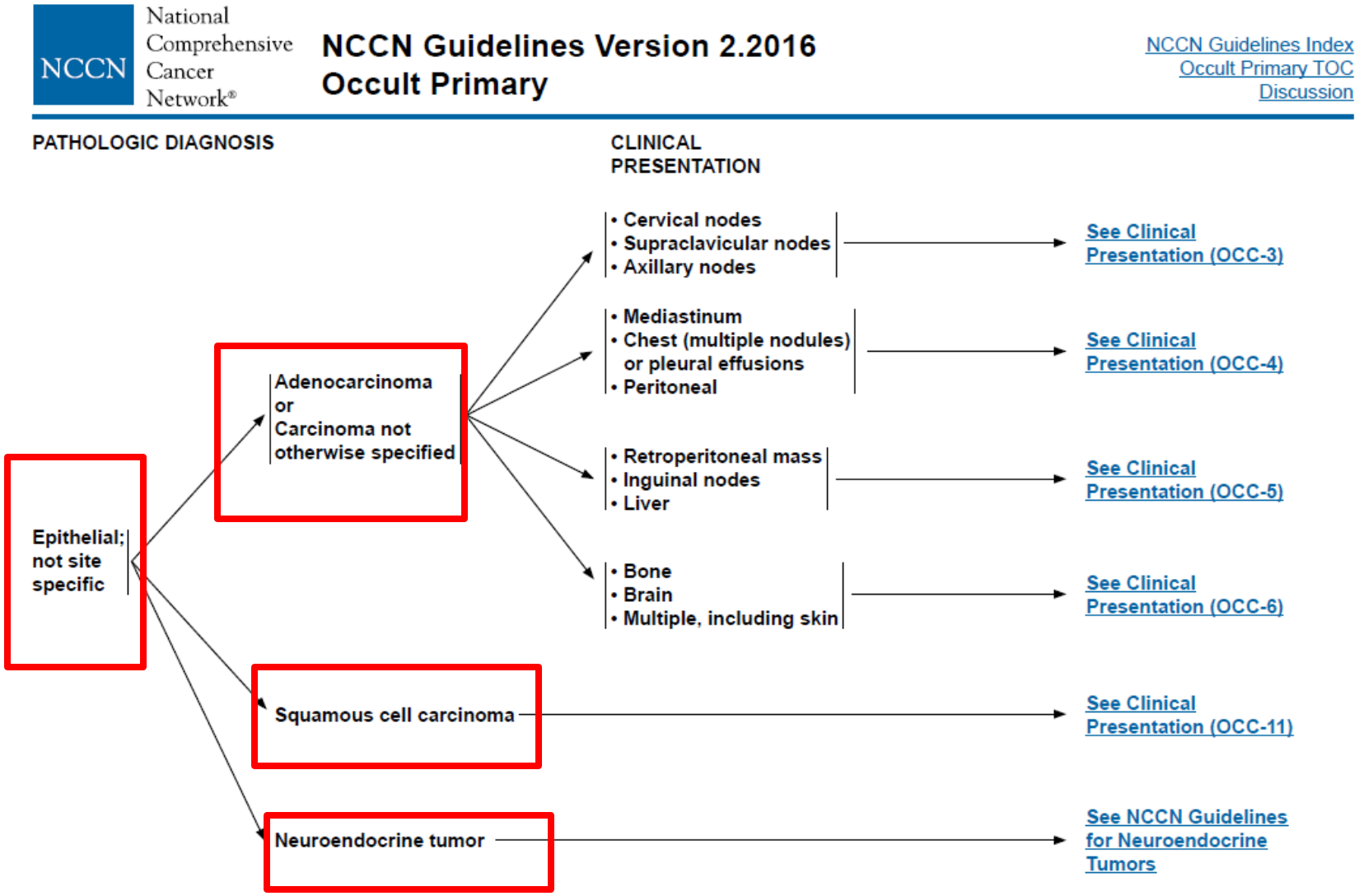
A list of definitions for abbreviations used on the slides are referenced at the end of the presentation.

Dr. Atkins: So I am the first presenter, and I am going to spend some time trying to give a broader introduction to immune therapy and just a little bit about how it is applied to kidney cancer over time. So, in 1971, President Nixon declared war on cancer and that started the National Cancer Institute. But in truth, we have been at war against cancer throughout history, as thi grave that was uncovered showing a medieval Saxon man with a large tumor on the left femur attests.

Primeri Bilinmeyen Kanserler



Primeri Bilinmeyen Kanserler



Primeri Bilinmeyen Kanserler

Tumör Tipi	Pan-keratin	CD 45	S-100 protein	Vimentin
Karsinoma	+	–	–	– /+
Lymphoma	–	+	–	– /+
Melanom	–	–	+	+
Sarcom	–	–	–	+

Primeri Bilinmeyen Kanserler

clinical practice guidelines

Annals of Oncology

Table 1. Immunohistochemical work-up in patients with cancers of unknown primary site (CUPs)

	Cytokeratins	PSA	ER, PgR	CDX2+, CK20+, CK7–	TTF1, NapsinA, CK7+	Thyroglobulin, calcitonin	NSE, chromogranin, synaptophysin	AFP, OCT4, hCG, PLAP	LCA	S100, HMB45	Vimentin, desmin
Undifferentiated carcinoma	+	–	±	–	–	–	–	–	–	–	±
Prostate cancer	+	+	–	–	–	–	–	–	–	–	–
Breast cancer	+	–	±	–	–	–	–	–	–	–	±
Colorectal cancer	+	–	–	+	–	–	–	–	–	–	–
Lung adenocarcinoma	+	–	–	–	+	–	–	–	–	–	–
Thyroid cancer	+	–	–	–	±	+	±	–	–	–	–
Neuroendocrine	+	–	–	–	±	±	+	–	–	–	–
Germ-cell cancer	+	–	–	–	–	–	–	+	–	–	±
Lymphoma	–	–	–	–	–	–	–	–	+	–	–
Melanoma	–	–	–	–	–	–	–	–	–	+	±
Sarcoma	–	–	–	–	–	–	–	–	–	±	+

The table shows general staining patterns but exceptions exist, especially for S100 and vimentin
Thyroid and neuroendocrine cancers often positive with CK7 and TTF1 but not with NapsinA.
PSA, prostate specific antigen; ER, oestrogen receptor; PgR, progesterone receptor; CK, cytokeratin; TTF1, thyroid transrcription factor 1; NSE, neuron-specific enolase; AFP, alpha fetoprotein; hCG, human chorionic gonadotropin; PLAP, placental alkaline phosphatase; LCA, leukocyte common antigen.

Primary markers

Additional markers

Primeri Bilinmeyen Kanserler

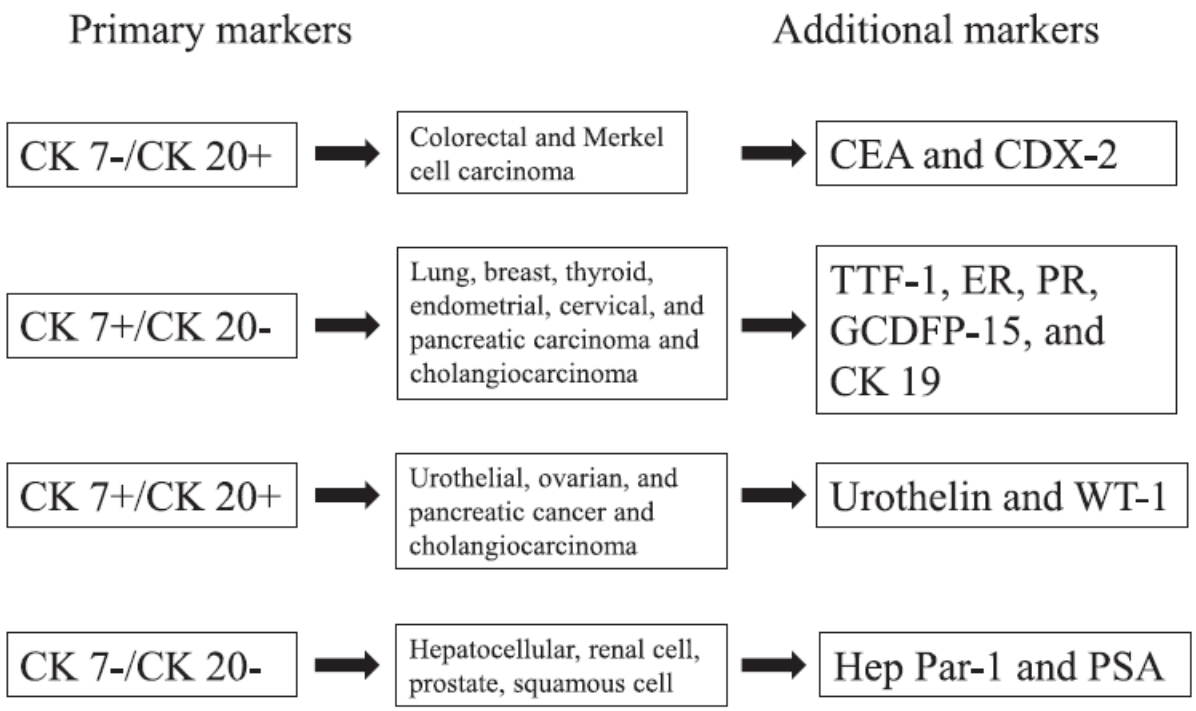


Figure 1. Basic immunohistochemical work-up of cancers of unknown primary. Reproduced with permission: [5]. CK, cyrokeratin; CEA, carcinoembryonic antigen; TTF1, thyroid transcription factor 1; ER, oestrogen receptor; PgR, progesterone receptor; GCDFP-15, gross cystic disease fluid protein-15; WT-1, Wilms tumour gene 1; PSA, prostate specific antigen.

KLİNİK DEĞERLENDİRME

- Anamnez
- Fizik muayene
- Tam kan sayımı, biyokimyasal tetkikler
- Toraks, Batın, Pelvik BT
- Kadınlarda mamografi ve jinekolojik muayene
- Erkeklerde PSA (>40 y)
- Genç erişkinlerde serum AFP and β-hCG düzeyi(50 y<)
- Semptomatik sistemlerin endoskopik incelemesi
- PET-CT

Primeri Bilinmeyen Kanserler Ailesel Risk?

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 Kanserler Ailesel Risk?

- Swedish Family–Cancer Databese

  PBC'in % 2.8 ailesel geçiş (Birinci derece)

- 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)

İYİ DİFERANSİYE ADENO CA; %60

KÖTÜ DİFERANSİYE KARSİNOM, ADENOKARSİNOM; % 29

SKUAMÖZ HÜCRELİ KARSİNOM; % 5

İNDİFERANSİYE KARSİNOM ; %5

NEUROENDOKRİNE KARSİNOM; %1

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

POSTMORTEM OTOPSİ YAPILANLARDA %25-30 PRİMER TESPİT EDİLEMEMEKTEDİR.

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Pavlidis N Pentheroudakis G Lancet 2012.

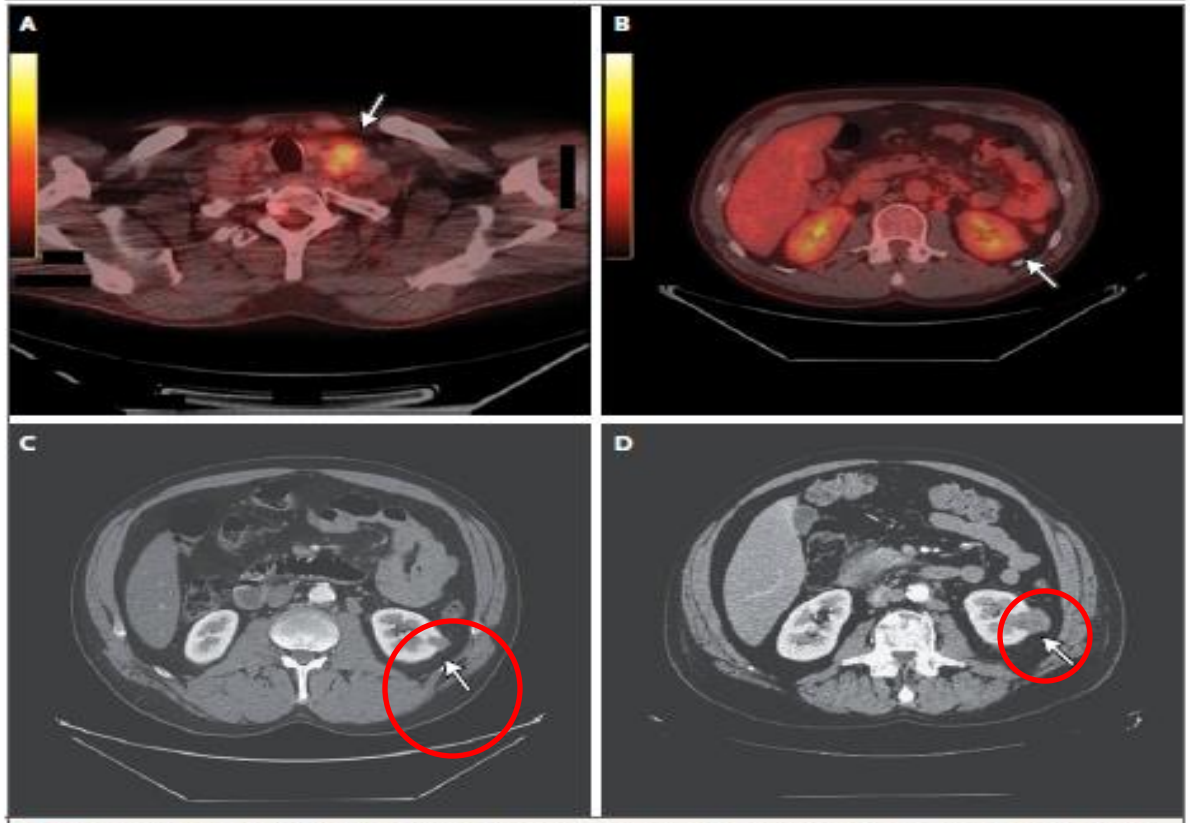
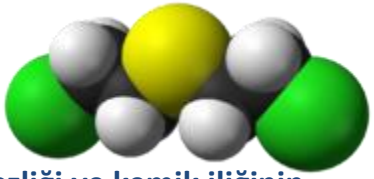


Figure 2. Drawback of Baseline ^{18}F-fluorodeoxyglucose Positron-Emission Tomography (PET)–CT as the Initial Imaging Method in Unknown Primary Cancer.

A 51-year-old man who was a smoker presented with neck adenopathy. Biopsy of the left supraclavicular lymph node revealed metastatic, poorly differentiated carcinoma. Immunostains were negative for cytokeratin (CK) 7, CK20, synaptophysin, chromogranin, S-100, melanoma antigen recognized by T cells (MART-1), prostate-specific antigen, thyroid transcription factor 1 (TTF1), inhibin, and thyroglobulin. The tumor was focally positive for Hep Par-1, CD10, and low-molecular-weight keratin, and final pathological results were reported as nonspecific. A PET-CT scan that was ordered as the baseline study in the head and neck oncology clinic showed multiple hypermetabolic nodes in the neck (Panel A, arrow). The PET-CT scan did not show a renal primary cancer, although in retrospect there was a hint of a small lesion (Panel B, arrow). The patient received chemotherapy with paclitaxel and carboplatin for unknown primary cancer favoring a lung-cancer profile. He had mild disease progression while receiving this regimen. In parallel, he underwent a tissue-of-origin molecular-profiling study that showed a kidney-cancer profile. Additional renal-specific immunohistochemical testing on the nodal tissue showed the tumor to be positive for PAX-8, renal-cell carcinoma, CD10, epithelial membrane antigen, and vimentin — findings that are consistent with conventional-type, metastatic renal-cell carcinoma. A CT scan obtained with the use of intravenous contrast material showed a mass (1.0 by 1.2 cm) in the lower pole of the left kidney (Panel C, arrow). The patient was treated with targeted therapies, including everolimus, axitinib, and pazopanib; he had a mixed response initially, followed by disease progression in lymph nodes, liver, bones, and the primary site (Panel D, arrow). This patient did not have unknown primary cancer on presentation; instead, he had metastatic renal-cell cancer that had been evaluated with a suboptimal workup. Unfortunately, even with accurate diagnosis, directed therapies do not have a clear therapeutic effect in most patients with advanced renal-cell cancer.

Kanser Tarihçesi



- Hardal gazı (mustard gas) ilk kez birinci dünya savaşında kullanılan biyolojik bir silahtır.
- Gaza maruz kalma sonucu ciltte sulu yaralar, körlük, akciğerde sıvı birikimi, akciğer yetmezliği ve kemik iliğinin baskılanması gibi ölümcül etkiler ortaya çıkar.
- Yale Üniversitesinde çalışan iki ilâç bilimci, Louis Goodman ve Alfred Gilman, mustard gazının kemik iliği baskılama özeliği nedeniyle kanser tedavisinde kullanılabileceğini ilk düşünenlerdir.
- Farelerde yaptıkları çalışmalar tümörün belirgin olarak gerilediğini gösteriyordu. Nitrogen Mustardın artık insanda denenebileceğine inanmaya başlamışlardı. Nitrogen mustardın bir örneği olan "mustine" isimli bileşiği, 48 yaşında radyasyon tedavisine yanıtsız bir lenfoma olgusuna uyguladılar.
- İlacı ne dozda ve ne kadar süre verecekleri hakında bir fikirleri olmayan bilim adamları, birbirini izleyen 10 gün boyunca ilacı farklı dozlarda denediler. Sonuç, hastanın tümör kitlesinde ikinci gün yumuşama olmuş ve tedavi sonunda belirgin bir küçülme ortaya çıkmıştı. Fakat, elde edilen bu yanıt geçiciydi ve hastalık kısa sürede tekrar etti.
- Gilman ve arkadaşları Yale Üniversitesinde 67 hastaya ilacı uyguladılar. İkinci Dünya savaşı sürüyordu, bilgileri askeri sır olarak sayılıyordu, makalelerini ancak savaştan sonra 1946 yılında yayınlandı.
- Bu makalenin onkoloji tarihinde ki yeri, kanseri ilaç ile tedavi etmek. Mısırlıların ilk kez şifalı otları hastalıkların tedavisinde kullanmaya başlamaları kadar önemli tarihsel bir olaydır.

Kanser Tarihçesi

- 1989 yılında William Halsted Amerikan Cerrahi Birliği'nin New Orleans 'taki konferansında ameliyat ettiği 76 meme kanserli hatanın verilerini sundu, hastalarının yarısı 3 yıl üçünde kaybedilmişti. Mücadele sürüyor, fakat nihaiyi çözüme çok uzaktık. William Halsted bu ekolde çok sayıda Harvey Cushing gibi ünlü cerrah yetiştiriyor

- 1895 Wilim Röntgenin X ışınlarını bulmasıyla, bu mücadeleye radyoterapi giriyor.

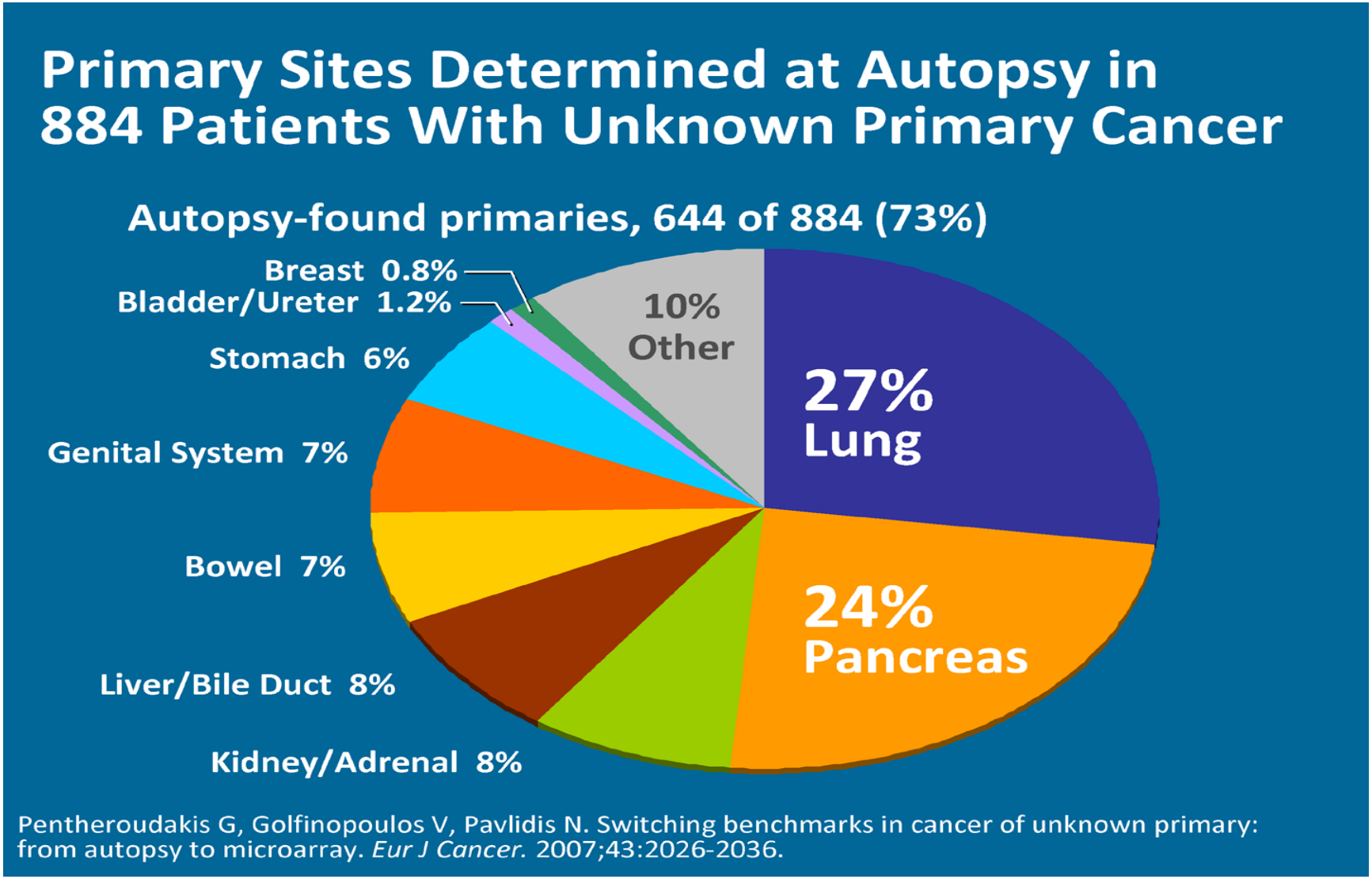
- 1896 yılında 21 yaşında bir öğrenci olan Emil Grubbe hastalığı tekrar etmiş bir meme kanserli hastasında X ışınlı tüpüyle tedavi ediyor.

- 1947 Sindey Farber , New York'da antifolatı lösemili çocuklarda kullanarak, kemoterapi kavramını kanserle olan mücadele gündeme sokuyor. Bonadonanın 1970 yılların sonlarında CMF rejmininin meme kanserinde kullanılmaya başlanmasıyla uzun yıllar kemoterapi kanserle mücadelede önemli silah olarak görüldü.

- 1990 yılların sonu ve 2000 yılların başlarında hedefe yönelik tedaviler kanser mücadelesinde yerini aldı. Bu jenerasyonun ilk örneği FDA 2001 yılında onayladığı bcr-abl füzyon genin tirozin kinaz aktivitesini inhibe eden Glivec molekülün kronik myeloid lösemide kullanılmasıdır. Bu buluştan sonra çok sayıda kanser türünde çok sayıda hedefe yönelik molekül günlük pratiğe girdi.

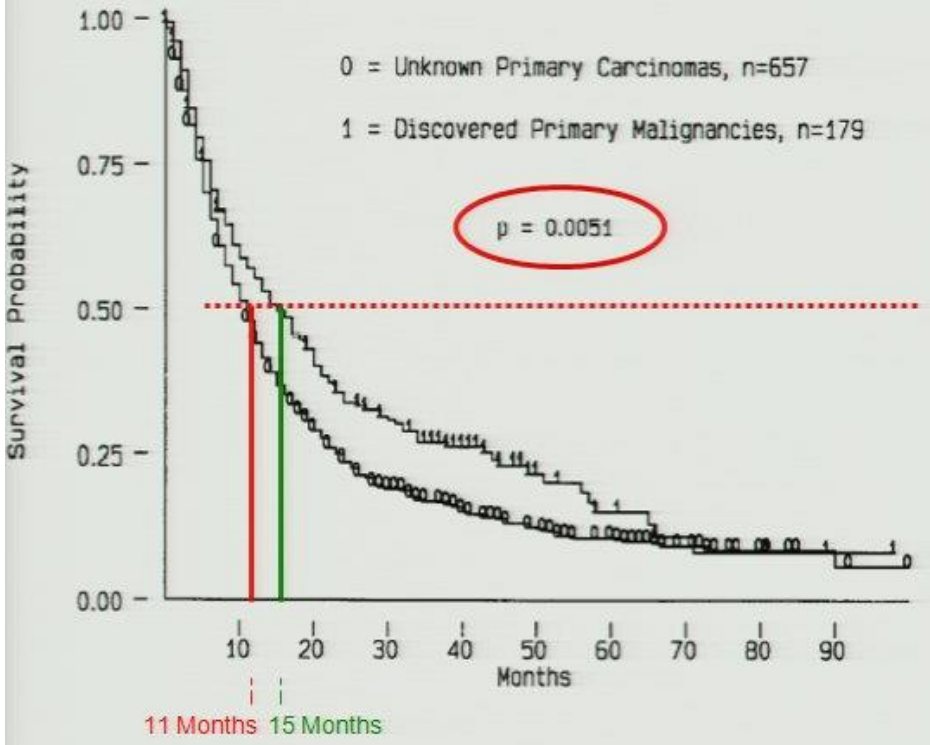
- 2013 yılında İpilimumab adlı molekül agresif cilt kanseri olan maling melanomda uzun yıllar sonra ilk defa hayatı uzatan sonuçları açıklandı. Bu çalışmayla beraber immünoterapi çok sayıdaki kanserde tedavi yerini aldı. 2015 Amerikan ulusal kanseri kongresinde Pemriluzumab adlı immüno tedavi 13 'den fazla kanser türünde kullanılmasıyla ilgili verileri sunuldu.

Primeri Bilinmeyen Kanserler Otopsi Serileri?



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

PBK Tanıya Ulaşmanın Sağkalıma Faydası?

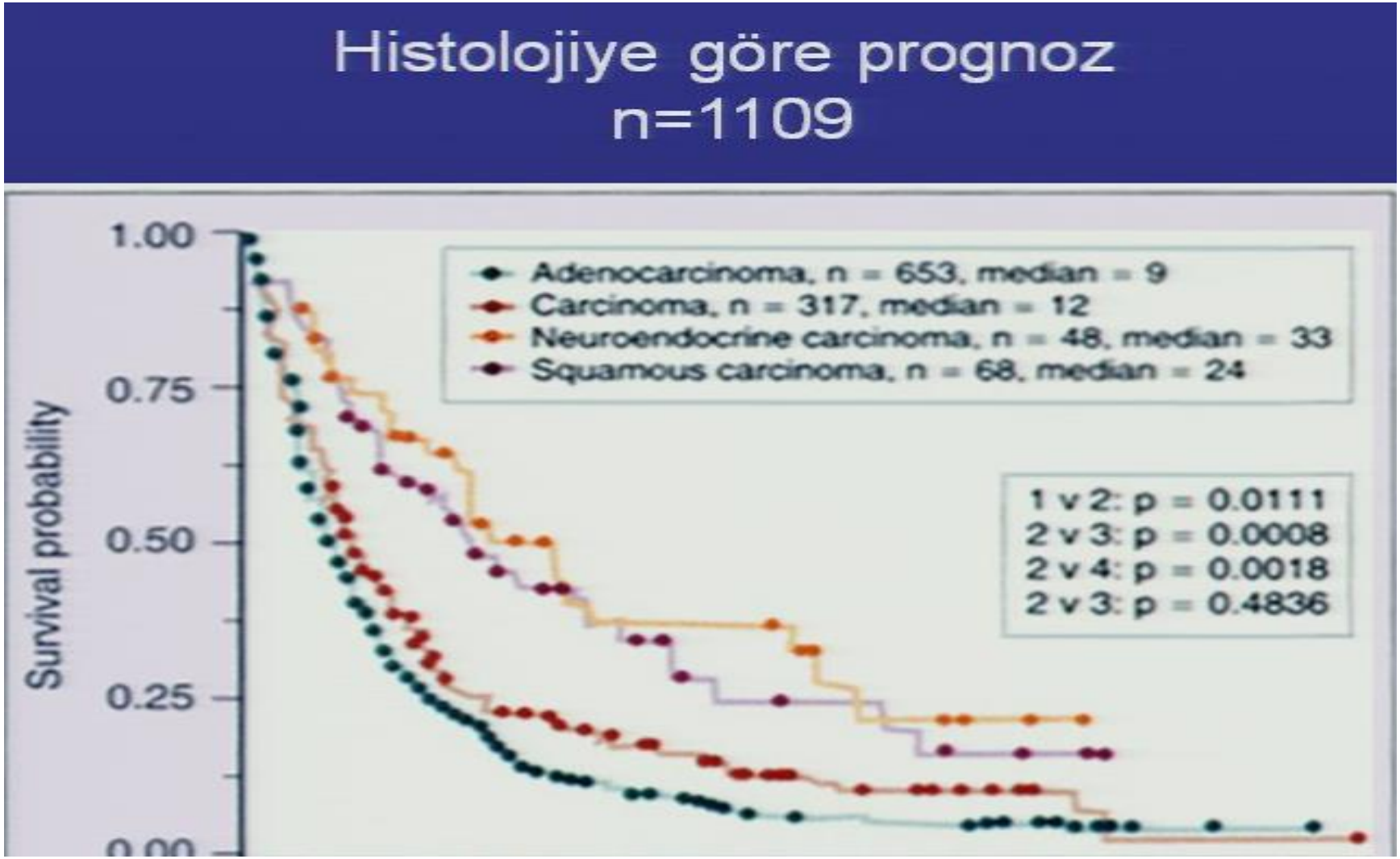


Tedaviye iyi CEVAP veren kanserler[2]:

- 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

Primeri Bilinmeyen Kanserler



PBK Tanıya Ulaşmanın Sağkalıma Faydası?

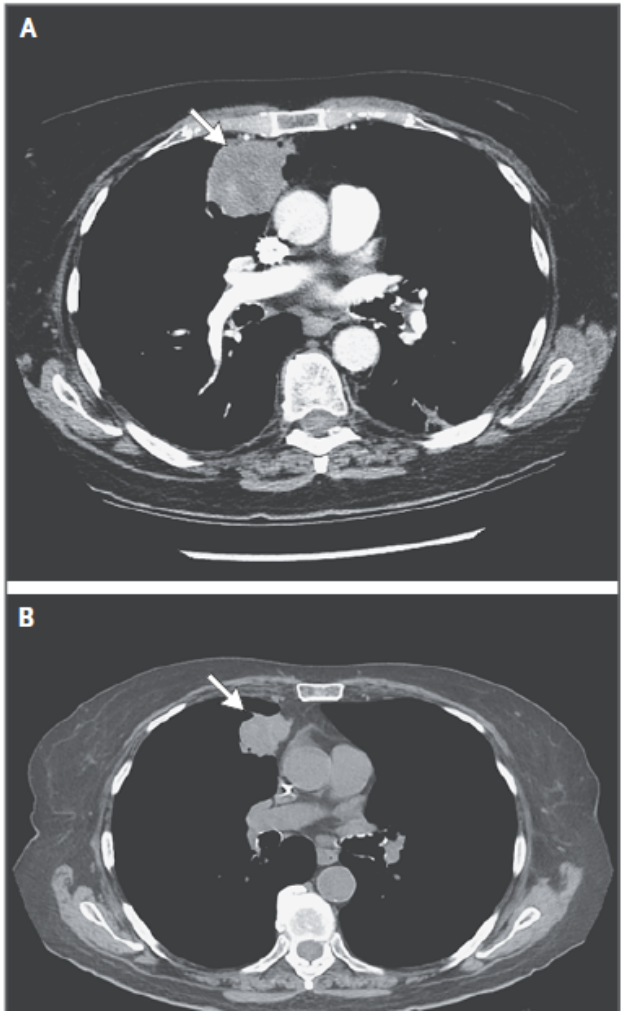
Tumör Tipi	Antikor
Meme	GCDFP-15, östrojen reseptörü
Akciğer	TTF-1
Gastrointestinal karsinom	CDX-2
Mide	CDX-2 + Hep-Par
Kolon	CDX-2 + CK20+
Karaciğer	Hep-Par
Böbrek	CD10
Prostat	Prostat-spesifik antijen
Mesane	CK7+, CK20+, CK5/6+
Seminom/ embriyonel karsinom	OCT-4
Over	WT-1, CA125
Mezotelyoma	Kalretinin
Tiroid	TTF-1 + thyroglobulin
Nöroendokrin	Kromogranin + sinaptofizin

Primeri Bilinmeyen Kanserler

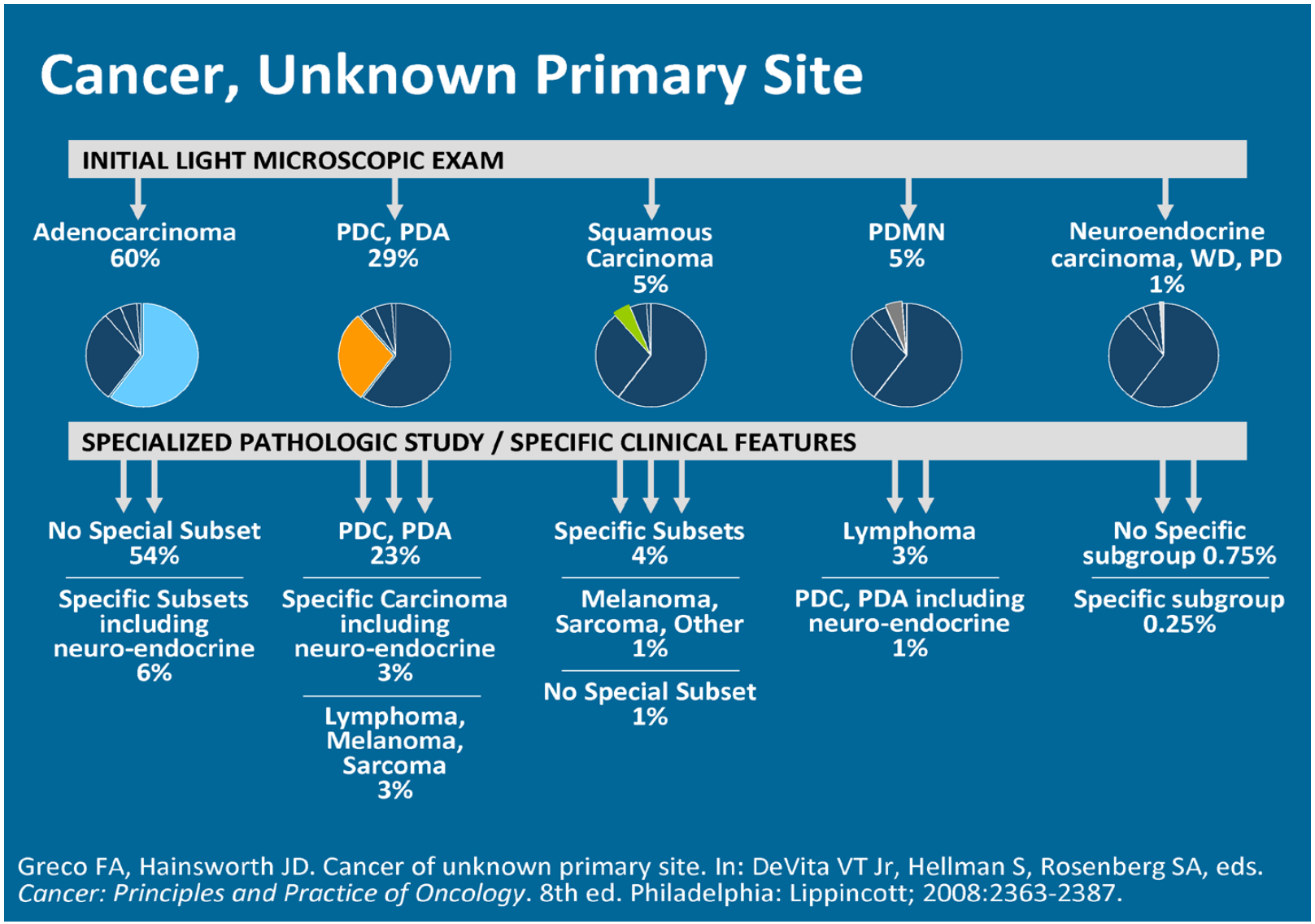
CDX-2 +, CK20 +, TTF1 - Adenokarsinom

Figure 3. Discordant Immunohistochemical and Radiologic Findings in Assessing Unknown Primary Cancer.

The patient was a 77-year-old nonsmoking woman who was seen initially in the thoracic oncology department. CT of the chest that was performed as follow-up for pneumonia revealed a 5.7-cm "lung cancer" in the right upper lobe, with minor fissure and right-middle-lobe involvement (Panel A, arrow). Biopsy of the mass revealed a moderately differentiated adenocarcinoma, strongly and diffusely positive for homeobox protein CDX-2, CK20, villin, and carcinoembryonic antigen and negative for CK7 and TTF1. The pathology report concluded that the findings favored cancer of the lower gastrointestinal tract, including the appendix and colorectum. Upper endoscopy and colonoscopy showed no abnormalities. There was no clear evidence of a primary cancer in the small bowel or appendix. After a short course of preoperative fluorouracil and oxaliplatin, the patient underwent resection of the mass (Panel B, arrow). The final pathology report was unchanged (presumed metastatic colorectal cancer). The patient received the same chemotherapy after surgery. Subsequent colonoscopies were negative. The patient was enrolled in a microRNA tissue-of-origin clinical trial, and molecular assay confirmed a colon-cancer profile. Although the benefit of chemotherapy for this presentation is unknown, clinicians who provide care for patients with unknown primary cancer have to integrate the pathological information in therapy decisions. Common presentations of unknown primary cancer with a colon-cancer profile are isolated carcinomatosis and ovarian metastases.[46]



Primeri Bilinmeyen Kanserler



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

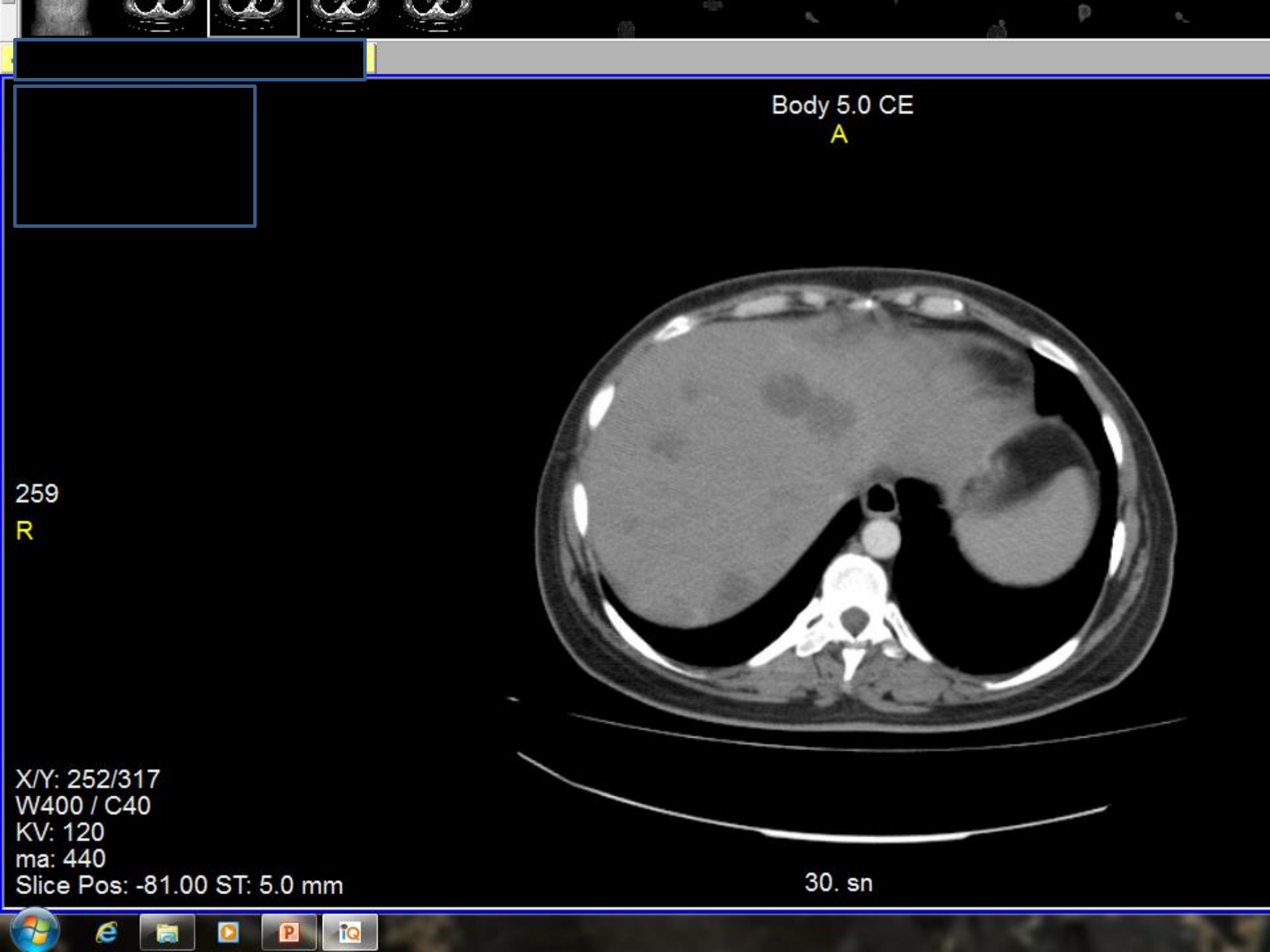
- Orta hat az diferansiye karsinom
- Az diferansiye NET
- Rezektable soliter metastazlar
- Kolon profilinde metastatik karsinom(CK20+,CK7 – CDX2+)

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

Olgu 1: Multiple Karaciğer metastazı

- 49 y, kadın
- Halsizlik, bulantı, kusma, cilt renginde sararma, kabızlık
- Öz geçmiş; Özelik yok
- Soy geçmiş; Abla meme CA
- FM; İkterik, hepatomegali, asit
- Biyokimya; Bilirubin yükse(20 mg/dl)

  AST, ALT, ALP, GGT ↑
- Lökositoz
- Histoloji (KC tru-cut); Az diferansiye adeno CA, CK 20 + ,CDX2+, CK7 -


Body 5.0 CE
A
259
R
X/Y: 252/317
W400 / C40
KV: 120
ma: 440
Slice Pos: -81.00 ST: 5.0 mm
30. sn

Olgu 1: Multiple Karaciğer metastazı, Ne yapmalı?

- Kolonoskopi ?
- Batın USG?
- Kolostomi ?
- PET-CT ?
- Tümör markırları ?
- Kemoterapi ?

PBK'de; Kolonoskopi, Bronkoskopi Hangi Hastaya?

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

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

PET-CT HANGİ GURUBA? NEYİ DEĞİŞTİRİR

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.

J Cancer Res Ther. 2014 Jan-Mar;10(1):121-6. doi: 10.4103/0973-1482.131445.

PET-CT changes the management and improves outcome in patients with recurrent colorectal cancer.

Tural D, Selçukbiricik F, Saqer S, Akar E[1], Yildiz O, Serdengeçti SH.

Author information

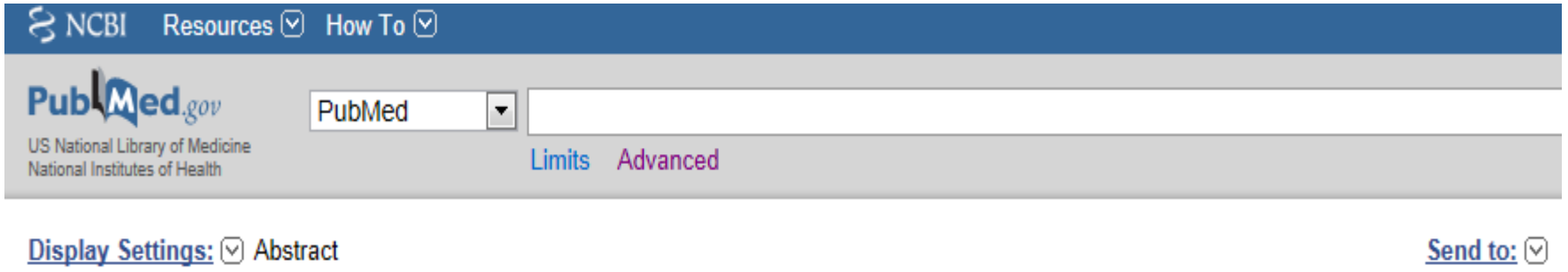
Abstract

BACKGROUND: The present study aims to analyze the impact of positron emission tomography/computed tomography (PET/CT) on management change in patients with suspected or proven colorectal cancer recurrence, and to assess the effect of this management change on progression-free survival (PFS) and overall survival (OS).

MATERIALS AND METHODS: We retrospectively evaluated 122 patients with suspected potentially resectable recurrent colorectal cancer who underwent PET/CT scan. We determined management plans for these patients before and after the PET/CT examination.

RESULTS: While previous conventional imaging studies had revealed solitary metastases, additional sites of disease were determined by PET/CT scan in 52/122 (42%) patients. PET/CT examination results changed the treatment plan to curative intent in 35 (37%) patients. While the median PFS was 22 months (95% CI, 11.2-32.6 months) among the patients planned to receive curative treatment after the PET/CT scan, it was 11 months (95% CI, 8.1-13.9 months) in patients planned to receive curative treatment before the PET/CT examination, and the difference between median PFS durations was statistically significant (HR, 0.51 [95% CI, 0.32 - 0.88], P = 0.004). Furthermore, OS was significantly longer in patients planned to receive curative treatment after the PET/CT scan (27 months [95% CI, 22.1-31.9]) compared with those who received curative treatment before the PET/CT scan (21 months [95% CI, 15.6 - 26.4]), and the difference was statistically significant (HR, 0.63 [95% CI, 0.42 - 0.89], P = 0.045).

CONCLUSION: The present study demonstrates the significant impact of PET/CT on the management and outcome in patients with recurrent colorectal cancer.



- PET-CT; PRİMERİ BİLİNMEYEN BAŞ BOYUN CA
- PRİMERİ BİLİNMEYEN SOLİTER ORGAN METASTAZLARI
- TANI VE TEDAVİ YAKLAŞIMI DEĞİŞTİRECEK HASTA GURUPLARINDA İSTENMELİ

Serum Tümör Markırları

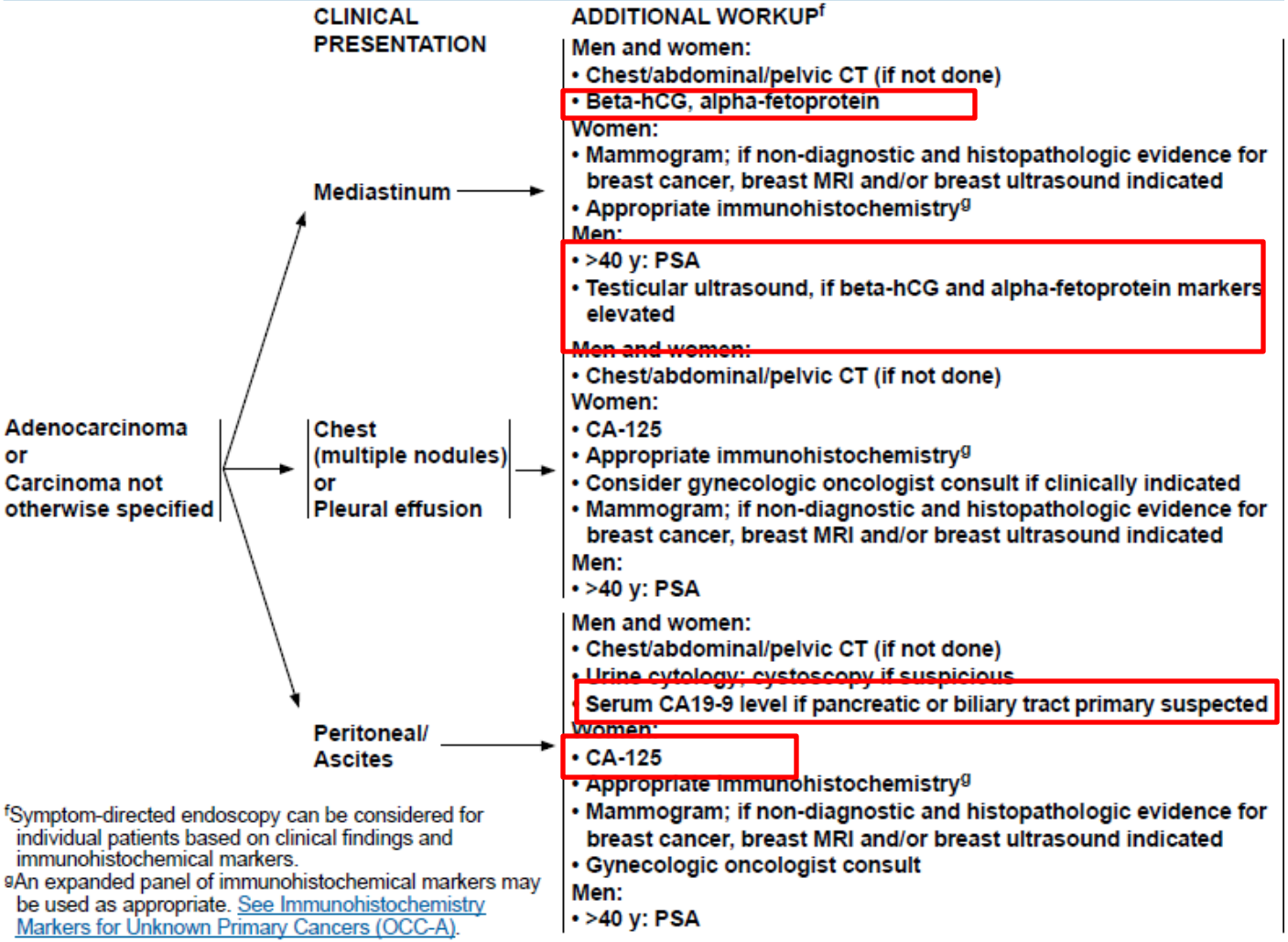
- PBK'de; CEA, CA-125, CA19-9, aFP, ßHCG yüksekliğinin tek başına tanısal ,prognostik, prediKtive değeri yoktur[1]
- Orta hat kötü diferansiye karsinomlar da aFP, ßHCG yüksekliği[2]
- Kemik metastastazı erkek hastada PSA yüksekliği[2]
- Primer seröz peritoneal adeno kanserlerde CA-125 yüksekliği[2]
-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

Serum Tümör Markırları

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2015
Occult Primary



[f]Symptom-directed endoscopy can be considered for individual patients based on clinical findings and immunohistochemical markers.

[g]An expanded panel of immunohistochemical markers may be used as appropriate. See Immunohistochemistry Markers for Unknown Primary Cancers (OCC-A).

Olgu II. İzole Aksilla Metastazı

- 58 y, postmenopozal kadın
- Öz geçmiş; Tip 2 DM, HT
- Hala meme ca
- İzole, fikse ele gelen aksiler LAM
- Aksiler Tru-cut bx; Az differansiye adeno ca

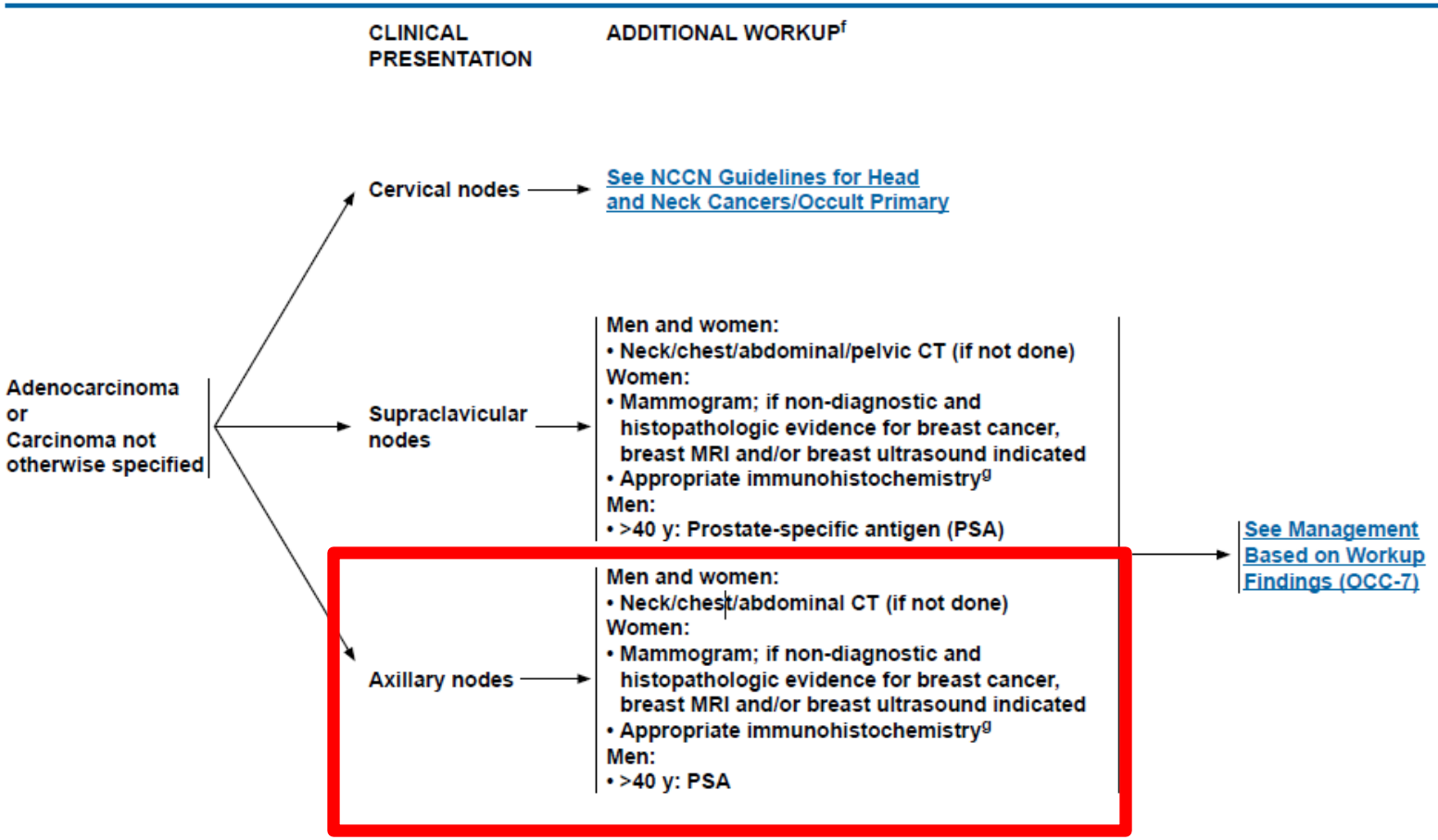
  CK-7 +,CK 20-,GCDPF-15 +,ER +,PR+,Cerb-2 -

İzole Aksilla Metastazı

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2015
Occult Primary

NCCN Guidelines Index
Occult Primary TOC
Discussion



İzole Aksiler Lenf Nodu Metastazı Olan Kadın

- Evre II meme cancerine 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.

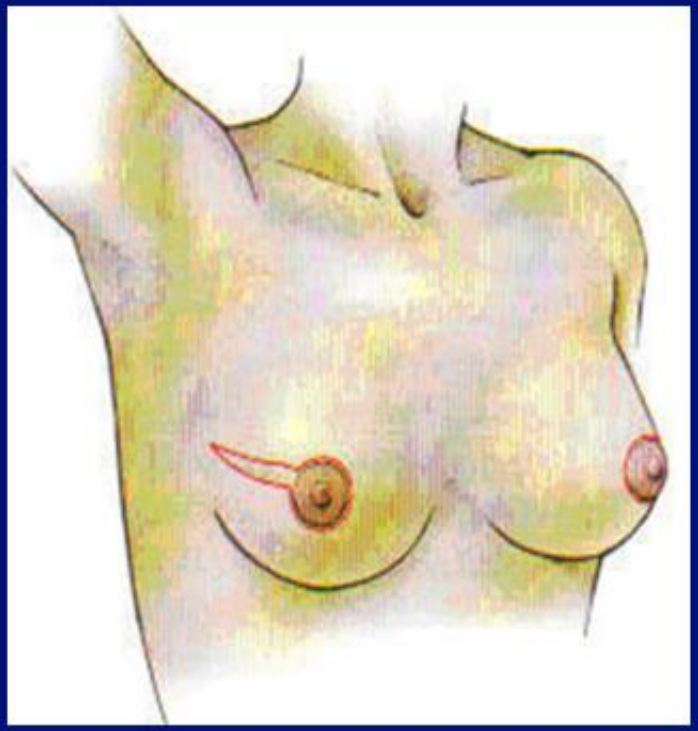
3-Axillary nodal metastases from carcinoma of unknown primary (CUPAX): a systematic review of published evidence. Breast Cancer Res Treat 2010; 119: 1–11.

İzole Aksiller Metastazı

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 Aksiller diseksiyon
- Standart Yaklaşım MRM
- Hasta isteğine bağlı olarak tüm meme ışınlaması düşünülebilir
- Karşılaştırmalı çalışma yoktur.

İzole Aksilla Metastazı

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

MR MAMOGRAFİNİN TESPİT ETMEDİĞİ HASTALARDA PRİMER ODAĞI TESPİT EDEBİLİR

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]

MeSH Terms

İzole Aksiller Metastazı Tedavi

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.

EVRE II/III MEME KANSERİ GİBİ TEDAVİ EDİLMELİDİR

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.

Olgu III; Batın içi yaygın asit kadın hasta

- 45 y, kadın
- Özgeçmişinde özelik yok
- Anne meme ca
- Batın çapında artma, dispeptik yakınmaları
- Biyokimya; N Hemogram; Anemi
- FM; Yaygın asit

Olgu III; Batın içi yaygın asit kadın hasta

- **Thoraks /batın BT;**

  Sağ plevral efüzyon, batın içi yaygın peritoneal implantlar, tüm batın yaygın masif asit

- **Laparaskopik bx**; Seröz papiler adenoca

  CK -7+,CK-20 -,MUC-5+

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 cerrahi

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

Tumour Biol. 1992;13(1-2):18-26.

Use of serum tumor markers in the differential diagnosis between ovarian and colorectal adenocarcinomas.

Yedema CA, Kenemans P, Wobbes T, Thomas CM, Bon GG, Mulder C, Voorhorst FJ, Verstraeten AA, van Kamp GJ, Hilgers J.

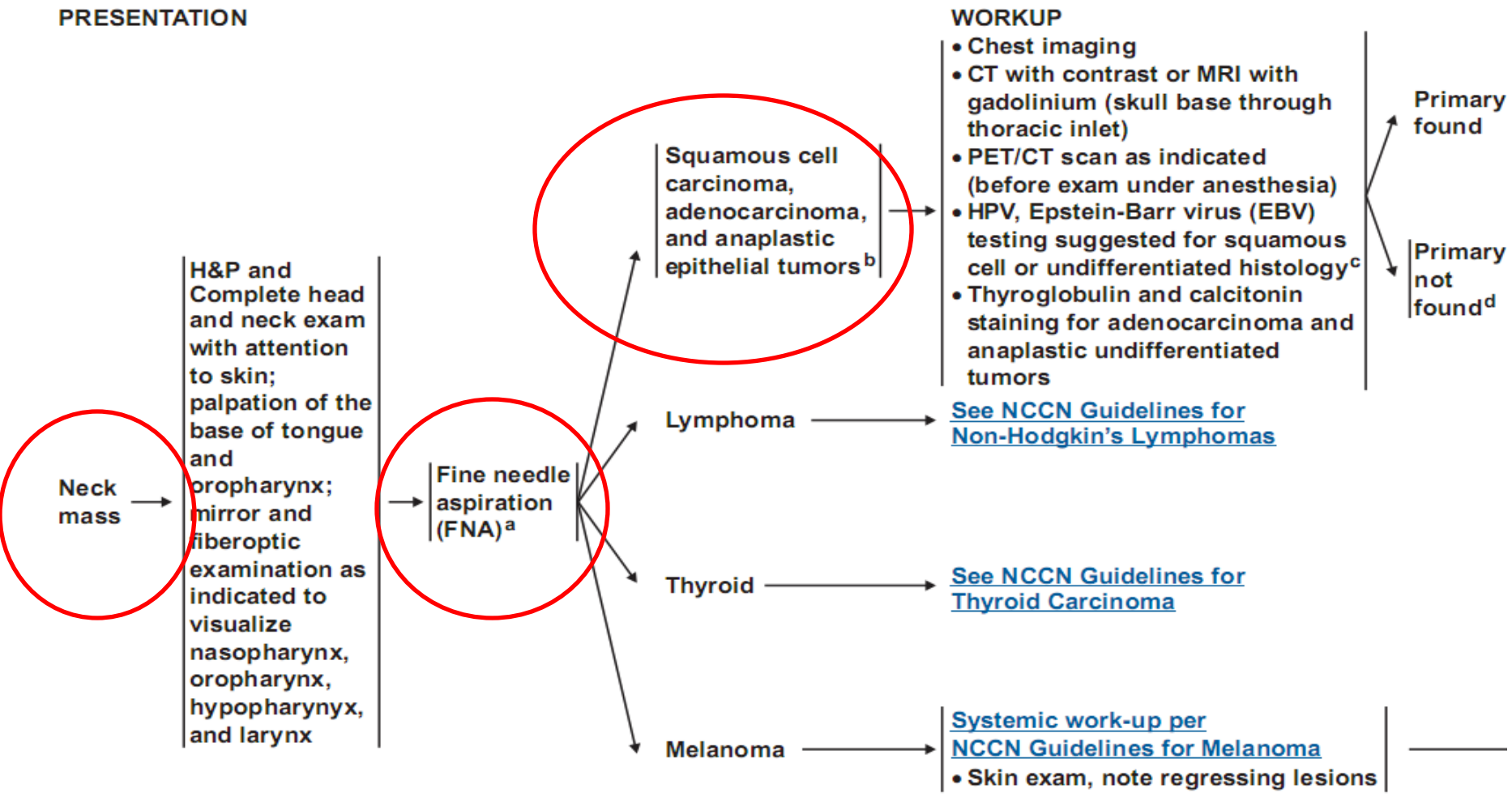
Department of Obstetrics and Gynecology, Clinical Chemistry, Amsterdam, The Netherlands.

Abstract

In the search for a method to facilitate the preoperative discrimination of ovarian carcinomas from colorectal carcinomas serum levels of 6 tumor markers were measured in 47 patients presenting with ovarian cancer and compared to levels found in 24 female patients with advanced, untreated colorectal cancer. The markers studied were CA 125, CA 15.3, CA 19.9, CEA and two recently developed mucin markers, CA M29 and CA M26. Levels of CA 125, CA 15.3, CEA and CA M29 showed significant differences between both groups. In predicting ovarian cancer, sensitivity was highest for CA 125 at 94% (35 U/ml cutoff level). However, the specificity of CA 125 was at 71% low. Specificity increased significantly by using a combination of a CA 125-positive score (greater than 35 U/ml) and a simultaneous negative CEA score (less than or equal to 5 ng/ml) (specificity 100%, sensitivity 81%). A CA 125/CEA serum ratio greater than 25 resulted in the highest discriminative power with a specificity of 100% and a sensitivity of 91% resulting in an overall test accuracy of 94%. It is concluded that the serum tumor markers used, especially a combination of CA 125 and CEA, are helpful in the preoperative differential diagnosis between adenocarcinomas of ovarian and colorectal origin.

PMID: 1589694 [PubMed - indexed for MEDLINE]

Servikal lenf nodu metastazı(SCC)



Servikal lenf nodu metastazı

- 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.

Figure 1

Anatomic sites and subsites of the head and neck

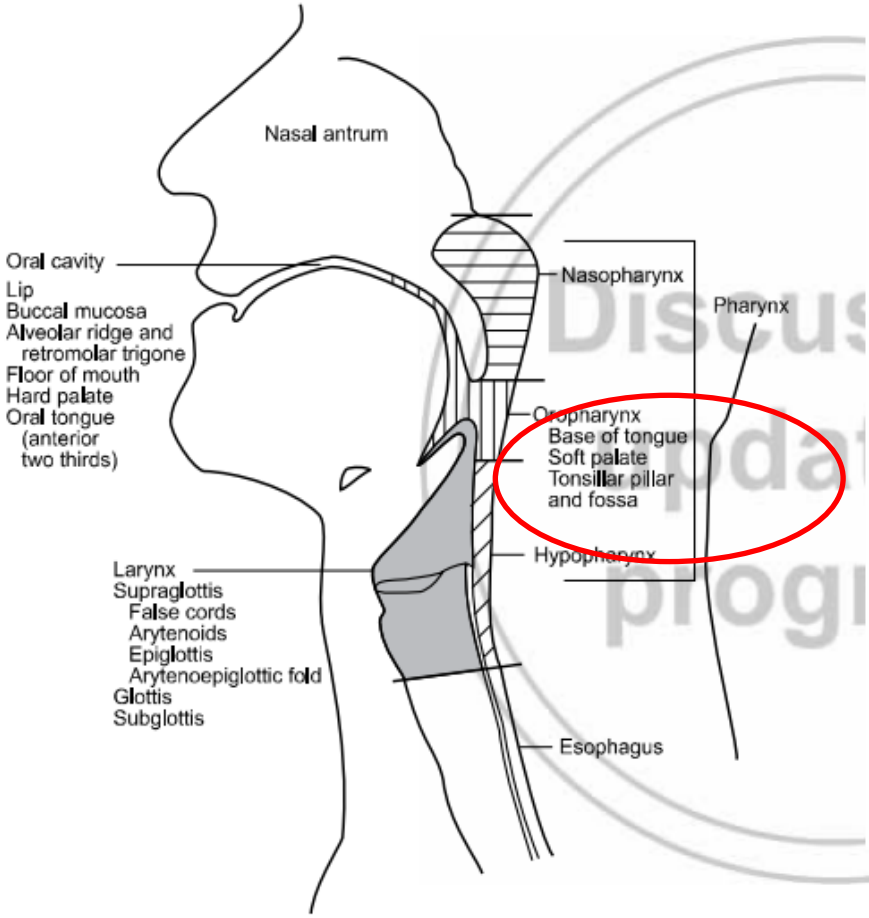
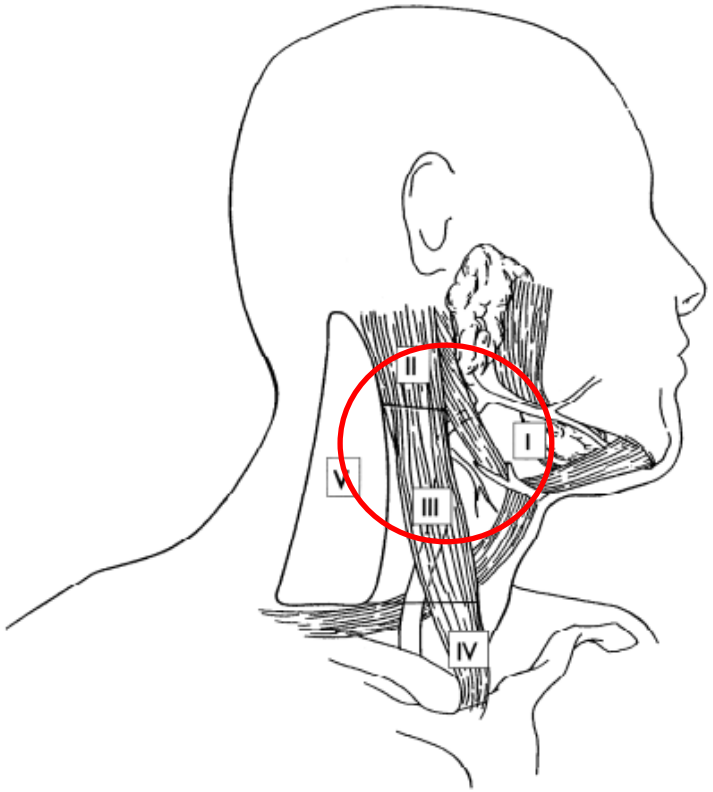


Figure 2

Level designation for cervical lymphatics in the right neck



PBM; Servikal lenf nodu metastazı (SCC)

- 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 KRT(kategori 3)

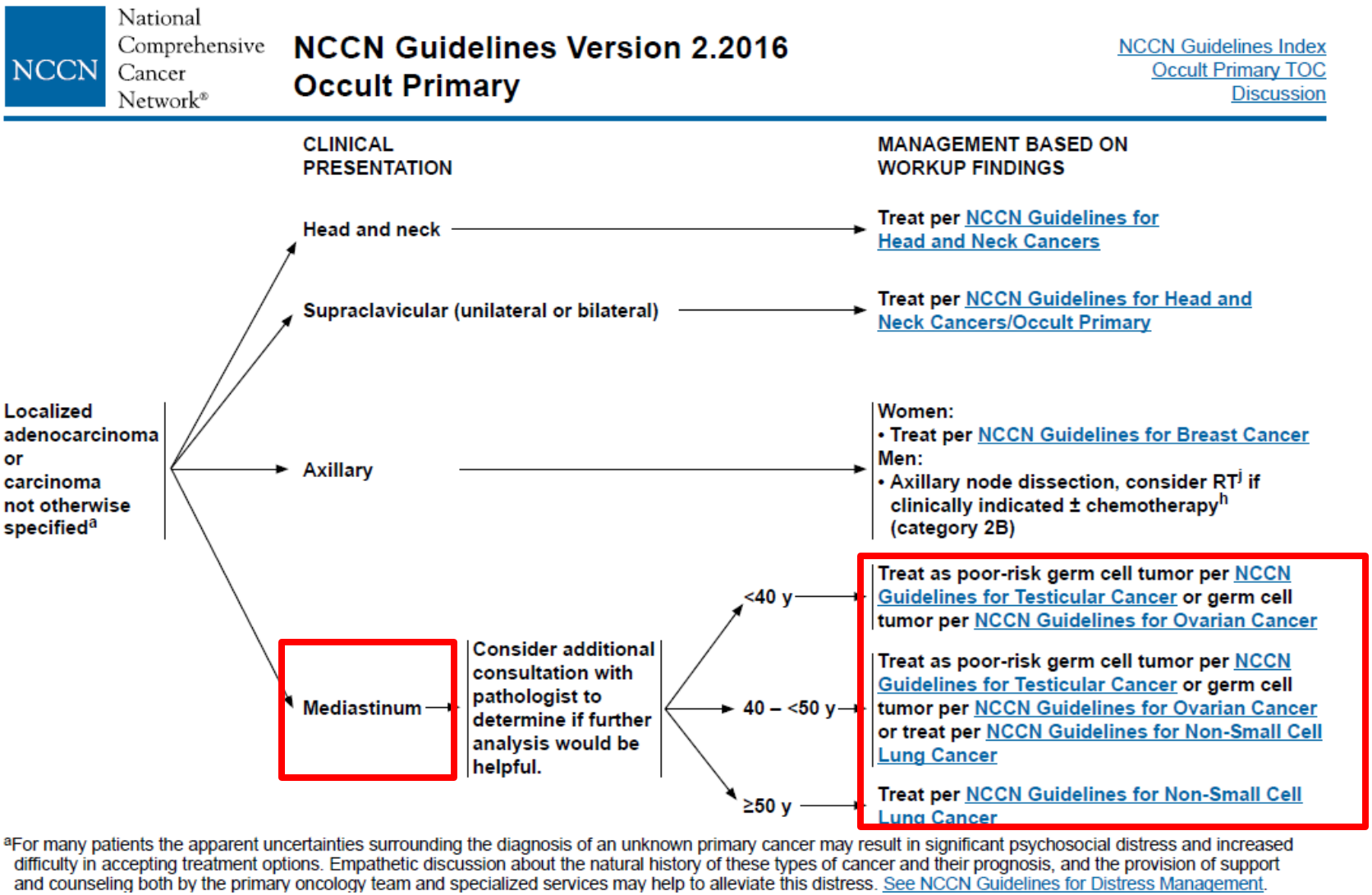
Olgu IV; Multiple mediastinal metastaz erkek hasta

- 42 y, Erkek
- Sol supraklaviculer elle gelen 3x4 cm LAM
- Özgeçmişinde özelik yok
- Soygeçmişinde özelik yok
- 15 paket/ yıl sigara

Supraklaviculer ve mediastinal metastaz erkek hasta

- Toraks/batın BT;
  Supraklavikuler ve mediyastinal yaygın LAM
- Sol servikal İBx; Az differansiye adeno ca
- aFP ; 1000, ßHCG;1, LDH;100

Supraklaviculer ve mediastinal metastaz erkek hasta



[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.

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

Orta hat kötü diferansiyeli karsinom/adenokarsinom

RISK CLASSIFICATION FOR ADVANCED DISEASE
(post-orchiectomy)[1]

Risk Status	Nonseminoma	Seminoma
Good Risk	Testicular or retroperitoneal primary tumor and No nonpulmonary visceral metastases and Post-orchiectomy markers- all of: AFP < 1,000 ng/mL hCG < 5,000 iu/L LDH < 1.5 x upper limit of normal	Any primary site and No nonpulmonary visceral metastases and Normal AFP Any hCG Any LDH
Intermediate Risk	Testicular or retroperitoneal primary tumor and No nonpulmonary visceral metastases and Post-orchiectomy markers- any of: AFP 1,000-10,000 ng/mL hCG 5,000-50,000 iu/L LDH 1.5-10 x upper limit of normal	Any primary site and Nonpulmonary visceral metastases and Normal AFP Any hCG Any LDH
Poor Risk	Mediastinal primary tumor or Nonpulmonary visceral metastases or Post-orchiectomy markers- any of: AFP > 10,000 ng/mL hCG > 50,000 iu/L LDH > 10 x upper limit of normal	No patients classified as poor prognosis

Source: Figure 4 from the International Germ Cell Cancer Collaborative Group: International Germ Cell Consensus Classification: A Prognostic Factor-Based Staging System for Metastatic Germ Cell Cancers. J Clin Oncol 1997;15(2):594-603. Reprinted with

İzole ingunal lenf nodu SCC metastazı

- Tümör genellikle anorektal veya genital bölgede lokalizedir

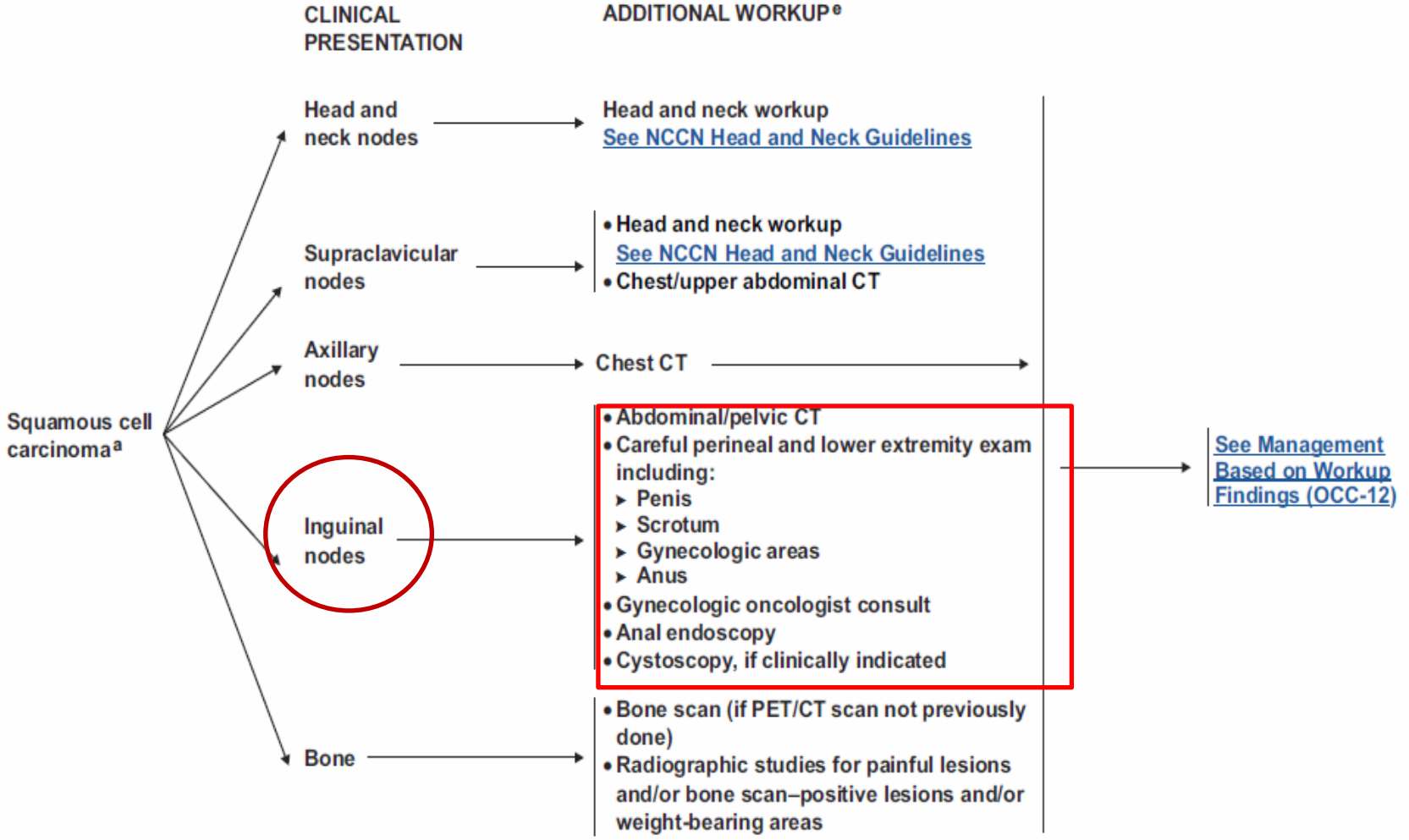
- Primer odak bulunmadığı zaman

  İnguinal lenf nodu diseksiyonu *+* RT tedavi

  seçeneği olarak düşünülebilinir

  İlave kemoterapi ?

İzole ingunal lenf nodu SCC metastazı



[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 Distress Management Guidelines.

[e] Symptom directed endoscopy based on clinical findings and immunohistochemical markers can be considered for individual patients.

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

Kötü diferansiye neroendokrine tümör

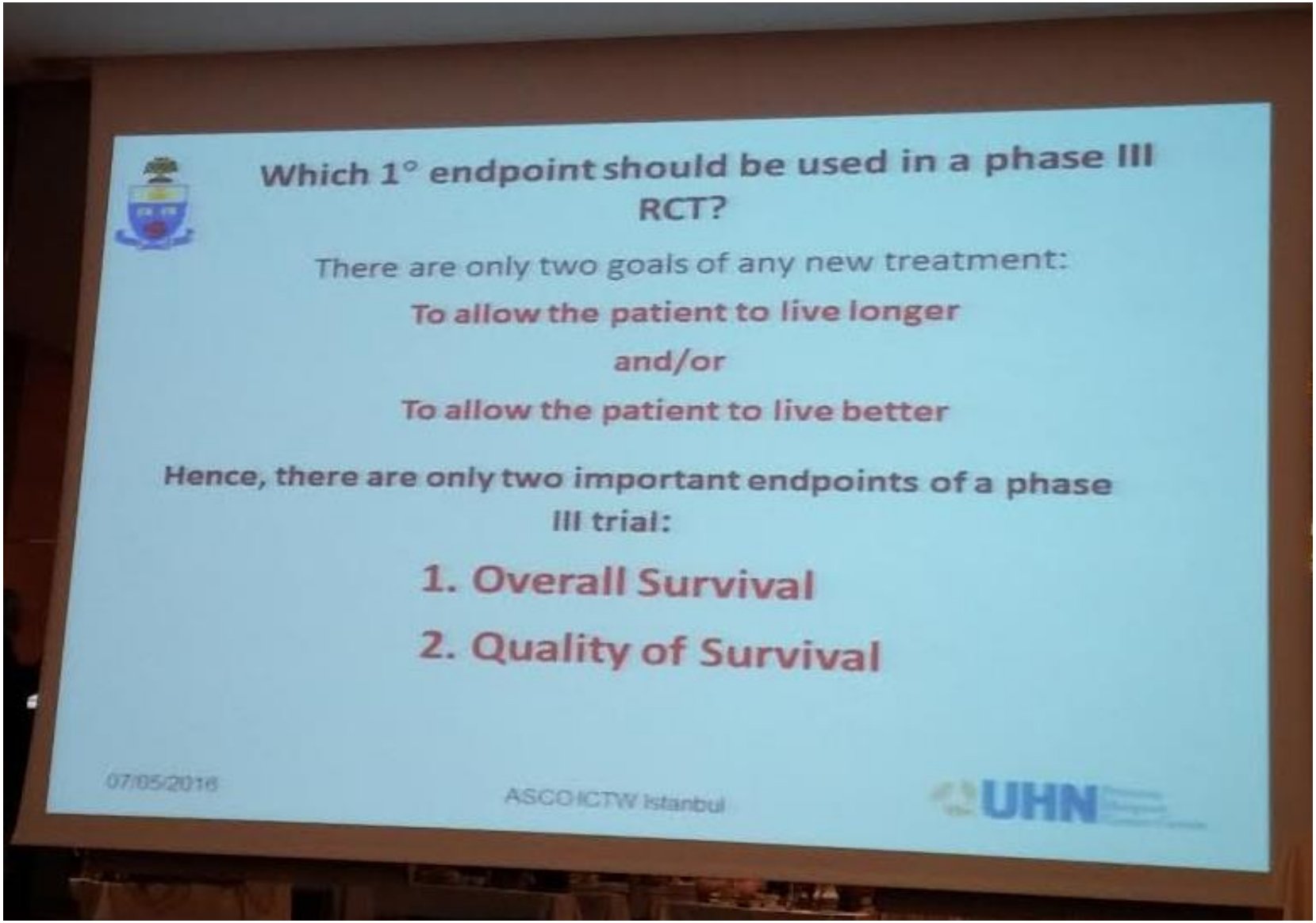
- Agresif seyirlidir
- Genellikle multiple karaciğer ve kemik metastazı ile preente olur
- Platin bazlı KT iyi yanıt verir

Az diferansiye karsinom	Genç erkek, Mediastinal Retroperitoneal lenf nodu Akciğer met	B-HCG AFP Kromozom 12 FISH	Extragonadal germ hücreli tümör gibi tedavi
Adenokarsinom	Aksiller LAP-kadın	Meme MR ER-PR HER-2	Evre II meme gibi
	Peritoneal karsinomatoza-kadın	Ca-125	Evre III over gibi tedavi
	Blastik kemik met PSA yüksekliği-erkek		Metastatik prostat gibi tedavi
	Tek metastaz	PET-CT	Lokal tedavi
Skuamöz karsinom	Servikal LAP	KBB muayenesi Nazofarenks Biyopsi Endoskopi Pet-CT	Lokal İleri baş boyun gibi
	İnguinal LAP		Inguinal lenf nodu diseksiyonuRT±KT
Nöroendokrin karsinom	İyi diferansiye Az diferansiye		Karsinoid veya adacık Küçük Hücreli gibi

KÖTÜ PROGNOSTİK GRUPLAR

- Multiple KC metastazı
- Multiple Kemik metastazları
- Non-papiller malign asit
- Multiple akciğer/plevral metastazlar
- Perikard metastazı

Tedavinin Amacı Ne Olmalı?



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].

PRINCIPLES OF CHEMOTHERAPY

- Consider chemotherapy in symptomatic patients PS 1-2 or asymptomatic patients (PS 0) with an aggressive cancer.
- Base the chemotherapy regimen (list below and others) to be used on the histologic type of cancer.

SELECTED CHEMOTHERAPY REGIMENS FOR OCCULT PRIMARIES

Adenocarcinoma	
Paclitaxel[1]	200 mg/m^2/3 h IV d 1
Carboplatin[1]	AUC = 6 d 1, repeat cycle every 3 wks
Paclitaxel[2]	200 mg/m^2/1 h IV d 1
Carboplatin[2]	AUC = 6
Etoposide[2]	50 mg/d PO alternating with 100 mg/d PO d 1-10, repeat cycle every 3 wks
Docetaxel[3]	65 mg/m^2 IV d 1
Carboplatin[3]	AUC = 6 d 1, repeat cycle every 3 wks
Gemcitabine[4]	1250 mg/m^2 IV d 1 and 8
Cisplatin[4]	100 mg/m^2 IV d 1, repeat cycle every 3 wks
Gemcitabine[5]	1000 mg/m^2 IV d 1 and 8
Docetaxel[5]	75 mg/m^2 IV d 8, repeat cycle every 3 wks

Squamous Cell Carcinoma	
Paclitaxel[6]	175 mg/m^2/3 h IV d 1
Cisplatin[6]	100 mg/m^2 IV d 2
5-FU[6]	500 mg/m^2/d continuous infusion over 120 h, repeat cycle every 3 wks
Docetaxel[7]	75 mg/m^2 IV d 1
Cisplatin[7]	75 mg/m^2 IV d 1
5-FU[7]	750 mg/m^2/d continuous infusion d 1-5, repeat cycle every 3 wks

Neuroendocrine Tumors
For poorly differentiated (high grade or anaplastic) or small cell subtype other than lung neuroendocrine tumors, see NCCN Small Cell Lung Cancer Guidelines
For moderate and well-differentiated neuroendocrine tumors, see NCCN Neuroendocrine Tumors Guidelines-Carcinoid Tumors

See references on OCC-B 2 of 2

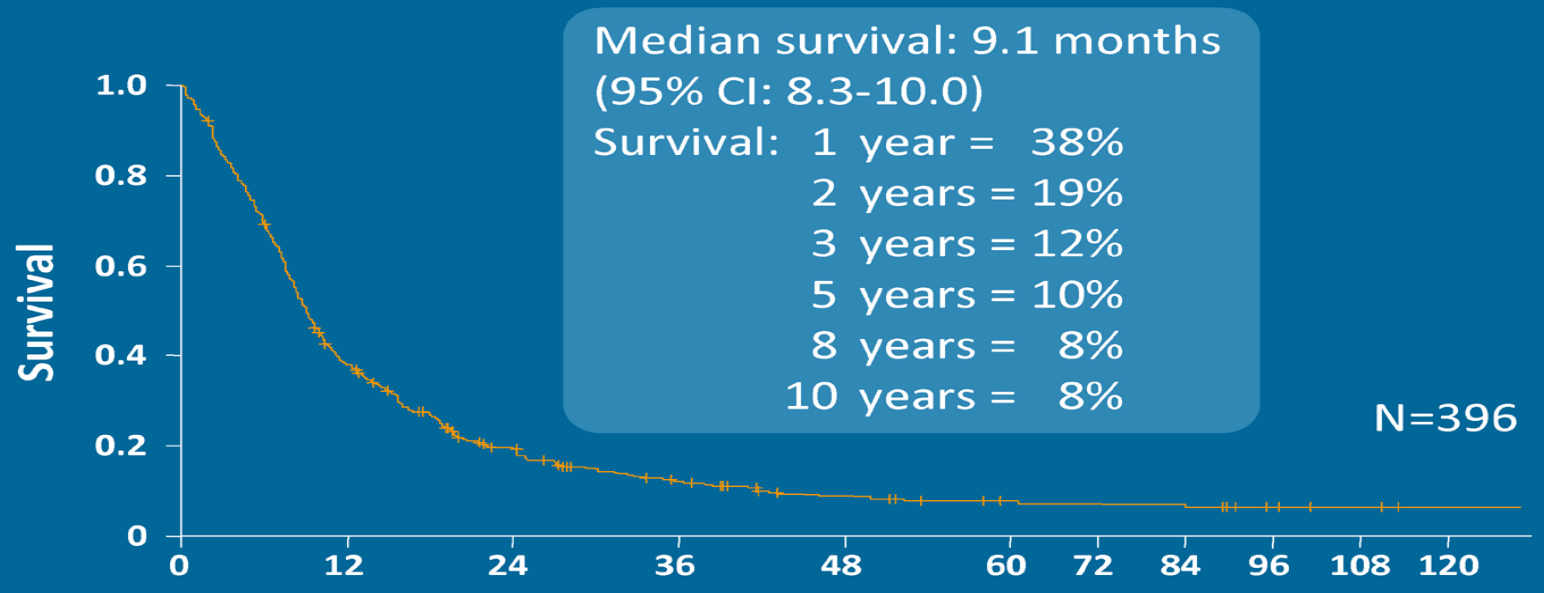
ECOG PERFORMANCE STATUS (PS)

Grade	
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hrs
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair

Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbone PP. Toxicity and response criteria of The Eastern Cooperative Oncology Group. Am J Clin Oncol 1982:5;649-655.

Kötü prognostik grupta tedavi

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.

- Pasifik Porsuk Ağacı
- Taxaceae familyasından, *Taxus* cinsinden
- Türkiyede; Kuzey Anadolu, Toroslar bölgesinde genelde yetişir
- Uzun ömürlü, 2000-3000 yılık olanlar vardır
- Yaprakları oldukça zehirlidir.
- Kızıl deriler zehirli ok uçları bu ağaçtan elde etmişler
- NCI ilk çalışmalarında; bir gram taksol elde etmek için, yüz kadar prosuk ağacı gerekmiştir.

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].

JOURNAL OF CLINICAL ONCOLOGY

Phase II Trial of Bevacizumab and Erlotinib in Carcinomas of Unknown Primary Site: The Minnie Pearl Cancer Research Network

John D. Hainsworth, David R. Spigel, Cindy Farley, Dana S. Thompson, Dianna L. Shipley and F. Anthony Greco

[+] Author Affiliations

Address reprint requests to John D. Hainsworth, MD, Sarah Cannon Research Institute, 250 25th Ave North, Suite 220, Nashville, TN 37203; e-mail: jhainsworth@tnonc.com

Abstract

Purpose Treatment remains poor for many patients with carcinoma of unknown primary site (CUP), and no effective second-line treatment has been identified. Combination inhibition of vascular endothelial growth factor (VEGF) and the epidermal growth factor receptor (EGFR) with bevacizumab and erlotinib has proved efficacious and well tolerated in other solid tumors. We therefore have evaluated the efficacy and toxicity of this combination in patients with CUP.

Patients and Methods Patients with CUP who either had received previous chemotherapy or were previously untreated with poor-prognosis clinical features were eligible for this study. All patients received bevacizumab 10 mg/kg IV every 2 weeks, along with erlotinib 150 mg orally daily. Patients were re-evaluated after 8 weeks of treatment; those with objective response or stable disease continued treatment until disease progression.

Results Forty-seven (92%) of 51 patients received at least 8 weeks of treatment. Five patients (10%) had partial responses, and 29 patients (61%) had stable disease as the best response. The median survival for the entire group was 7.4 months, with 33% of patients alive at 1 year. This regimen was well tolerated by most patients.

The Oncologist®

The official journal of the Society for Translational Oncology

Paclitaxel/Carboplatin plus Bevacizumab/Erlotinib in the First-Line Treatment of Patients with Carcinoma of Unknown Primary Site

John D. Hainsworth[a,b], **David R. Spigel**[a,b], **Dana S. Thompson**[b], **Patrick B. Murphy**[b], **Cassie M. Lane**[a], **David M. Waterhouse**[c], **Yuval Naot**[d] and **F. Anthony Greco**[b]

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This Article

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The Oncologist **December 2009** vol. 14 no. 12 **1189–1197**

» Abstract
Full Text
Full Text (PDF)

[−] Classifications

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Hainsworth JD. Oncologist. 14. 2009 (dörtlü kombinasyon)

- Faz II çalışma, ilk basamak tedavi
- 60 hasta
- Dört kür paklitaksel, karboplatin, bevacizumab ve erlotinib (4'lü kombinasyon)
- Daha sonra progresyon görülene kadar bevacizumab+erlotinibe devam

Hainsworth JD. Oncologist. 14. 2009

- Dört siklus tedaviyi %82 hasta tamamladı
- Hastaların %73 idame tedavisi aldı.
- %53 cevap.
- Median PFS 8 ay
- Median OS 12.6 ay
- İki yıllık OS %27

Primeri Bilinmeyen Kanserler

The NEW ENGLAND JOURNAL of MEDICINE

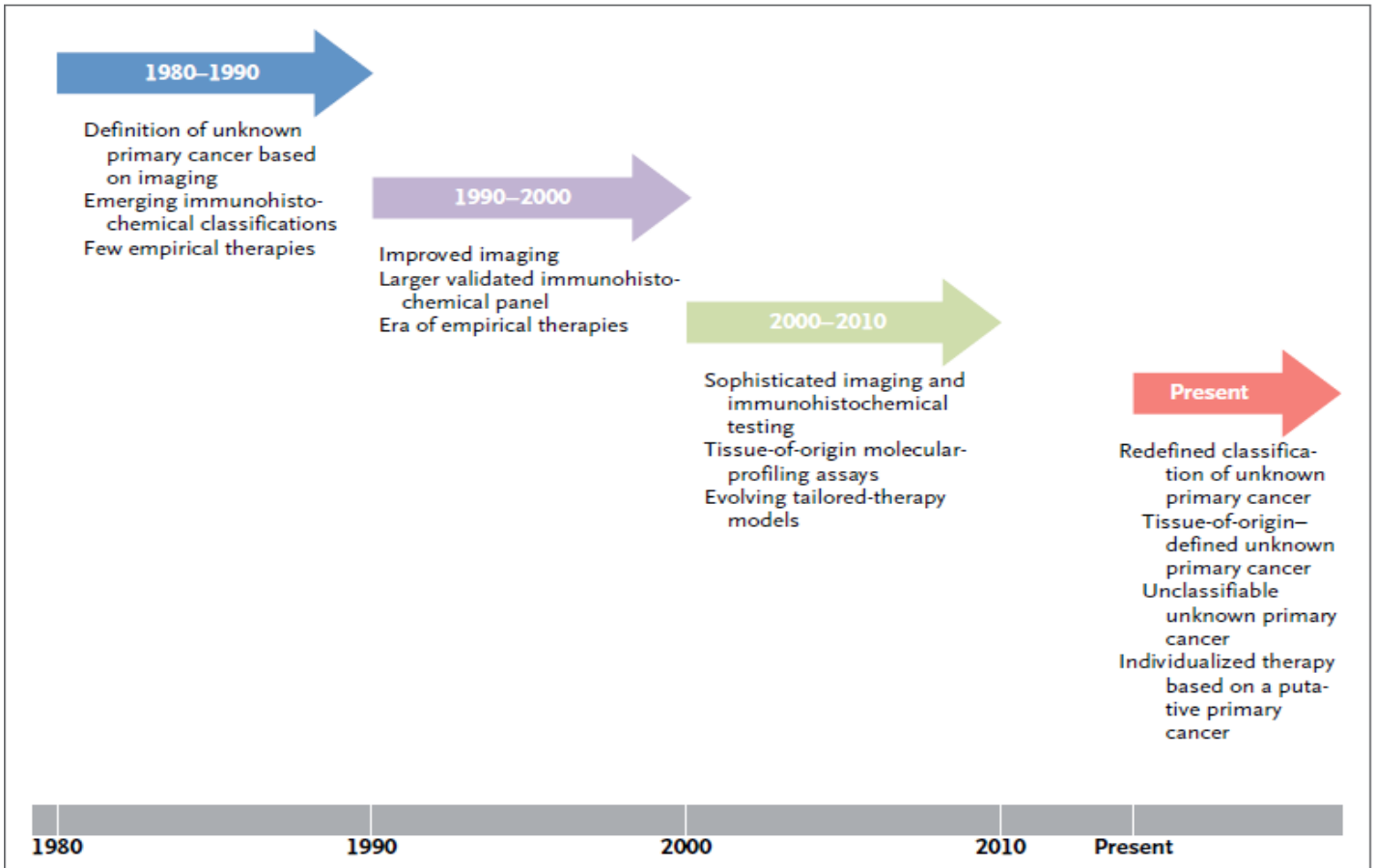

Figure 1. Classification of Unknown Primary Cancer through the Decades.
Over the years, we have seen an improvement in diagnostic methods, including imaging, pathological testing, and molecular markers. These advances have helped define the current taxonomy of unknown primary cancer.

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.

PBM Tedavi Algoritması(ESMO)

Table 3. Therapy for patients with favourable-risk cancers of unknown primary site (CUPs)

CUP subtype	Proposed treatment	Potential equivalent tumour
Poorly differentiated neuroendocrine carcinomas of an unknown primary	Platinum + etoposide combination chemotherapy	Poorly differentiated neuroendocrine carcinomas with a known primary
Well-differentiated neuroendocrine tumour of unknown primary	Somatostatin analogues, streptozocin+5-FU, sunitinib, everolimus	Well-differentiated neuroendocrine tumour of a known primary site
Peritoneal adenocarcinomatosis of a serous papillary histological type in females	Optimal surgical debulking followed by platinum–taxane-based chemotherapy	Ovarian cancer
Isolated axillary nodal metastases in females	Axillary nodal dissection, mastectomy or breast irradiation and adjuvant chemohormonotherapy	Breast cancer (found in 50%–70% when breast MRI is performed)
Squamous cell carcinoma involving non-supraclavicular cervical lymph nodes	Neck dissection and/or irradiation of bilateral neck and head–neck axis. For advanced stages induction chemotherapy with platinum-based combination or chemoradiation	Head and neck squamous cell cancer
CUP with a colorectal IHC (CK20+ CDX2+ CK7−) or molecular profile	Systemic treatment used for colorectal cancer	Metastatic colorectal cancer
Single metastatic deposit from unknown primary	Resection and/or RT ± systemic therapy	Single metastasis
Men with blastic bone metastases or IHC/serum PSA expression	Androgen deprivation therapy ± RT	Prostate cancer

5-FU, 5-fluorouracil; MRI, magnetic resonance imaging; IHC, immunohistochemistry; PSA, prostate-specific antigen; RT, radiotherapy; CK, cytokeratin.

PBM Tedavi Algoritması(ESMO)

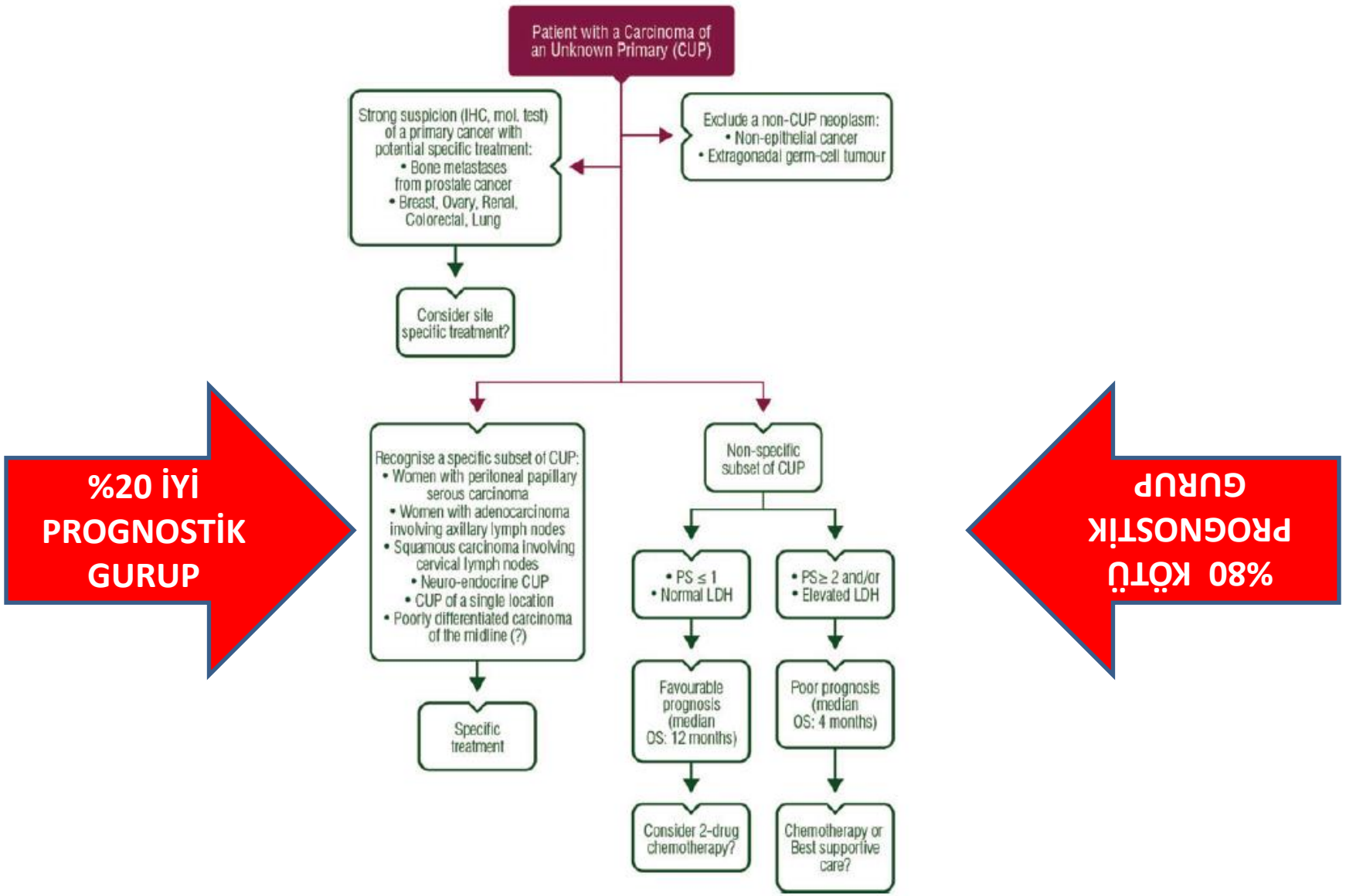

Figure 2. Clinical management of patients presenting with CUPs. IHC, immunohistochemistry; PS, performance status; LDH, lactate dehydrogenase; OS, overall survival.

I.SORU

Primeri bilinmeyen kanserlerde aşağıdaki histolojilerden hangisi en sık görülür?

A. Neroendocrine ca
B. Kötü diferansiye karsinom
C. Skuamöz ca
D. Adeno ca

II.SORU

40 y, kadın, premenopozal, sigara içmemiş. USG'de incidental olarak karaciğerde 3 cm lezyon saptanmış. Biyopsi; adeno ca ile uyumlu gelmiş. IHC; CK7 -, CA19.9 -, CK20+, CDX2 +, TTF-1 -, ER -, HER2-, CT ve PET-CT karaciğer dışında ek patoloji saptanmamış. Bundan sonraki aşamada hangi test yapılmalı?

A. Pankreas protokolünde CT
B. Meme MR
C. Bronkoskopi
D. Kolonoskopi

III. SORU

38 yaşında premenopozal kadın hasta, sigara içmemiş, sol aksilada ele gelen kitle ile başvuruyor. Thoraks-Batın BT , sadece sol aksilada 2.5 cm kitle var. Bx; adeno ca, CK 20-, TTF-1-, ER -, HER2-, CK-7+, mammaglobulin+, GCDFP-15+. Aşağıdaki testlerden hangisi tanı için yardımcı olur?

A. Bronkoskopi
B. Memeden multiple biyopsi
C. Meme MR
D. Yukarıdakilerin hepsi

IV. SORU

45 y, erkek, 25 yıl sigara içmiş, sağ servikal kitle ile başvurmuş. Tomografide sadece sağ servikal 2 cm kitle saptanmış. BX; skuamöz hücre ca, aşağıdaki testlerin hangisi primer odağı bulmada yardımcı olur?

A. Üst özofagus endoskopi
B. Pharenks ve larenks endoskopik değerlendirme
C. PET-CT
D. Hepsi

V.SORU

35 y, erkek, 3 aydır fark etiği giderek büyüyen 3cm inguinal kitle ile başvurmuş. Genital muayene, rektal tuşe, kolonoskopi normal. Bx; skuamöz hücreli ca, BT başka bölgede ek patoloji saptanmamış. Aşağıdaki yaklaşımların hangisi normaldir?

A. Palyatif kemoterapi
B. Definitip Radioyoterapi
C. Takip edelim
D. Cerrahi, radyasyon onkoloji, medikal onkoloji konsültasyonu

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