OLGU EŞLİĞİNDE ÇOCUKLUK ÇAĞINDA OSTEOSARKOM

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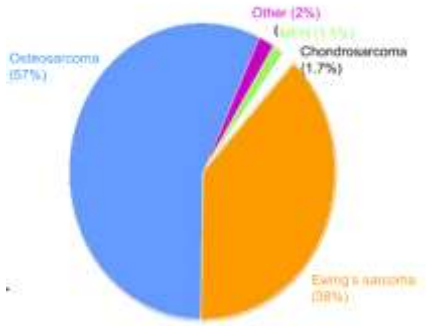
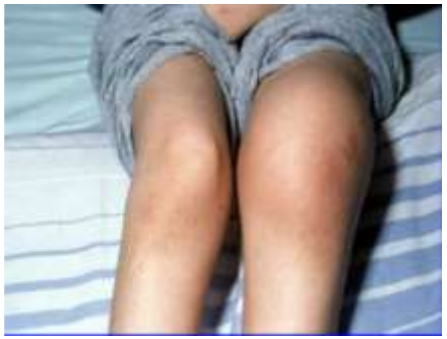
XIX. Ulusal Pediatrik Kanser Kongresi, Çeşme, 2016

Osteosarkom



- Mezenkim kökenli hücrelerin

transformasyonu sonucu osteoblastik farklılaşma sergileyen ve osteoid üretimi ile seyreden **malign** tümör



- Çocukluk çağı kemik

lezyonlarının %50'si malign,

diğerleri benign veya nonneoplastik lezyonlar.

- Çocukluk çağı kemik tümörleri nadirdir ve 6. sıklıkta
- En sık görülen malin kemik tümörü

- 20 yaş altında **her yıl 400 yeni hasta** tanı almakta.
- **Erkek çocuklarda** (E/K: 1,3/1) ve siyah ırkta daha fazla görülmekte.
- En fazla hayatın **2. dekadında**
- **%80 oranında ekstremite yerleşimli.**

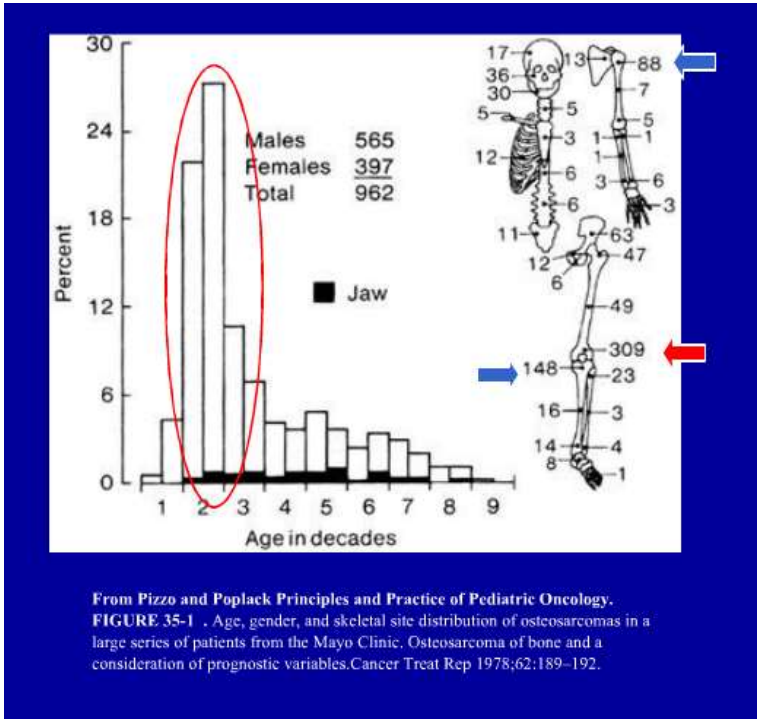
Türk Pediatrik Onkoloji Grubu (TPOG)& Pediatrik Tümör Kayıtları, 2002-2008

TÜMÖR TİPLERİ

	n	%
I Lösemi	2614	31,3
II Lenfoma ve retikuloendotelyal neoplaziler	1552	18,6
III Merkezi sinir sitemi tümörleri	1084	13,0
IV Sempatik sinir sistemi tümörleri	622	7,4
IX Yumuşak doku sarkomları	505	6,0
V Retinoblastom	193	2,3
VI Böbrek tümörleri	470	5,6
VII Karaciğer tümörleri	122	1,5
VIII Malign kemik tümörleri	509	6,1
X Germ hücreli, trofoblastik ve diğer gonadal neoplaziler	371	4,4
XI Karsinomlar ve diğer malin epitelyal neoplaziler	226	2,7
XII Other and Unspecified Malignant Neoplasm	87	1,0
Total	**8355**	**100,00**

T.Kutluk & A. Yesilipek, on behalf of TPOG/TPHD

Osteosarkom-Yerleşim Yeri



From Pizzo and Poplack Principles and Practice of Pediatric Oncology.
FIGURE 35-1 . Age, gender, and skeletal site distribution of osteosarcomas in a large series of patients from the Mayo Clinic. Osteosarcoma of bone and a consideration of prognostic variables.Cancer Treat Rep 1978;62:189–192.

- Hızlı büyüyen kemikleri özellikle seçmekte,
- En sık yerleşim yerleri **distal femur, proksimal tibia ve proksimal humerus**
- Ayrıca >60 yaş grubunda Paget hastalığına eşlik edebilir ve insidans bu yaş grubunda da daha yüksek

Yerleşim yerlerine göre Osteosarkomlar

TABLE 1: Characteristics of 4,173 patients with osteosarcoma according to tissue of origin.

Characteristic	Skeletal osteosarcoma (N = 3,917)	ESOS (N = 256)	P value
Mean age (range)	31.4 years* (0–99 years)	60.7 years** (9–96 years)	<0.0001
Sex			
Male	2,175 (55.5%)	117 (45.7%)	0.002
Female	1,742 (44.5%)	139 (54.3%)	
Primary site			
Lower extremity	2,392 (62.6%)	80 (32.7%)	
Upper extremity	467 (12.2%)	18 (7.3%)	
Head	398 (10.4%)	18 (7.3%)	
Spine	114 (3%)	1 (0.4%)	<0.0001
Ribs/sternum	105 (2.8%)	0	
Pelvis	343 (9%)	31 (12.7%)	
Thorax	0	70 (28.6%)	
Abdomen/retroperitoneum	0	27 (11%)	
Primary tumor location			
Axial	961 (25.1%)	154 (61.1%)	<0.0001
Appendicular	2,870 (74.9%)	98 (38.9%)	
Regional lymph node			
Present	61 (2.4%)	13 (7.7%)	<0.0001
Absent	2,519 (97.6%)	155 (92.3%)	
Stage			
Distant metastasis	794 (22.3%)	43 (18.6%)	0.188
No distant metastasis	2,763 (77.7%)	188 (81.4%)	

Predispozan Faktörler

- Radyasyon
- Alkilleyici ajanlarla tedavi
- Erişkin döneminde Paget hastalığı
- Kronik osteomyelit, multipl herediter exostoz, fibröz displazi, kemik infarktları, metalik implantlar
- Kalıtsal nedenler
  - Herediter retinoblastom (Rb1 gen mutasyonu),
  - Li-Fraumeni syndromu (p53 tümor süpresör germline mutasyonu),
  - Rothmund-Thomson sendromu (RECQL4 gen mutasyonu),
  - Bloom sendromu
  - Werner sendromu

Osteosarkomda predispozan faktör olarak Radyoterapi

- Çocukluk çağı solid tümörlü hastalarda, radyoterapiyi takiben görülen en sık sekonder malinite
- Öncesinde RT alma oranı %3.
- İnterval dönem 4-40 yıl (ortalama 12-16 yıl)
- Alkilleyici ajanlar da RT etkisini potansiyelize ediyor mu?

Patogenez

- Hızlı kemik büyümesi ile ilişkisi var

  Adolesanlarda pik yapması, kemiklerin büyüme yerlerini tercih etmesi, kızlarda daha erken yaşta görülmesi

- Spesifik aberasyon tanımlanmamış
- Karakteristik translokasyon veya moleküler genetik anomali yok
- Çoğunda kompleks karyotip mevcut
- LOH 3q,13q (RB gen), 17p (p53), (18q)
- RB ve p53 kombine inaktivasyonu

Bulgular

- **Ağrı**, en önemli belirtidir. Başlangıçta aralıklı, giderek sıklaşan veya sürekli karakter alır.
- **Yumuşak doku kitlesi**
- **Konstitüsyonel semptomlar**
- **Şişlik ve fonksiyon kaybı** ancak haftalar sonra ortaya çıkar
- Kemik yapısı bozulduğu için küçük travmalarla **patolojik kırıklar**

Osteosarkom, ancak kuvvetli şüphe duyulduğunda erken evrede yakalanabilir.

Olgu sunumu

İSTANBUL ÜNİVERSİTESİ
ONKOLOJİ ENSTİTÜSÜ

- AB
- Doğum tarihi: 09/01/2001
- Başvuru tarihi: 04/08/2015
- **Ondört yaş kız** hasta
- Şikayeti: Sağ göğüs arka tarafında ağrı, nefes alırken batma
- Hikayesinden başvurudan **2 ay önce** başlayan şikayetlerinin giderek arttığı, 1 ay önce Göğüs Hastalıkları ve Göğüs Cerrahisi Hastanesine başvurduğu, orada da kitle biyopsisi yapılarak Çocuk Onkoloji Birimine yönlendirildiği öğrenildi

- Fizik muayenede genel durumu orta-kötü, soluk, efor dispnesi mevcuttu.
- Solunum sesleri sağ hemitoraksta azalmıştı. DSS:32/dk, KTA:96/dak/R, O2 saturasyon %95
- Hepatosplenomegali, lenfadenopati ve batında kitle yok.

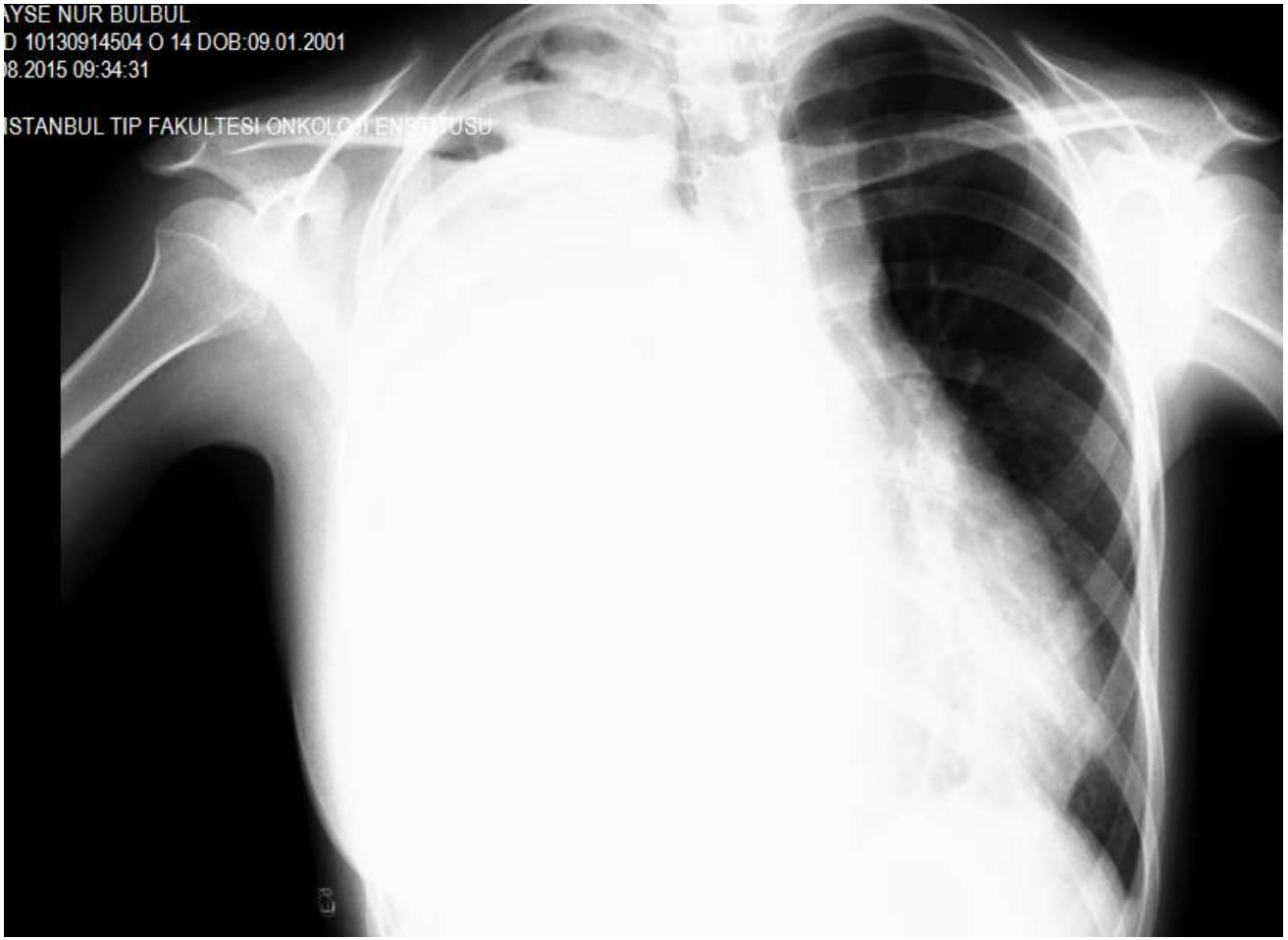
Hemogram, biokimyasal değerleri, alkalen fosfataz normal sınırlarda,

Sedimentasyon 100 mm/saat

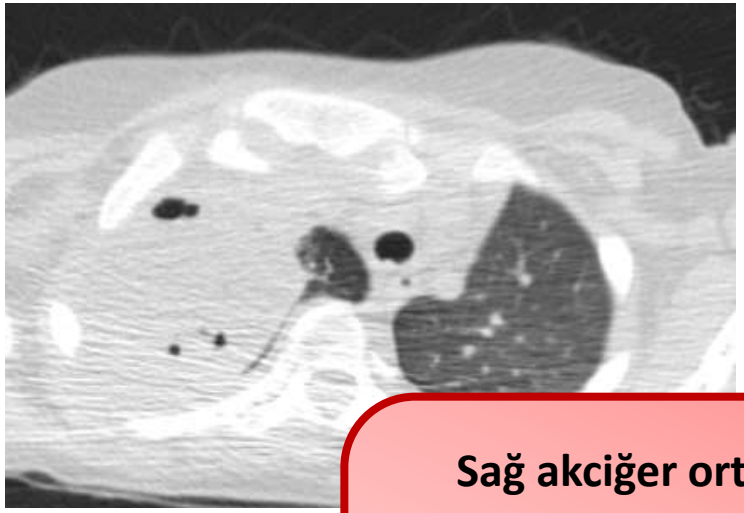
LDH artmış (530 U/L) idi.

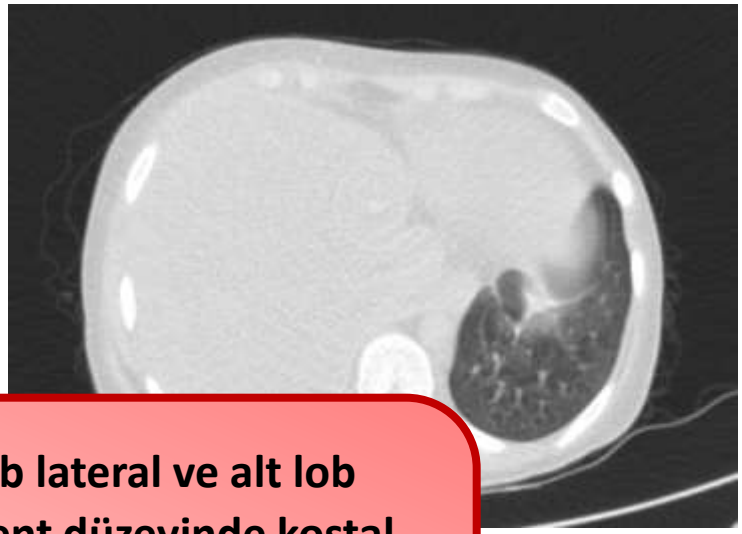
Radyoloji 5.8.2015

Başvuru sırasında PA Akciğer Grafisi

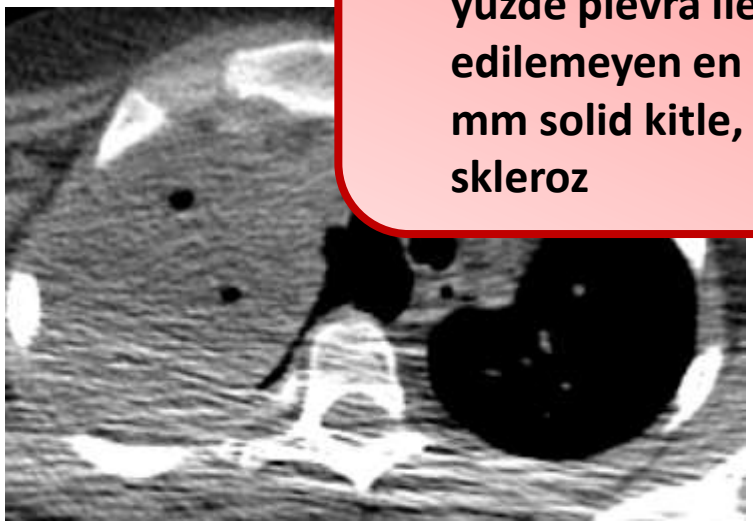


Başvuru sırasında Toraks BT



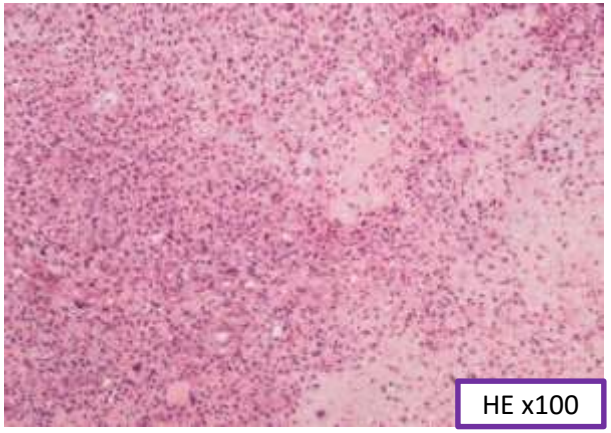


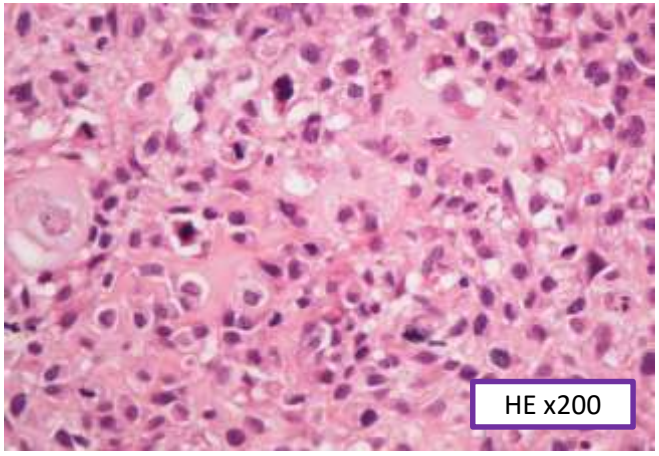
Sağ akciğer orta lob lateral ve alt lob anterobazal segment düzeyinde kostal yüzde plevra ile konturları ayırt edilemeyen en geniş yerinde 62x133 mm solid kitle, 8. ve 9. ön kotlarda skleroz

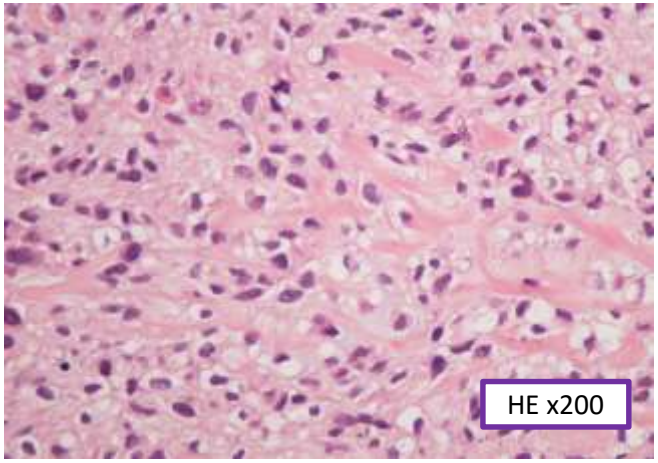


Patoloji

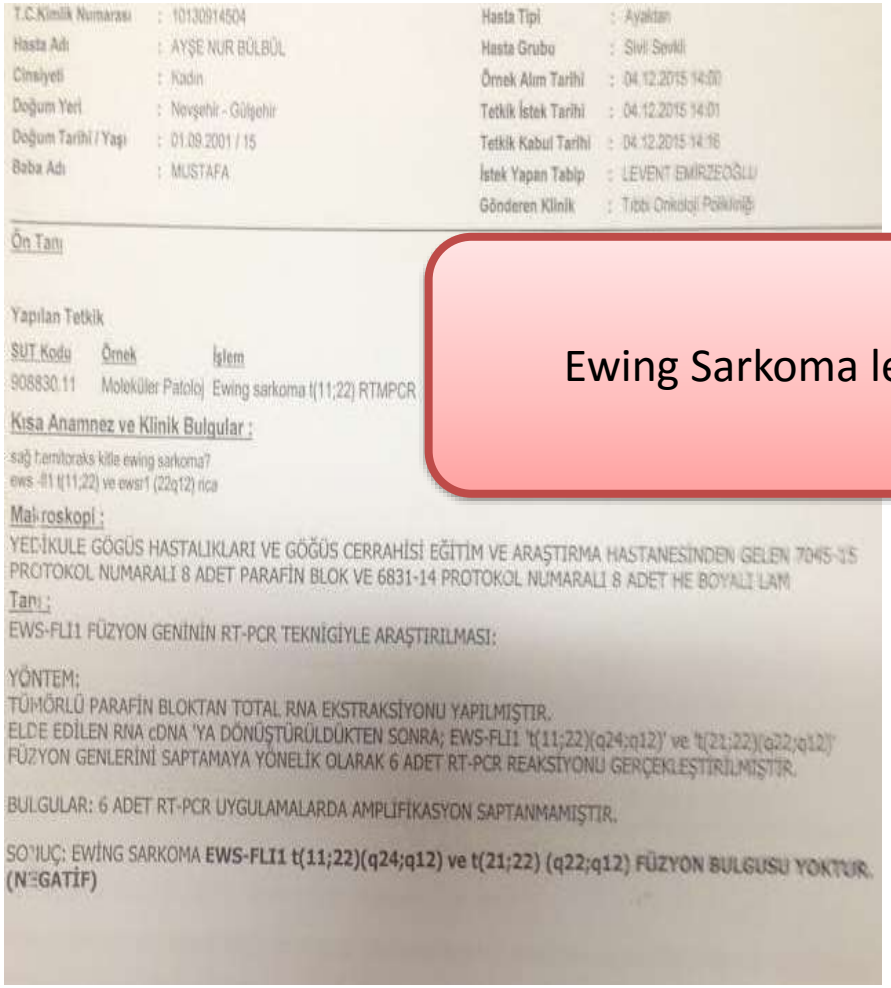
Başvurudan önce alınan biyopsi materyalinin patoloji konsültasyonu ile **kondroblastik alanlar içeren pleomorfik osteosarkom** tanısı aldı.







Moleküler Patolojik İnceleme



T.C.Kimlik Numarası : 10130914504
Hasta Adı : AYŞE NUR BÜLBÜL
Cinsiyeti : Kadın
Doğum Yeri : Nevşehir - Gülşehir
Doğum Tarihi / Yaşı : 01.09.2001 / 15
Baba Adı : MUSTAFA

Hasta Tipi : Ayaktan
Hasta Grubu : Sivil Sevkli
Örnek Alım Tarihi : 04.12.2015 14:00
Tetkik İstek Tarihi : 04.12.2015 14:01
Tetkik Kabul Tarihi : 04.12.2015 14:16
İstek Yapan Tabip : LEVENT EMİRZEOĞLU
Gönderen Klinik : Tıbbi Onkoloji Polikliniği

Ön Tanı

Yapılan Tetkik

SUT Kodu	Örnek	İşlem
908830.11	Moleküler Patoloj	Ewing sarkoma t(11;22) RTMPCR

Kısa Anamnez ve Klinik Bulgular :

sağ hemitoraks kitle ewing sarkoma?
ews -81 t(11;22) ve ewsr1 (22q12) rica

Makroskopi :

YEDİKULE GÖĞÜS HASTALIKLARI VE GÖĞÜS CERRAHİSİ EĞİTİM VE ARAŞTIRMA HASTANESİNDEN GELEN 7045-15 PROTOKOL NUMARALI 8 ADET PARAFİN BLOK VE 6831-14 PROTOKOL NUMARALI 8 ADET HE BOYALI LAM

Tanı :

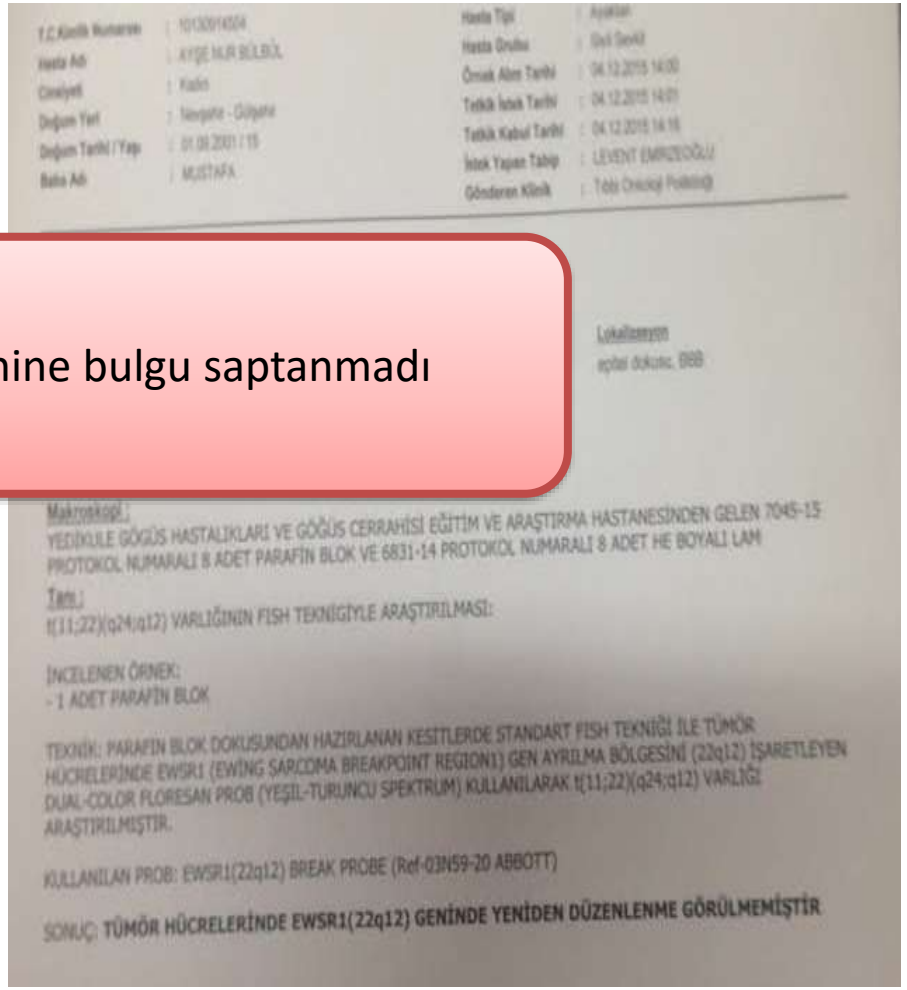
EWS-FLI1 FÜZYON GENİNİN RT-PCR TEKNİĞİYLE ARAŞTIRILMASI:

YÖNTEM:
TÜMÖRLÜ PARAFİN BLOKTAN TOTAL RNA EKSTRAKSİYONU YAPILMIŞTIR.
ELDE EDİLEN RNA cDNA 'YA DÖNÜŞTÜRÜLDÜKTEN SONRA; EWS-FLI1 't(11;22)(q24;q12)' ve 't(21;22)(q22;q12)' FÜZYON GENLERİNİ SAPTAMAYA YÖNELİK OLARAK 6 ADET RT-PCR REAKSİYONU GERÇEKLEŞTİRİLMİŞTİR.

BULGULAR: 6 ADET RT-PCR UYGULAMALARDA AMPLİFİKASYON SAPTANMAMIŞTIR.

SONUÇ: EWİNG SARKOMA **EWS-FLI1 t(11;22)(q24;q12) ve t(21;22) (q22;q12) FÜZYON BULGUSU YOKTUR. (NEGATİF)**

Ewing Sarkoma lehine bulgu saptanmadı



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Baba Adı : MUSTAFA

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Hasta Grubu : Sivil Sevkli
Örnek Alım Tarihi : 04.12.2015 14:00
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İstek Yapan Tabip : LEVENT EMİRZEOĞLU
Gönderen Klinik : Tıbbi Onkoloji Polikliniği

Lokalizasyon
epitel dokusu, BBB

Makroskopi :

YEDİKULE GÖĞÜS HASTALIKLARI VE GÖĞÜS CERRAHİSİ EĞİTİM VE ARAŞTIRMA HASTANESİNDEN GELEN 7045-15 PROTOKOL NUMARALI 8 ADET PARAFİN BLOK VE 6831-14 PROTOKOL NUMARALI 8 ADET HE BOYALI LAM

Tanı :

t(11;22)(q24;q12) VARLIĞININ FISH TEKNİĞİYLE ARAŞTIRILMASI:

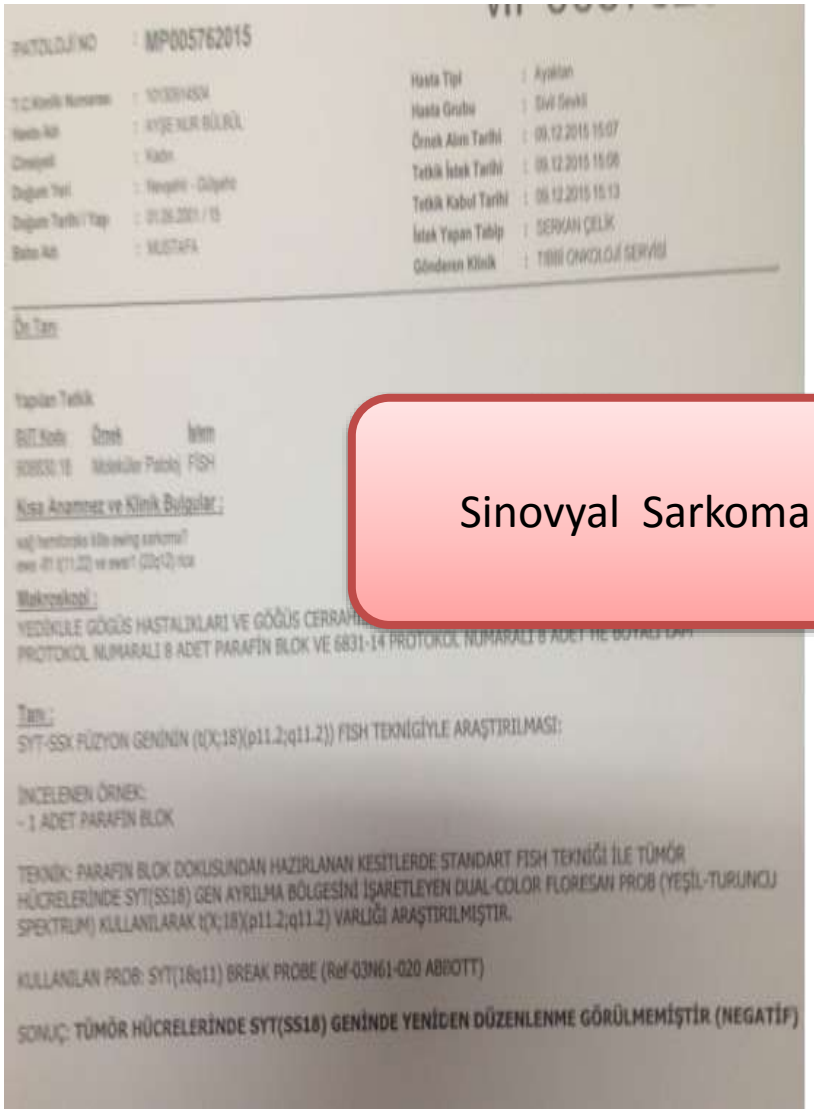
İNCELENEN ÖRNEK:
- 1 ADET PARAFİN BLOK

TEKNİK: PARAFİN BLOK DOKUSUNDAN HAZIRLANAN KESİTLERDE STANDART FISH TEKNİĞİ İLE TÜMÖR HÜCRELERİNDE EWSR1 (EWING SARCOMA BREAKPOINT REGION1) GEN AYRILMA BÖLGESİNİ (22q12) İŞARETLEYEN DUAL-COLOR FLORESAN PROB (YEŞİL-TURUNCU SPEKTRUM) KULLANILARAK t(11;22)(q24;q12) VARLIĞI ARAŞTIRILMIŞTIR.

KULLANILAN PROB: EWSR1(22q12) BREAK PROBE (Ref-03N59-20 ABBOTT)

SONUÇ: **TÜMÖR HÜCRELERİNDE EWSR1(22q12) GENİNDE YENİDEN DÜZENLENME GÖRÜLMEMİŞTİR**

Moleküler Patolojik İnceleme



PATOLOJİ NO : MP005762015

T.C.Kimlik Numarası : 10130914504
Hasta Adı : AYŞE NUR BÜLBÜL
Cinsiyeti : Kadın
Doğum Yeri : Nevşehir - Gülşehir
Doğum Tarihi / Yaşı : 01.09.2001 / 15
Baba Adı : MUSTAFA

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Tetkik Kabul Tarihi : 09.12.2015 15:13
İstek Yapan Tabip : SERKAN ÇELİK
Gönderen Klinik : 1998 ONKOLOJİ SERVİSİ

Ön Tanı

Yapılan Tetkik

BİT Kodu	Örnek	İsim
608830.18	Moleküler Patoloji	FISH

Kısa Anamnez ve Klinik Bulgular :

Makroskopi :

YEDİKULE GÖĞÜS HASTALIKLARI VE GÖĞÜS CERRAHİ
PROTOKOL NUMARALI 8 ADET PARAFİN BLOK VE 6831-14 PROTOKOL NUMARALI 8 ADET HE BOYALI LAM

Tanı :
SYT-SSX FÜZYON GENİNİN (t(X;18)(p11.2;q11.2)) FISH TEKNİĞİYLE ARAŞTIRILMASI:

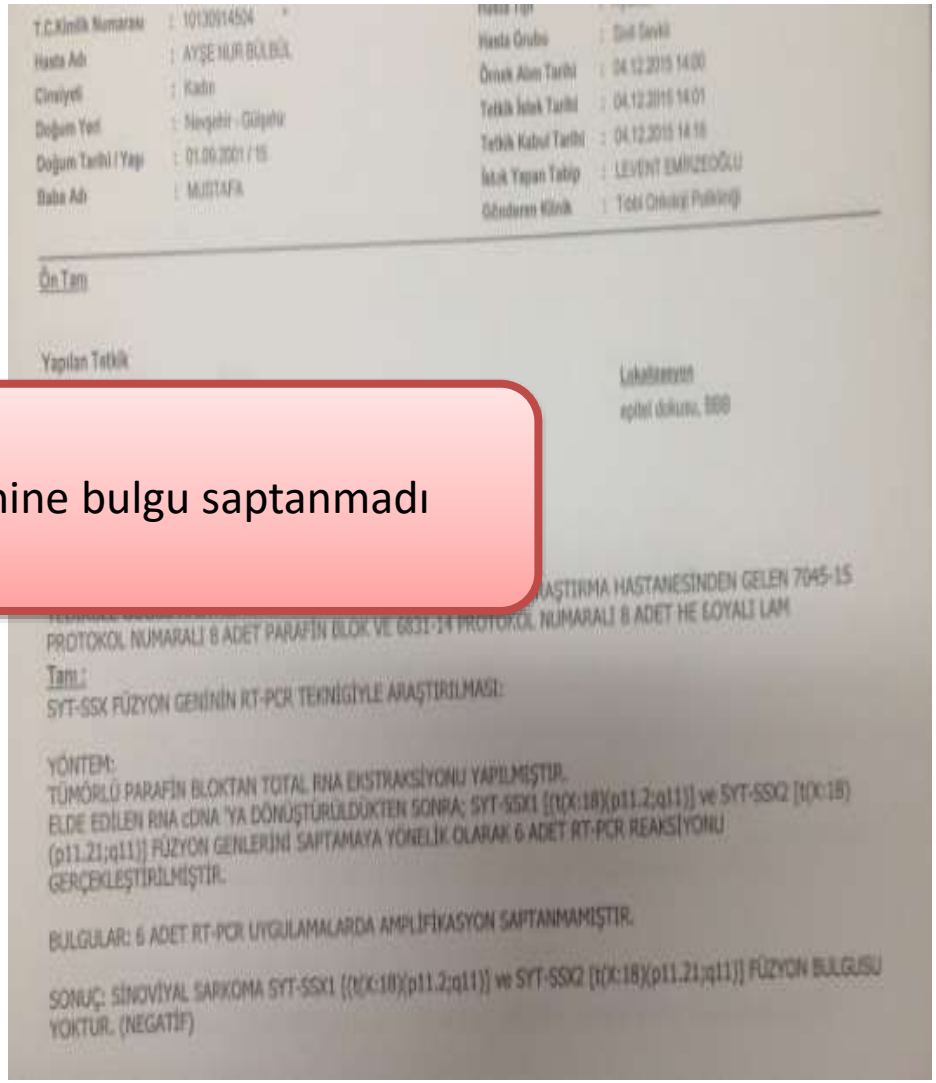
İNCELENEN ÖRNEK:
- 1 ADET PARAFİN BLOK

TEKNİK: PARAFİN BLOK DOKUSUNDAN HAZIRLANAN KESİTLERDE STANDART FISH TEKNİĞİ İLE TÜMÖR HÜCRELERİNDE SYT(SS18) GEN AYRILMA BÖLGESİNİ İŞARETLEYEN DUAL-COLOR FLORESAN PROB (YEŞİL-TURUNCU SPEKTRUM) KULLANILARAK t(X;18)(p11.2;q11.2) VARLIĞI ARAŞTIRILMIŞTIR.

KULLANILAN PROB: SYT(18q11) BREAK PROBE (Ref-03N61-020 ABBOTT)

SONUÇ: TÜMÖR HÜCRELERİNDE SYT(SS18) GENİNDE YENİDEN DÜZENLENME GÖRÜLMEMİŞTİR (NEGATİF)

Sinovyal Sarkoma lehine bulgu saptanmadı



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Cinsiyeti : Kadın
Doğum Yeri : Nevşehir - Gülşehir
Doğum Tarihi / Yaşı : 01.09.2001 / 15
Baba Adı : MUSTAFA

Hasta Grubu : Sivil Sevkli
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Tetkik Kabul Tarihi : 04.12.2015 14:18
İstek Yapan Tabip : LEVENT EMİROĞLU
Gönderen Klinik : Tıbbi Onkoloji Polikliniği

Ön Tanı

Yapılan Tetkik

Lokalizasyon
epitel dokusu, BBB

ARAŞTIRMA HASTANESİNDEN GELEN 7045-15
PROTOKOL NUMARALI 8 ADET PARAFİN BLOK VE 6831-14 PROTOKOL NUMARALI 8 ADET HE BOYALI LAM

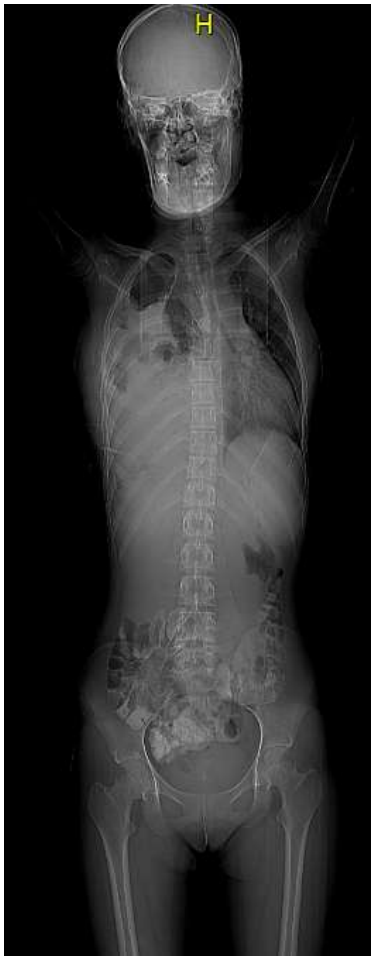
Tanı :
SYT-SSX FÜZYON GENİNİN RT-PCR TEKNİĞİYLE ARAŞTIRILMASI:

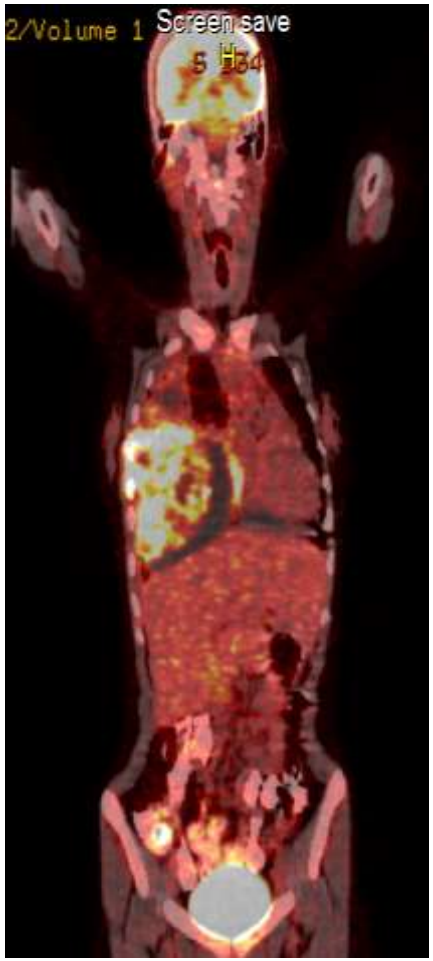
YÖNTEM:
TÜMÖRLÜ PARAFİN BLOKTAN TOTAL RNA EKSTRAKSİYONU YAPILMIŞTIR.
ELDE EDİLEN RNA cDNA 'YA DÖNÜŞTÜRÜLDÜKTEN SONRA; SYT-SSX1 [(t(X:18)(p11.2;q11)] ve SYT-SSX2 [t(X:18)(p11.21;q11)] FÜZYON GENLERİNİ SAPTAMAYA YÖNELİK OLARAK 6 ADET RT-PCR REAKSİYONU GERÇEKLEŞTİRİLMİŞTİR.

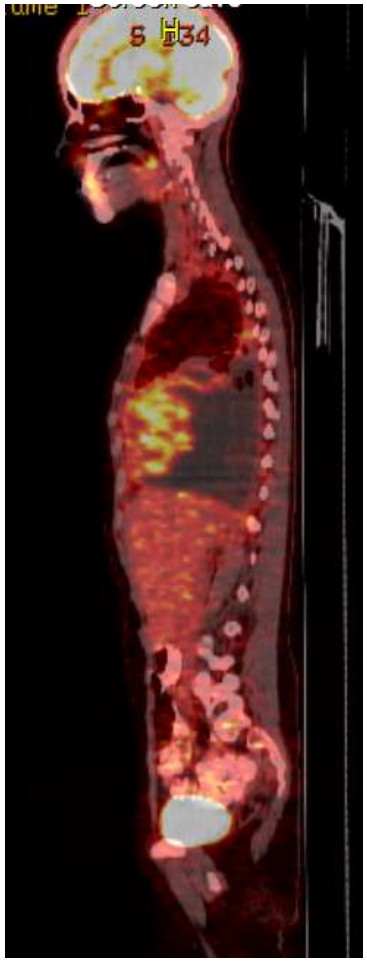
BULGULAR: 6 ADET RT-PCR UYGULAMALARDA AMPLİFİKASYON SAPTANMAMIŞTIR.

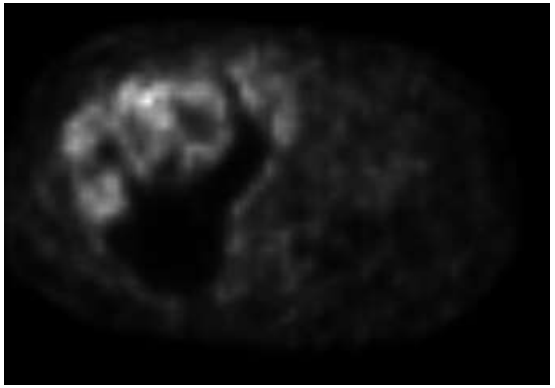
SONUÇ: SİNOVİYAL SARKOMA SYT-SSX1 [(t(X:18)(p11.2;q11)] ve SYT-SSX2 [t(X:18)(p11.21;q11)] FÜZYON BULGUSU YOKTUR. (NEGATİF)

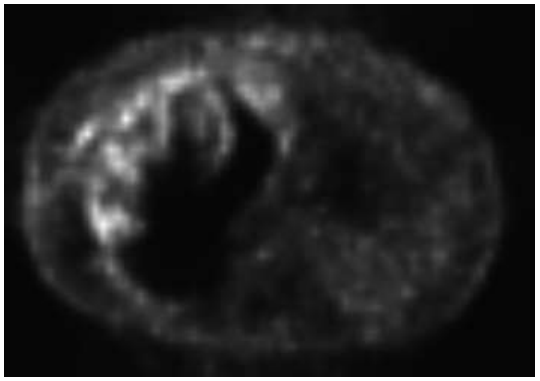
PET-BT











PET-BT

Baş boyun taramada; patolojik FDG tutulumu saptanmamıştır.

Her iki supraklaviküler, aksiller, mammar alanlarda FDG tutulumu fizyolojik sınırlardadır.

Toraks taramada; sağ akciğer orta lob lateral, alt lob anterobazal segmentleri içine alan kostal yüzde plevrayla konturları ayırt edilemeyen içerisinde kalsifikasyonlar bulunan 120x134mm boyutlarında nekrotik komponentleri ve buna bağlı hipometabolik yapıları bulunan hipermetabolik kitle(SUV 12-16).

Kitle toraks duvarına invazyon oluşturmuş VIII, ve IX. ön kotlarda ve toraks duvarında artmış FDG tutulumu gözlenmiştir.

Sağ hemitoraks üst girim seviyesinden başlayan anterior ve posterioda diyafragmatik yüze kadar devamlılık gösteren hava/sıvı seviyelenmelerinin izlendiği plevral effüzyon izlenmektedir.

Bazal segmentler düzeyinde plevrada özellikle mediastinal yüzde daha belirgin yer yer asimetri gösteren yumuşak doku dansitesinde plevral kalınlık artışı ve artmış FDG tutulumu izlenmektedir(SUV 8-10).

Batın taramada; karaciğer, dalak, pankreas, her iki böbrek, her iki sürrenal, aort, paraaortik lenf nodlarına uyan salılarda patolojik FDG tutulumu saptanmamıştır.

Pelvik taramada; patolojik FDG tutulumu saptanmamıştır.

İskelet sistemi taramasında; FDG dağılım fizyolojik sınırlardadır.

SONUÇ

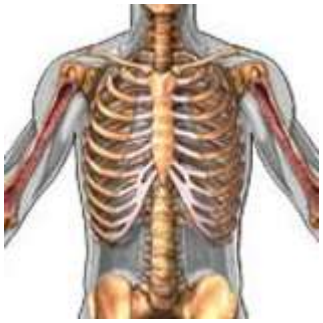
Sağ akciğer orta lob lateral, alt lob anterobazal segmentleri içine alan kostal yüzde plevra ile devam eden, VIII ve IX. ön kotlarda invazyon gösteren 120x134mm boyutlarında hipermetabolik kitle(primer tm)

Sağ hemitoraksta anteroposterior diyafragmatik yüze kadar devamlılık gösteren hava/sıvı seviyelenmeleri, bazal segmentler düzeyinde plevrada kalınlaşma ve artmış FDG tutulumu(met?)

Osteosarkom-
Ayırıcı Tanı

- Ewing sarkoma
- Lenfoma
- Primer malinite metastazları
- Benin kemik tümörleri
  (kondroblastom, osteoblastom)
- Osteomyelit
- LCH
- Anevrizmal kemik kisti

Göğüs duvarında yerleşen kitlelerin ayırıcı tanısı



- Göğüs duvarı tümörleri kemik, kıkırdak, yumuşak doku (kas, damar, sinir), hematolojik hastalıklardan kaynaklanabilir.
- Bu m… daha azını…
- Prim…
- Mali…
- %20… sapta…
- Malin tümörler direkt invazyon veya yanındaki torasik tümörden yayılım yaparlar.
- Osteosarkomun primer tümör yerleşim yeri olarak göğüs duvarında bulunması %3 olarak bildirilmektedir

- Malin küçük yuvarlak hücreli tümörler (Ewing/PNET ailesi)
- Rabdomyosarkom
- Osteosarkom
- Kondrosarkom

Çocukluk Çağında Göğüs Duvarı Tümörleri

- Nadir tümörler
- Başvuru şekli genelde kitle basısına bağlı solunum sıkıntısı
- Akciğer, kemik, kemik iliği, karaciğer ve beyne metastaz
- Lokal nüks

Schamberger RC, Grier HE. Chest wall tumors in infants and children. Semin Ped Surgery 1994 Nov; 3(4):267-76

Chest wall tumors: Diagnosis, treatment and reconstruction

- Göğüs duvarı maliniteli 50 çocuk ve erişkin hasta
- %74 erkek
- Kosta %48, göğüs duvarı %34, klavikula %12, skapula %6
- Hepsine biyopsi
- Cerrahi tedavi ve radyoterapi

rates of patients suffering from osteosarcoma (78%) were higher

palpable masses. Osteosarcoma with a less favorable prognosis

No. of patients	Age (years)/gender (M:F)	Diagnosis	Primary site	Metastasis	Chemotherapy	Radiotherapy (cGy)	Outcome	Follow-up interval (years)
14	4–50/10:4	MSRCT	Chest wall and ribs	8 bones 2 pulmonary 4 bone	D-VAC+IE and Cp in some patients	1400–4700 except in three cases	9 NED 5 DOD	1.2–6.0
9	4–46/7:2	Alveolar RMS	Clavicle and chest wall	4 bones 2 pulmonary 3 bone	VAC-I+D, E and Cp in some patients	1800–3400 except in two cases	7 NED 2 DOD	1.2–6.0
6	6–50/5:1	Embryonal RMS	Chest wall and ribs	3 bones 2 pulmonary 1 bone	VDC-IE+A in some patients	1300–2600 except in one case	5 NED 1 DOD	3.0–6.0
9	6–50/6:3	Osteosarcoma	Chest wall and scapula	3 bones 3 pulmonary 3 bone	I-HDM+L in some patients	2500–4600 except in one case	6 NED 3 DOD	1.2–6.0
6	8–50/4:2	Synovial sarcoma	Chest wall	3 bones 1 pulmonary 2 bone	VAC-IE+D in some patients	1400–2000 except in one case	3 NED 3 DOD	3–6
6	17–41/4:2	Fibrosarcoma	Chest wall	1 bone 3	VDC-IE+D and Cp in some patients	1400–4800 except in two cases	5 NED 1 DOD	1.2–6.0

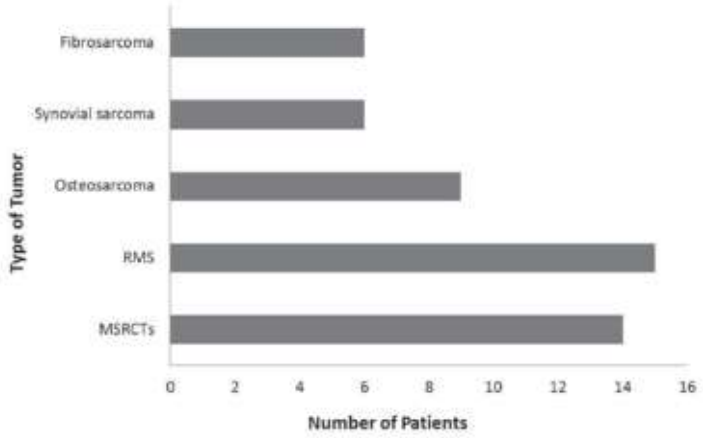


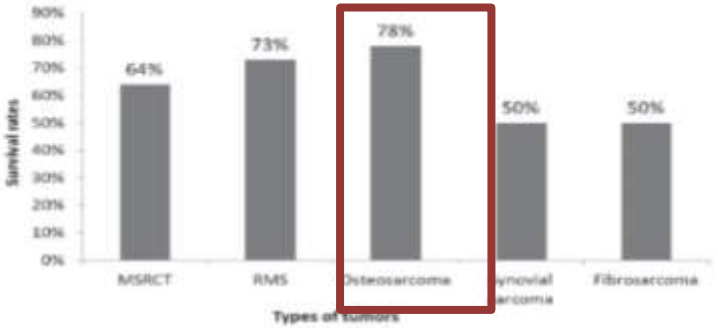
Table II. Representative number of patients subjected to various types of surgical procedures.

Surgical procedure	Number of patients
Chest wall resection	24
En bloc resection	11
Biopsy	10
Distal clavicle resection	3
Scapular resection	2

Patients were assigned a surgical procedure based on the diagnosis, treatment, severity of disease, recovery percentage and follow-up over a certain period of time.

Radiation therapy. Radiotherapy is usually applied to the cancerous tumor. A total of 15 out of 40 patients were treated with image-guided radiation therapy (IGRT) and 20 with brachytherapy. The remaining five patients underwent intensity-modulated radiation therapy (IMRT).

EXPERIMENTAL AND THERAPEUTIC MEDICINE 9: 1807-1812, 2015



Göğüs Duvarı kitlelerinde Radyolojik Benign-Malin ayrımı mümkün mü?

- Kortikal kemik bütünlüğünün bozulması
- Periost reaksiyonu
- Subperiosteal yeni kemik yapımı
- Kemikte litik ve sklerotik değişiklikler
- Yumuşak doku kitlesi
- Yumuşak doku ossifikasyonu

Laboratuar

- LD yon artışı
- Ha çok yü

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Research Paper

Pre-treatment serum lactate dehydrogenase and alkaline phosphatase as predictors of metastases in extremity osteosarcoma

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ABSTRACT

Background: The prognosis of patients with metastatic osteosarcoma remains poor. However, the chance of survival can be improved by surgical resection of all metastases. In this study we investigate the value of serum alkaline phosphatase (ALP) and lactate dehydrogenase (LDH) in predicting the presence of metastatic disease at time of diagnosis.

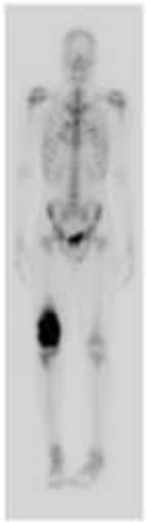
Methods: Sixty-one patients with histologically confirmed conventional osteosarcoma of the extremity were included in the study. Only 19.7% of cases presented without evidence of systemic spread of the disease. Pre-treatment serum ALP and LDH were analysed in patients with and without skeletal or pulmonary metastases.

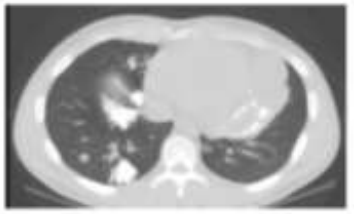
Results: Serum LDH and ALP levels were not significantly different in patients with or without pulmonary metastases ($p=0.88$ and $p=0.47$, respectively). The serum LDH and ALP levels did however differ significantly in patients with or without skeletal metastases ($p<0.001$ and $p=0.02$, respectively). The optimal breakpoint for serum LDH as a marker of skeletal metastases was 849 IU/L (AUC 0.839; Sensitivity=0.88; Specificity=0.73). LDH >454 IU/L equated to 100% sensitivity for detected bone metastases (positive diagnostic likelihood ratio (DLR)=1.32). With a cut-off of 76 IU/L a sensitivity of 100% was reached for serum ALP predicting the presence of skeletal metastases (positive DLR=1.1). In a multivariate analysis both LDH ≥850 IU/L (odds ratio [OR]=9; 95% confidence interval (CI) 1.8–44.3) and ALP ≥280 IU/L (OR=10.3; 95% CI 2.1–50.5) were predictive of skeletal metastases. LDH however lost its significance in a multivariate model which included pre-treatment tumour volume.

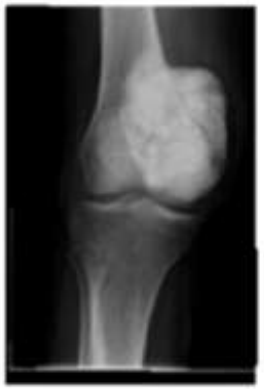
Conclusion: In cases of osteosarcoma with LDH >850 IU/L and/or ALP >280 IU/L it may be prudent to consider more sensitive staging investigations for detection of skeletal metastases. Further research is required to determine the value and the most sensitive cut-off points of serum ALP and LDH in the prediction of skeletal metastases.

Radyolojik değerlendirme

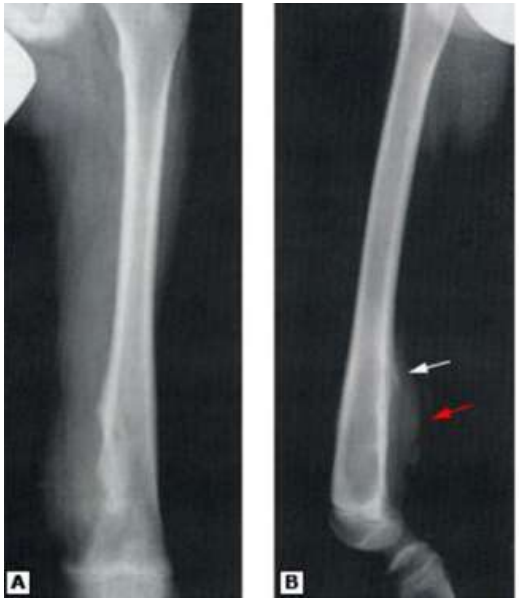
- Düz grafi
- Tutulan kemiklere yönelik MRI
  - Skip lezyonları ve/veya eklem ve kemik iliği değerlendirmede
- Toraks BT
- Kemik sintigrafisi ve/veya PET







Osteosarkom-Düz Kemik Grafisi



- Trabeküler kemik yıkımı ile
  - Belirsiz sınırlar
  - Radyodens ve radyolüsens alanların birlikteliği
  - Periosteal yeni kemik oluşumu
  - Korteksten ayrışma ile Codman üçgeni oluşumu
  - Değişik derecede ossifiye yumuşak doku kitlesi (radial veya sunburst paternli)

Osteosarkom-PET

Pediatr Blood Cancer. 2016 Apr 15. doi: 10.1002/pbc.26014. [Epub ahead of print]

Comparison of 18 F-FDG-PET-CT and Bone Scintigraphy for Evaluation of Osseous Metastases in Newly Diagnosed and Recurrent Osteosarcoma.

Hurley C[1], McCarville MB[2], Shulkin BL[2], Mao S[3], Wu J[3], Navid F[1], Daw NC[4], Pappo AS[1], Bishop MW[1,5].

Author information

Uzak kemik metastazlarının saptanmasında sensitivite, spesivite, tanısal doğruluk açısından kemik sintigrafisi, PET-BT ve kombine kullanımın karşılaştırması

2003

39 ha

5-19

PET-

Komb

FDG-PET in kemik sintigrafisine göre sensivitesinin daha fazla oluşu, osteosarkom evrelemesinde PET kullanımını desteklemekte

Kombine PET-BT ve kemik sintigrafisi, PET-BT ye üstün değil (p=0.25)

Spesifite kemik sintigrafisinde kombine kullanıma göre daha anlamlı (p=0.063)

combined. Sensitivity of PET-CT was superior to BS (P = 0.035); combined imaging modalities were superior to BS (P < 0.001) but not better than PET-CT alone (P = 0.25). Specificity for BS approached significance compared to combined imaging (P = 0.063). Examination-based analysis yielded similar results between individual and combined imaging modalities.

CONCLUSIONS: ^{18} F-FDG-PET-CT demonstrated superior sensitivity over BS for detecting osseous metastases, supporting the use of ^{18} F-FDG-PET-CT for staging of osteosarcoma.

Evreleme

- Lokalize hastalık
- Metastatik hastalık

- Metastatik hastalık tüm hastaların %15-20'sini oluşturmaktadır.

Tanı-Biyopsi

- Evreleme tetkiklerinden sonra, osteosarkom tedavisinde deneyimli cerrah tarafından alınmalı
- İğne veya insizyonel biyopsi
- Tanı için yapılacak biyopsi, daha sonra rezeksiyonuna olanak verecek şekilde ve kontamine olmamasına dikkat edilerek planlanmalı
- Longitudinel kesi tercih edilmeli
- Hemostaza dikkat edilmeli ve nörovaskuler yapılar kontamine edilmemeli

Patoloji

Primitif kemik yapıcı mezenkimden kaynaklanan tümör

- Konvansiyonel (osteoblastik, kondroblastik, fibroblastik)
- Küçük hücreli
- Telenjiektatik
- Multifokal
- Malin fibröz histiositom
- Juksta kortikal
  - Periosteal
  - Parosteal
- Çene OS
- Ekstraosseoz

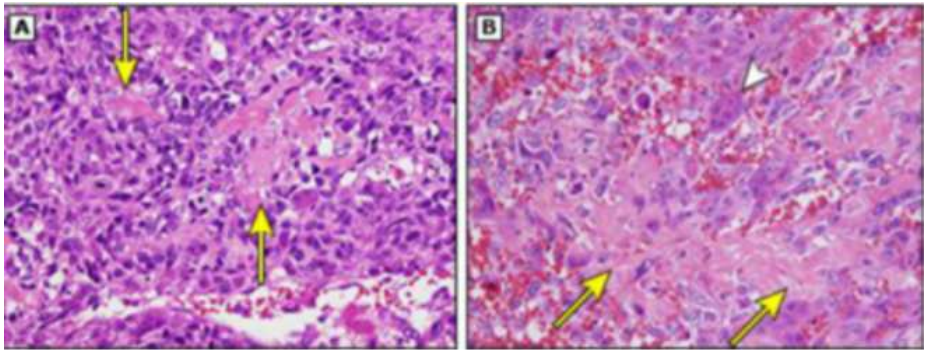
Parosteal osteosarkom dışındakiler histopatolojik olarak yüksek grade olarak gruplandırılır. Parosteal osteosarkom distal femur posteriorunda, korteks kaynaklı, sessiz gidişlidir.

Patoloji-Konvansiyonel Osteosarkom

- Tüm osteosarkomların %90'ı
- Uzun kemik metafizleri
- Adolesan ve genç erişkinlerde
- Osteoblastik, kondroblastik, fibroblastik
- Klinik gidişat ve tedavileri aynı

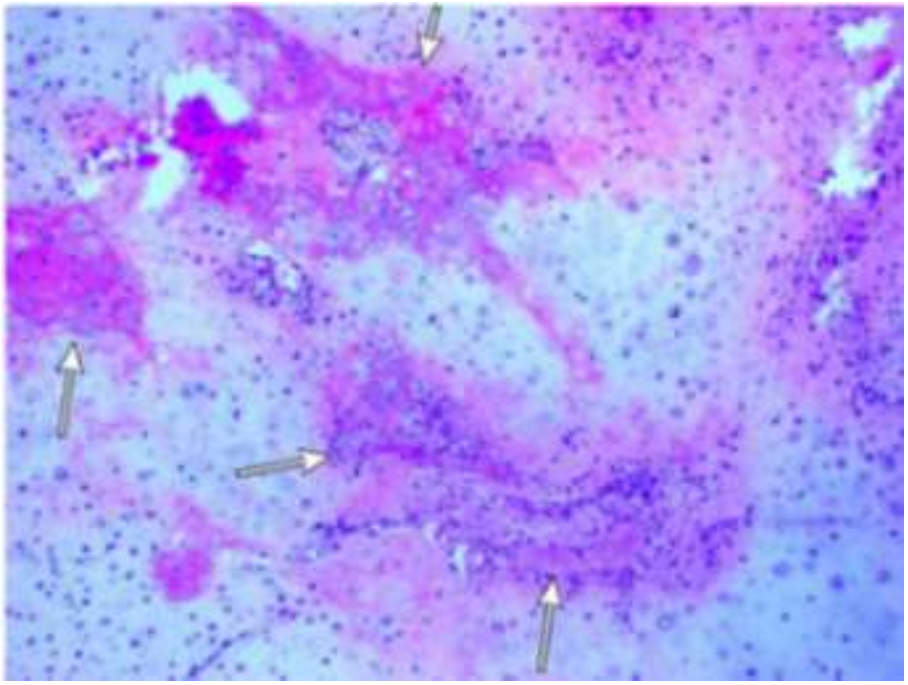
Osteoblastik Osteosarkom

- Konvansiyonel osteosarkomun %50'si
- Bol miktarda osteoid üretimi
- Tümör hücreleri çevresinde dantel gibi görünüm



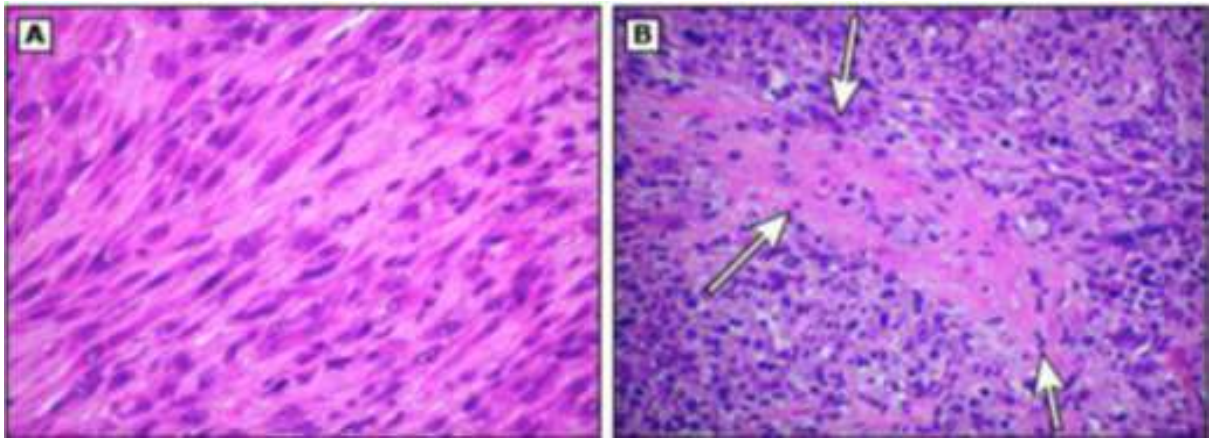
Kondroblastik Osteosarkom

- Konvansiyonel osteosarkomun %25'i
- Kıkırdaklı matriks



Fibroblastik Osteosarkom

- Konvansiyonel osteosarkomun %25'i
- Yüksek gradlı iğsi hücreli stroma
- Fokal osteoid üretimi



Osteosarkom- Diğer histolojik tipler

- **Küçük hücreli:** HE ile Küçük mavi yuvarlak hücreli diğer tümörlerden ayrımı zor
- **Telanjiektatik tip:** Yüksek dereceli vasküler tümör. Yaş dağılımı, tedavi ve kemoterapi yanıtı, konvansiyonel ile aynı.
- **Multifokal tip:** Prognoz kötü.
- **Malin fibröz histiositom:** Osteoid üretimi yok, nekroz oranı düşük, survi konvansiyonele benzer

Osteosarkom- Diğer histolojik tipler

Juksta kortikal (Yüzeyel) osteosarkomlar

Parosteal Osteosarkom

- En yaygın
- Düşük grade fibroblastik hücreler
- 20-40 yaşları arasında
- Korteksten kaynaklanır, zaman içinde korteksi invaze edebilir
- Sadece cerrahi rezeksiyon ile kür oranı %90

Periosteal Osteosarkom

- Orta grade
- Kondroblastik
- Konvansiyonel osteosarkom ile aynı yaş dağılımı
- Adjuvan kemoterapi tartışmalı, ancak %20 metastaz oranı nedeniyle sıklıkla önerilmekte.

Yüksek grade yüzeyel Osteosarkom

Osteosarkom- Diğer histolojik tipler

Çene Osteosarkomu

Yaşlı hastalarda
Yavaş gidişli
Lokal rekürrens> Uzak metastaz

Ekstraosseoz Osteosarkom

- Kemik veya periost tutulumu olmaksızın yumuşak doku tutulumlu
- Çoğunlukla primer radyasyon alanında
- Yaşlı hastalarda
- Diğerlerine göre daha kemorezistan tümörler

Tedavi

- Cerrahi ve kemoterapinin kombinasyonu
- Yalnız cerrahi ile survi <%20
- Tanı anında mikrometastazlar
- Genelde **10 haftalık preop KT yi takiben cerrahi, primer rezeksiyondan sonra KT 29 haftaya tamamlama**

Lokalize Hastalıkta Kemoterapi

- Sisplatin
- Doksorubisin
- Metotreksat
- İfosfamid
- Etoposid
- Karboplatin

Standart 5 yıllık EFS~ %70

St. Jude OS99	72	Carbo/Ifos/Doxo	5-yr EFS 67%	5-yr 79%
P9754 2004	111 54 56	CDDP/Doxo 600 mg/m^2/HDMTX CDDP/Doxo 600 mg/m^2/HDMTX+Ifos CDDP/Doxo/HDMTX+Ifos/VP-16	2-yr EFS 69%	
INT 0133 POG-9351 CCG-7921 (2005)	677	CDDP/Doxo/HDMTX CDDP/Doxo/HDMTX+MTP CDDP/Doxo/HDMTX+Ifos CDDP/Doxo/HDMTX+Ifos+MTP	4-yr EFS 66% 4-yr EFS 65% 4-yr EFS 60% 4-yr EFS 74%	4-yr S 78% 4-yr S 82% 4-yr S 77% 4-yr S 86%
POG-8651 (2003)	 55 45	CDDP/Doxo/HDMTX Surgery week 0 vs. Surgery week 10	 5-yr EFS 69% 5-yr EFS 61%	 5-yr S 79% 5-yr S 76%
St. Jude OS-91 (2001)	47	Carbo/Ifos/Doxo/HDMTX	5-yr EFS 66%	5-yr S 75%
T12 (1998)	31 30 61	HDMTX/BCD/CDDP/Doxo HDMTX/BCD/CDDP/Doxo (more intensive preop chemo) Both regimens	5-yr EFS 73% 5-yr EFS 78% 5-yr EFS 76%	
IOR/OS-4 (2001)	133	HDMTX/CDDP/Doxo/Ifos	5-yr EFS 56%	5-yr S 71%
SSG VIII (2003)	113	HDMTX/Doxo/CDDP	5-yr EFS 61%	5-yr S 74%
EOI (2003)	250 254	CDDP/doxo q 3 weeks vs. CDDP/doxo+G-CSF q 2 weeks	3-yr PFS 41% 3-yr PFS 46%	3-yr S 64% 3-yr S 67%

Tedaviyi nasıl yapalım?

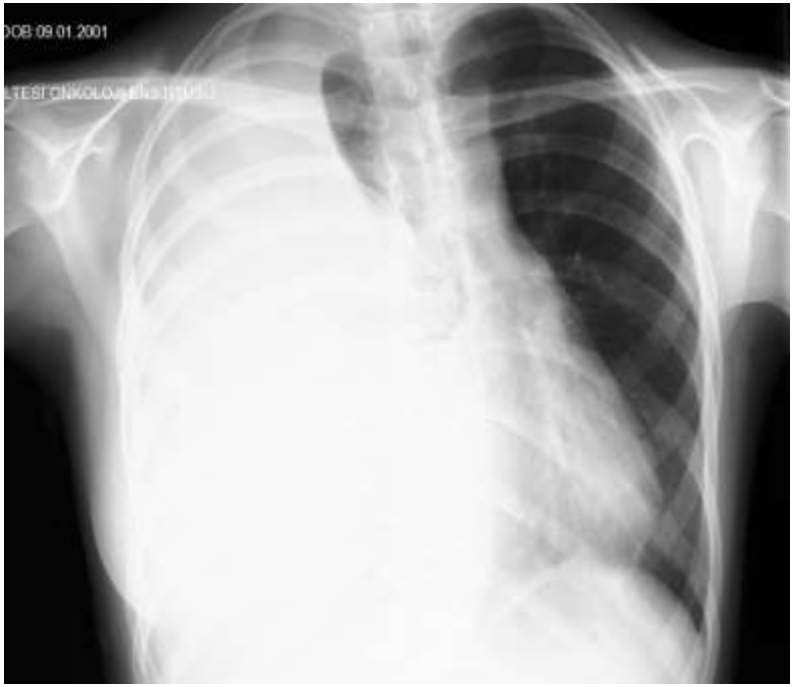
- Cerrahi eksizyon+kemoterapi
- Biyopsi+kemoterapi+cerrahi
- Biyopsi+kemoterapi+cerrahi+kemoterapi
- Biyopsi+kemoterapi+radyoterapi+cerrahi+ kemoterapi
- Biyopsi+kemoterapi+cerrahi+kemoterapi+ radyoterapi

Neoadjuvan Kemoterapi

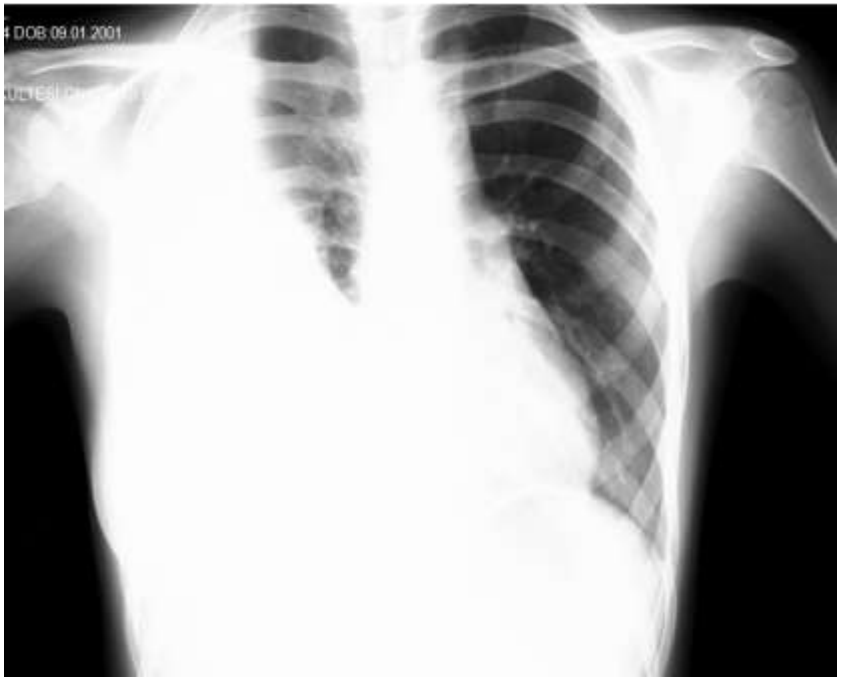
- Hastaya 3 haftada bir ifosfamid, epirubisin, sisplatinli (İfosfamid 1.8 g/m^2/gün,1-3 gün, Epirubisin 90 mg/m^2/gün,2. gün, sisplatin 50 mg/m^2/gün, 4 ve 5. gün neoadjuvan kemoterapi) başlandı.

Epirubicin	90 mg /m^2	2. gün	21 gün
Sisplatin	100 mg /m^2 (toplam doz)	4.- 5. gün	21 gün
İfosfamid	1,8 gr /m^2	1-3 gün	21 gün
Mesna	İfosfamid dozuna göre	1-3 gün	21 gün

31.08.2015
2. kür KT öncesi



28.09.2015
3. kür KT öncesi



19.10.2015
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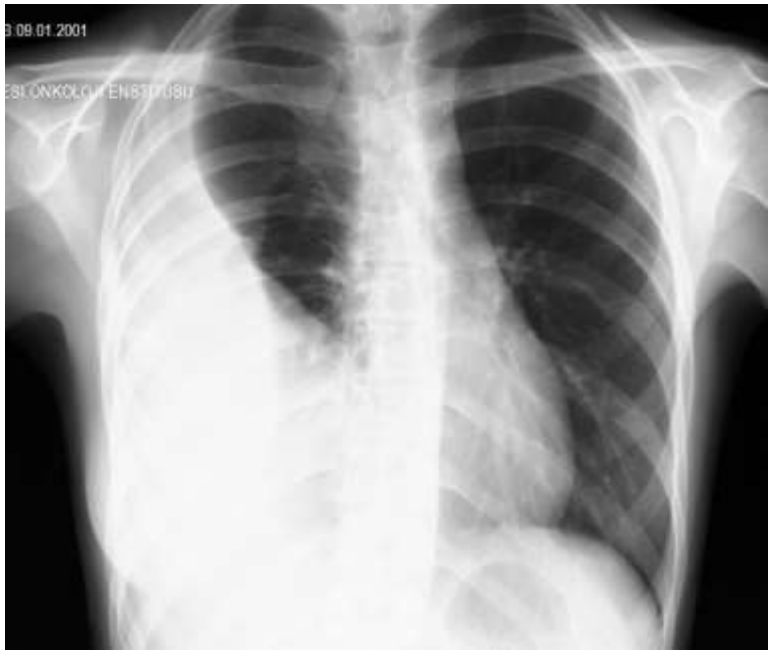
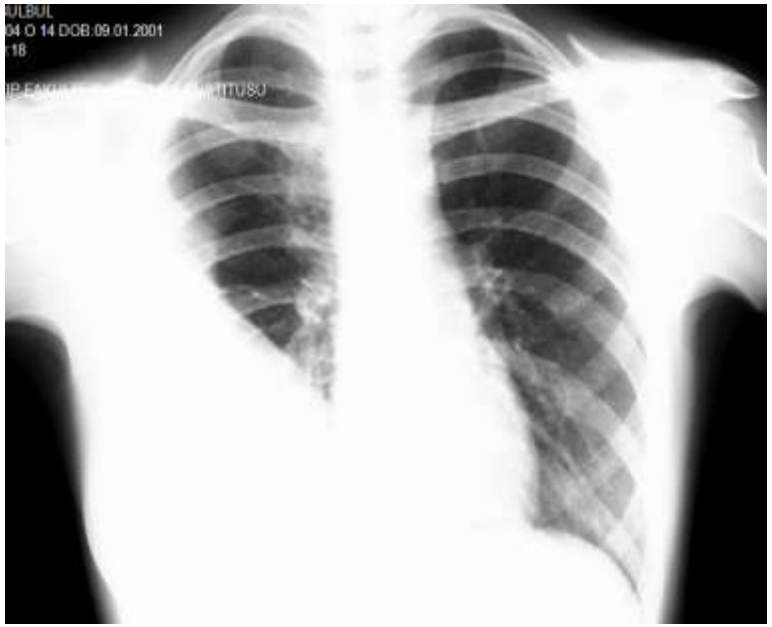
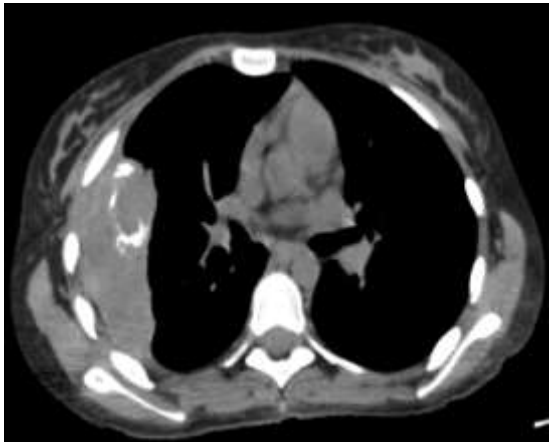
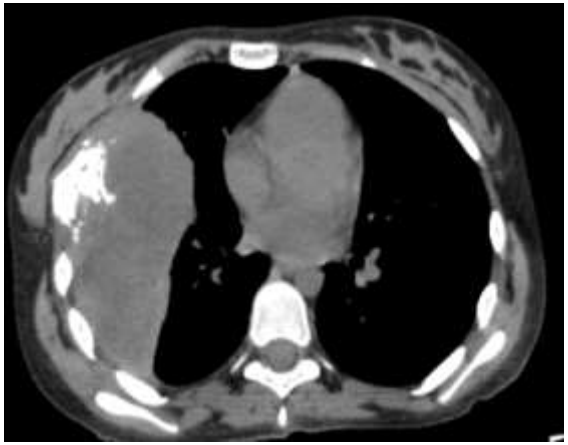


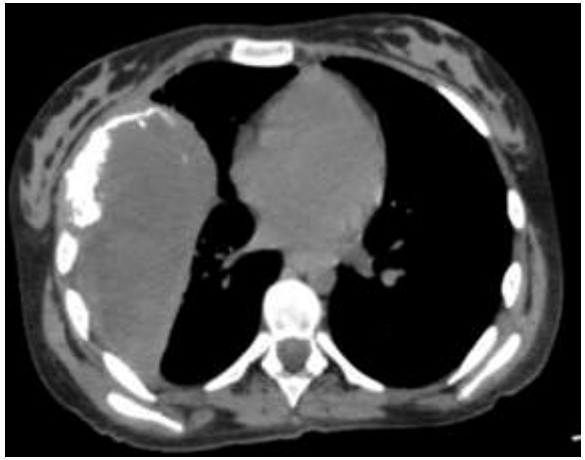
13.11.2015
5. kür KT öncesi

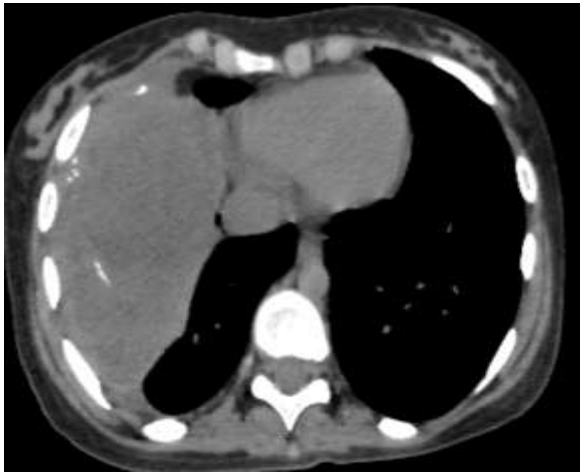


5. kür KT öncesi Toraks BT









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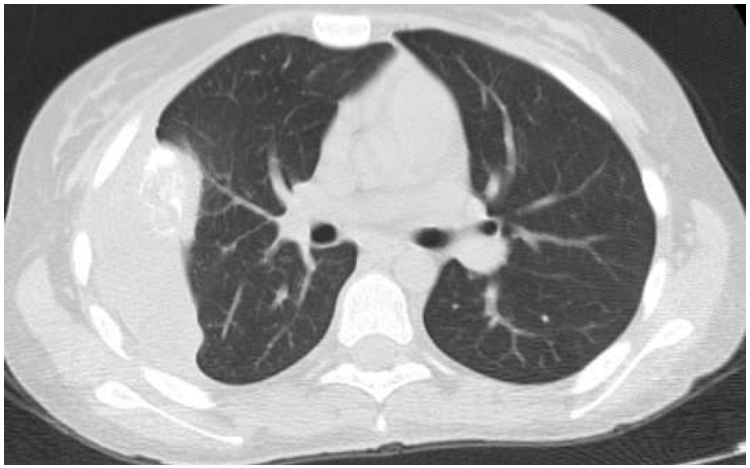
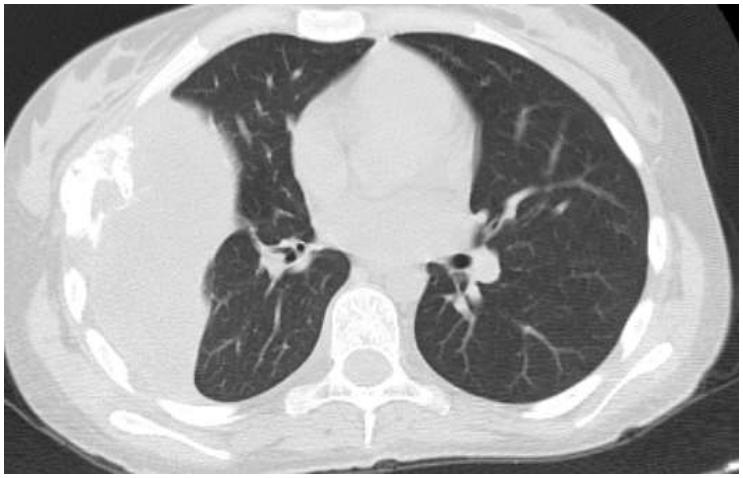
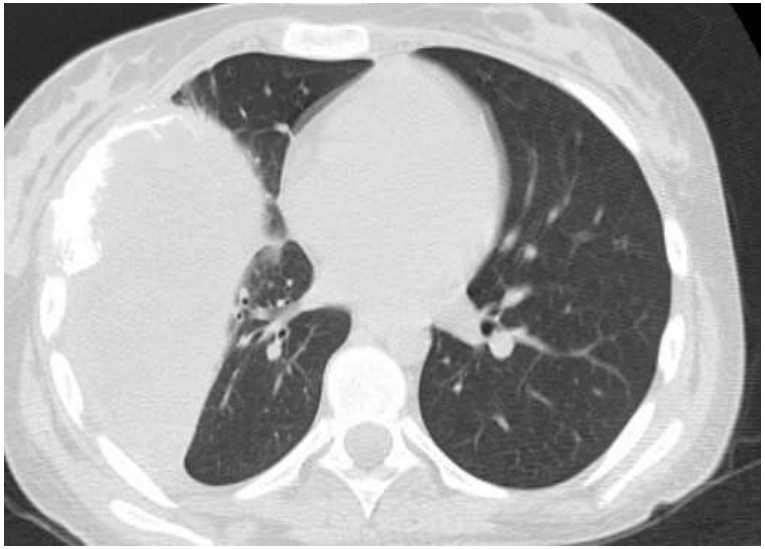
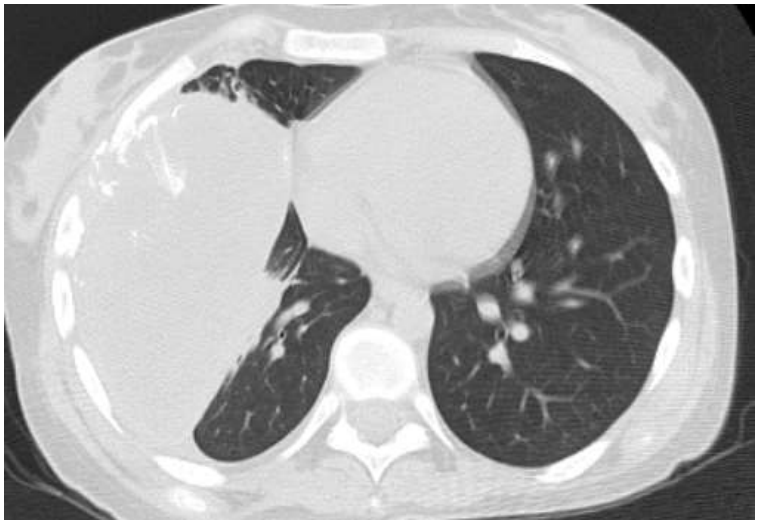
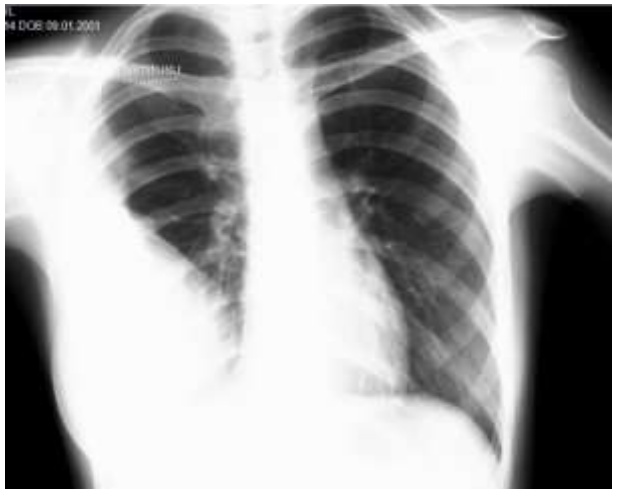


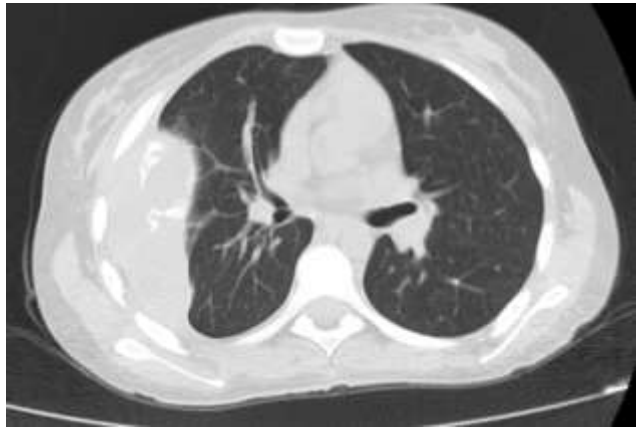


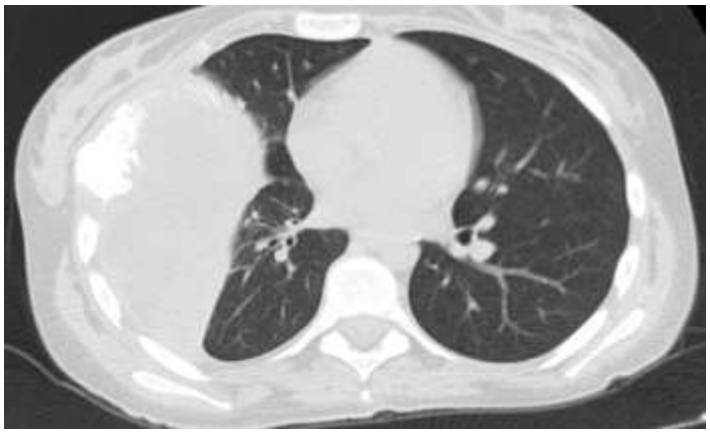


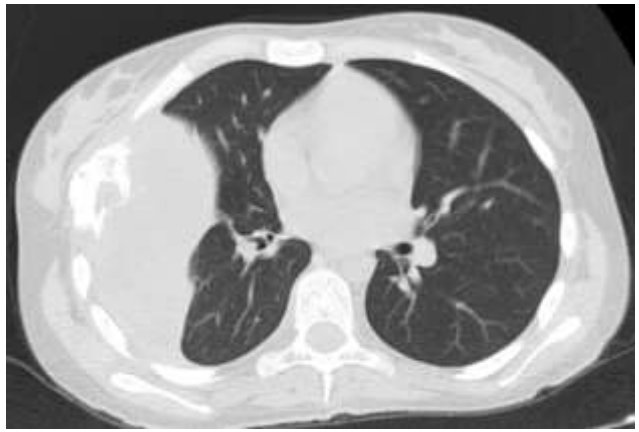


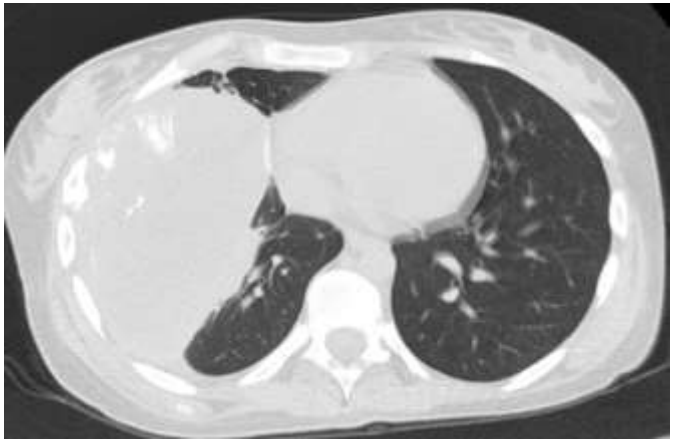


6. Kür öncesi
8.12.2015

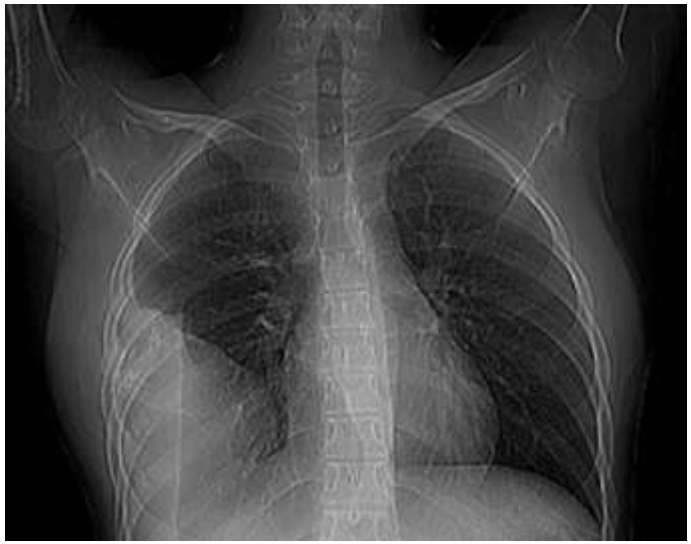


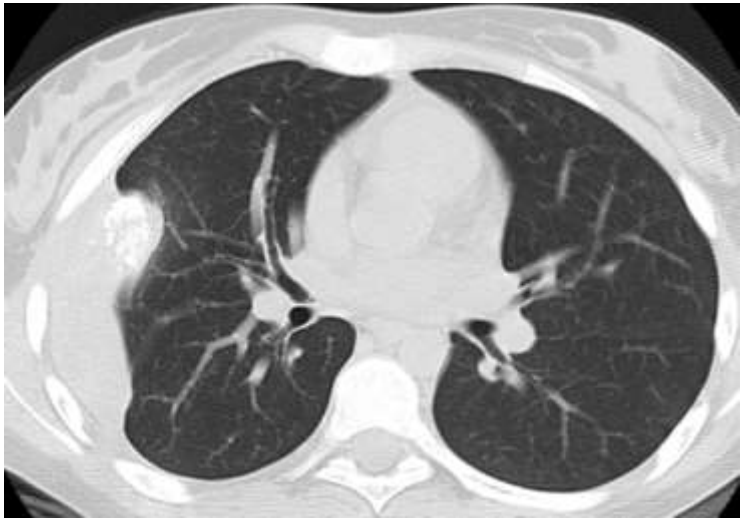


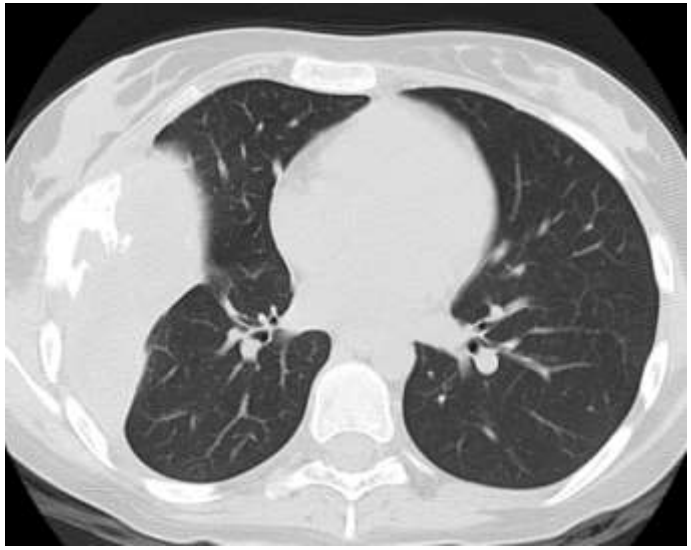


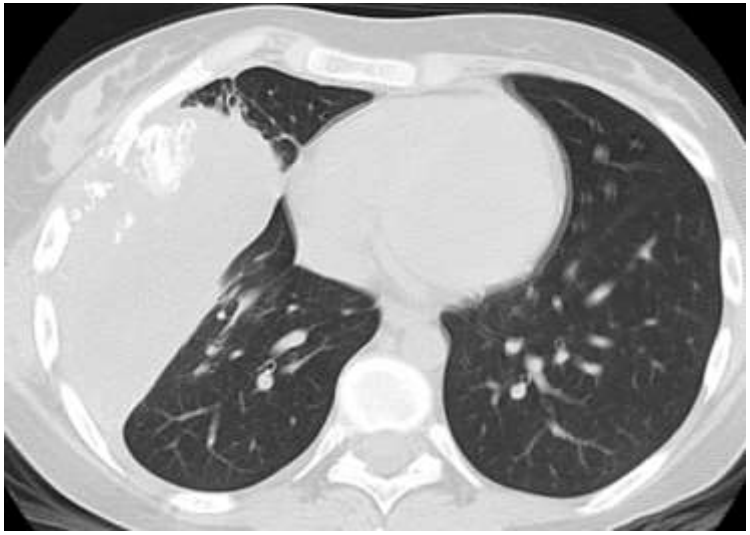


30.12.2015 6 kür sonu Toraks BT



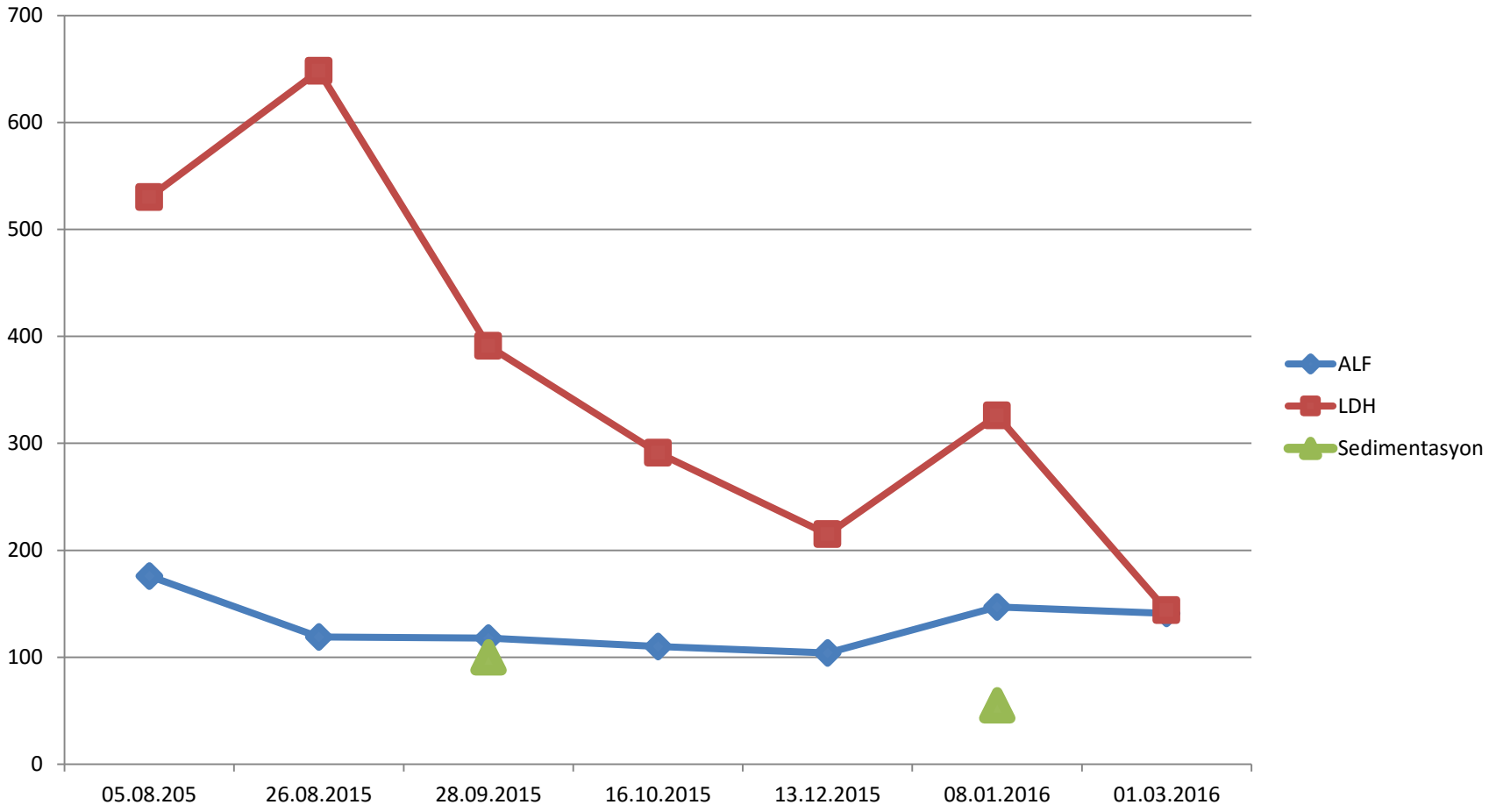






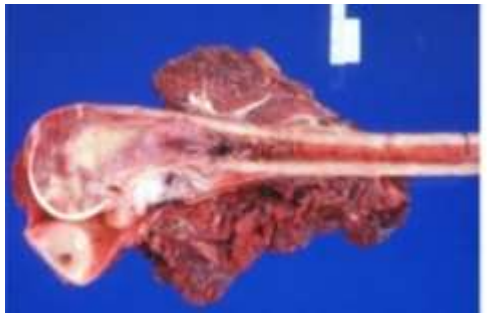
- 6 kür sonrasında, 1 kür IE verildi
- (Ifosfamid, mesna ile, 1.8 g/m^2/gün, 1-5 gün, Etoposid 100 mg/m^2/gün,1-5 gün) .
- Multidisipliner yaklaşım ile kemoterapi ve radyoterapi sonrası cerrahiye yönlendirildi.
- Cerrahi sonrası kemoterapisine devam edildi.

Hastamızın Laboratuar Bulguları



Osteosarkom-Cerrahi

- Aksiyel ve ekstremite tümörlerinde, komplet cerrahi eksizyon, uzun süreli hastalıksız sağkalım için gerekli
- Ekstremite tümörlerinde uzuv koruyucu cerrahi/amputasyon



Osteosarkom-Cerrahi Zamanı

- **Preoperatif kemoterapi faydaları**
  - Mikrometastazlara etkili
  - Ödemi azaltarak, köken aldığı organın korunmasında etkili
  - Cerrahi plan için zaman kazanma
  - Hastanın psikolojik olarak hazırlanması
  - Sonuçta değişiklik yok
- **Preoperatif kemoterapi zararları**
  - Tümör KTye rezistan ise metastaz için zaman geçirme

20.1.2016 Radyoterapi

- Radyoterapi sağ akciğer tümör lojuna 35 Gy R

İ.Ü. ONKOLOJİ ENSTİTÜSÜ

EKSTERNAL RADYOTERAPİ EPİKRİZİ

T.C. Kimlik No : 10130914504
Hasta Adı Soyadı : AYŞE NUR BÜLDÜL
Protokol No : 165361
Başvuru / Takip No : B_UWQR82 / 1VBGXDD
Hasta No : 44962
Adres : ÇOBANÇEŞME MAH. ALADAĞ SK. Dış Kapı No: 43 İç Kapı No: 7 BAHÇELİEVLER/İSTANBUL

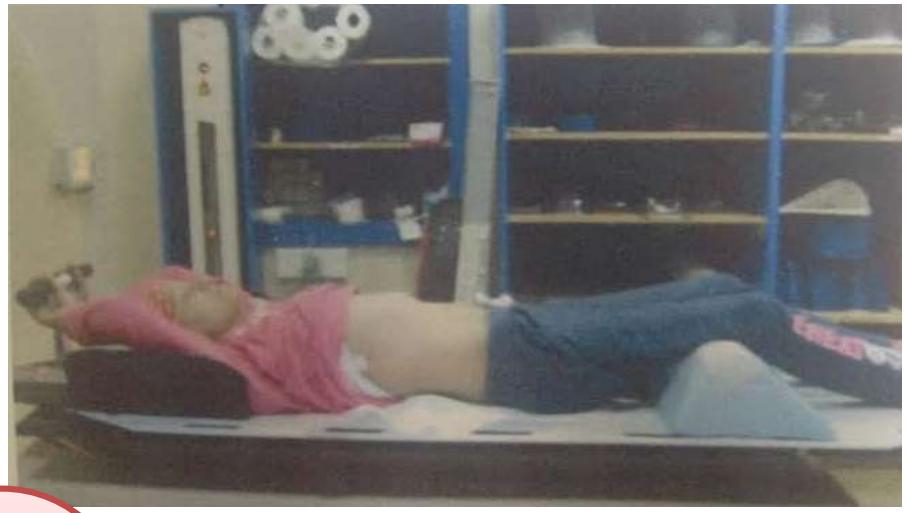
Lokalizasyon :
Evre / TNM :
Cerrahi Tip ve Tarih : /
Histopatoloji : OSTEOSARKOM
Gönderen Hekim/Klinik :
Tanı : (C41.9) Kemik ve eklem kıkırdakları maligne neoplazmı, tanımlanmamış
Hikaye : 15 Y K ŞİKAYETLERİ ÜZERİNE TETKİK EDİLEN VE OSTEOSARKOM TANISI KONULAN HASTAYA YAPILAN TETKİKLER SONUCUNDA RT PLANLANDI.

EKSTERNAL RADYOTERAPİ :

Başlangıç ve Bitiş Tarihleri : 20.01.2016 / 03.02.2016
Tedavi Aygıtı : ONCOR
Fraksiyonasyon Tipi : ☐ Konvansiyonel ☐ Akselere ☐ Hiperfraksiyone ☐ Hipofraksiyone
Işın Alanları : SAĞ AKCİĞER
RT Tedavi Epikrizi : HASTA RT ALTINDA SİMÜLE EDİLDİ.KONFORMAL PLANLAMA YAPILDI .SAĞ AKCİĞER TM LOJUNA 35 GY /10 FR RT UYGULANDI

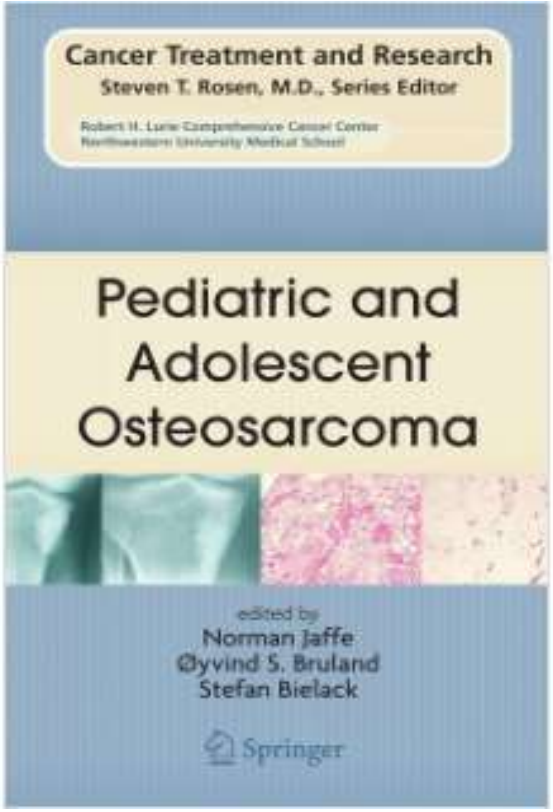
Risk Altındaki Organlar : MEDULA - KALP
Yan Etkiler :
Tedaviye Alınan Yanıt :
Uygulanan Eş Zamanlı Tedavi :
Son Muayene Tarihi ve Son Durum : 03.02.2016 RT TAMAMLANDI
Kullanılacağı Dozlar :
Öneriler : RUTİN POLİKLİNİK KONTROLÜ
Kontrol Tarihi :

Osteosarkomda Radyoterapi İndikasyonları



- 100 hasta
- Primer tm 66 hasta, lokal nüks 11 hasta, metastaz 23 hasta
- 94 eksternal foton, 2 proton, 2 nötron, 2 intraop RT
- 17 hasta kemik hedefli radyonuklid tedavi (Samarium)
- Medyan doz 55.8 Gy
- Medyan izlem 1.5 yıl (0.2-23 yıl)
- Lokal kontrol oranı kombine cerrahi+ RT ile cerrahiye göre daha yüksek (p=0.002)

d. This is due to
regard to the efficacy
Cooperative
COSS-registry
ible for analysis. The
. 94 pts got external
bone-targeted
RT was 55.8 Gy (30-
ars. Survival and
The overall survival
rs, local recurrence,
or local recurrence
erapy. Local control
(48% vs. 22%,
. Local control for pts
t effect on local
ors for local control
. Radiotherapy is an
metastases. Survival
erms of prolonged survival
and prolonged local control. The combination of surgery, radiotherapy, and chemotherapy can be curative. The consistent use of full-dose chemotherapy is of importance for the response to radiotherapy. Prognostic factors for survival are indication for RT, RT plus surgery vs. RT alone and tumor location. Prognostic factors for local control are indication for RT, and RT plus surgery vs. RT alone.



COMBINATION SHORT-COURSE PREOPERATIVE IRRADIATION, SURGICAL RESECTION, AND REDUCED-FIELD HIGH-DOSE POSTOPERATIVE IRRADIATION IN THE TREATMENT OF TUMORS INVOLVING THE BONE

TIMOTHY D. WAGNER, M.D., M.B.A.,* WENDY KOBAYASHI, B.A.,† SUSAN DEAN, B.S.,† SAVELI I. GOLDBERG, PH.D.,† DAVID G. KIRSCH, M.D., PH.D.,‖ HERMAN D. SUIT, M.D., D.PHIL.,† FRANCIS J. HORNICEK, M.D., PH.D.,‡ FRANCIS X. PEDLOW, M.D.,‡ KEVIN A. RASKIN, M.D.,‡ DEMPSEY S. SPRINGFIELD, M.D.,‡ SAM S. YOON, M.D.,§ MARC C. GEBHARDT, M.D.,¶ HENRY J. MANKIN, M.D.,‡ AND THOMAS F. DELANEY, M.D.†

*Department of Radiation Oncology, Brooke Army Medical Center, Fort Sam Houston, TX; †Department of Radiation Oncology; ‡Orthopaedic Oncology, Department of Orthopaedics; §Surgical Oncology, Department of Surgery, Massachusetts General Hospital, Boston, MA; ‖Department of Radiation Oncology, Duke University School of Medicine, Durham, NC; and ¶Orthopaedic Surgery, Beth Israel Deaconess Medical Center, Boston, MA

Purpose: To assess the feasibility and outcomes of combination short-course preoperative radiation, resection, and reduced-field (tumor bed without operative field coverage) high-dose postoperative radiation for patients with solid tumors mainly involving the spine and pelvis.

Methods and Materials: Between 1982 and 2006, a total of 48 patients were treated using this treatment strategy for solid tumors involving bone. Radiation treatments used both photons and protons.

Results: Of those treated, 52% had chordoma, 31% had chondrosarcoma, 8% had osteosarcoma, and 4% had Ewing's sarcoma, with 71% involving the pelvis/sacrum and 21% elsewhere in the spine. Median preoperative dose was 20 Gy, with a median of 50.4 Gy postoperatively. With 31.8-month median follow-up, the 5-year overall survival (OS) rate is 65%; 5-year disease-free survival (DFS) rate, 53.8%; and 5-year local control (LC) rate, 72%. There were no significant differences in OS, DFS, and LC according to histologic characteristics. Between primary and recurrent disease, there was no significant difference in OS rates (74.4% vs. 51.4%, respectively; $p = 0.128$), in contrast to DFS (71.5% vs. 18.3%; $p = 0.0014$) and LC rates (88.9% vs. 30.9%; $p = 0.0011$) favoring primary disease. After resection, 10 patients experienced delayed wound healing that did not significantly impact on OS, DFS, or LC.

Conclusion: This approach is promising for patients with bone sarcomas in which resection will likely yield close/positive margins. It appears to inhibit tumor seeding with an acceptable rate of wound-healing complications. Dose escalation is accomplished without high-dose preoperative radiation (likely associated with higher rates of acute wound healing delays) or large-field postoperative radiation only (likely associated with late normal tissue toxicity). The LC and DFS rates are substantially better for patients with primary than recurrent sarcomas. Published by Elsevier Inc.

Radiotherapy, Chordoma, Chondrosarcoma, Proton therapy, Tumor seeding.

JJCO Japanese Journal of Clinical Oncology

Japanese Journal of Clinical Oncology, 2016, 46(2) 138–143
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Advance Access Publication Date: 18 December 2015
Original Article

Original Article

Radiotherapy and gemcitabine–docetaxel chemotherapy in children and adolescents with unresectable recurrent or refractory osteosarcoma

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Received 1 September 2015; Accepted 26 October 2015

Abstract

Objective: Few reports have described the treatment outcome of osteosarcoma using radiotherapy. We evaluated the efficacy of radiotherapy and gemcitabine and docetaxel chemotherapy for patients with unresectable recurrent or refractory osteosarcoma.

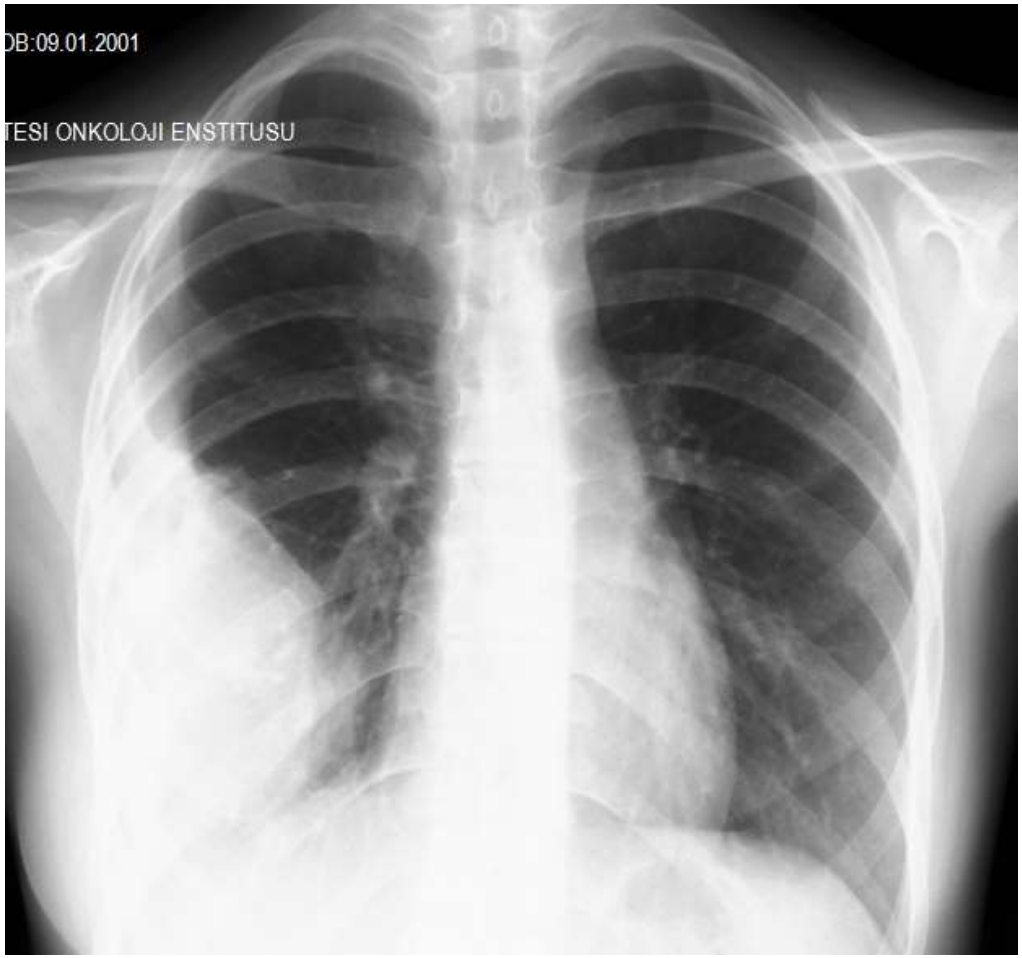
Methods: Data from six patients (five male, one female) who received radiotherapy and gemcitabine and docetaxel chemotherapy at the Korea Cancer Center Hospital were retrospectively reviewed. Tumor response was evaluated according to metabolic changes using ^{18}F-fluorodeoxy-D-glucose-positron emission tomography.

Results: The median age of the patients was 15.0 years (range, 14.0–15.8 years). Two patients had single bone lesions, and four had multiple metastatic bone lesions. Patients received a median 3.5 courses of gemcitabine and docetaxel chemotherapy (range, 2–6 courses). The median dose of radiotherapy was 50.0 Gy (range, 46–84 Gy). There were two complete metabolic responses and one partial metabolic response. The objective response rate was 50.0% (3/6). Responses were maintained for 4.6, 6.1 and 13.7 months, respectively. Patients were followed up for a median of 5.8 months (range, 2.7–84.6 months), and the median progression-free survival after this treatment was 3.6 months (range, 1.1–13.7 months). At the time of analysis, two patients were alive, one was lost to follow-up and three had died.

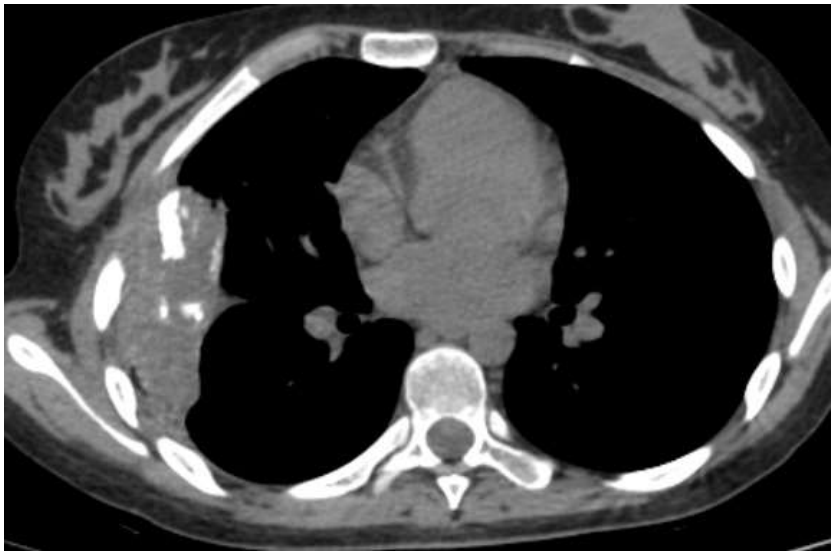
Conclusion: Radiotherapy with gemcitabine and docetaxel chemotherapy showed some improvement in cases of refractory tumors or multiple bone metastases. Further studies are needed to investigate the efficacy of newer radiotherapy modalities, as well as to identify new radiosensitizing chemotherapy regimens.

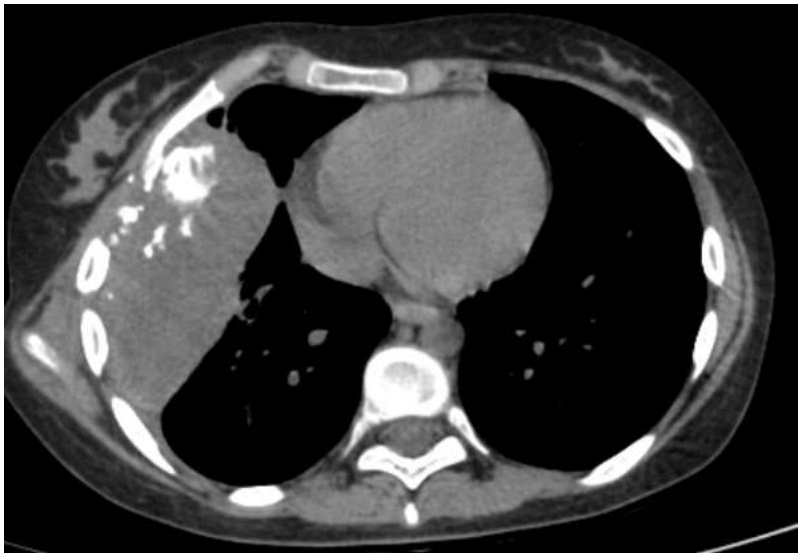
Key words: osteosarcoma, radiotherapy, gemcitabine, docetaxel

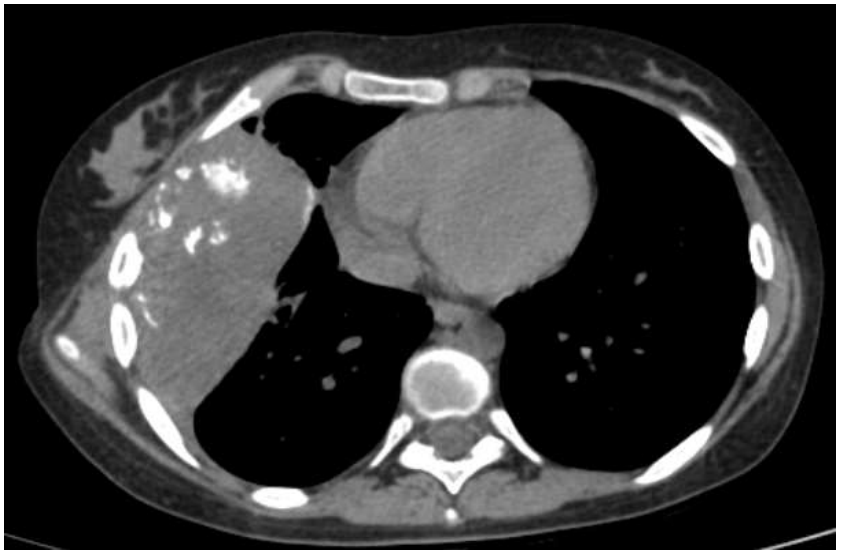
6 kür ESI ve 1 kür IE ve RT sonrası 1.2.2016

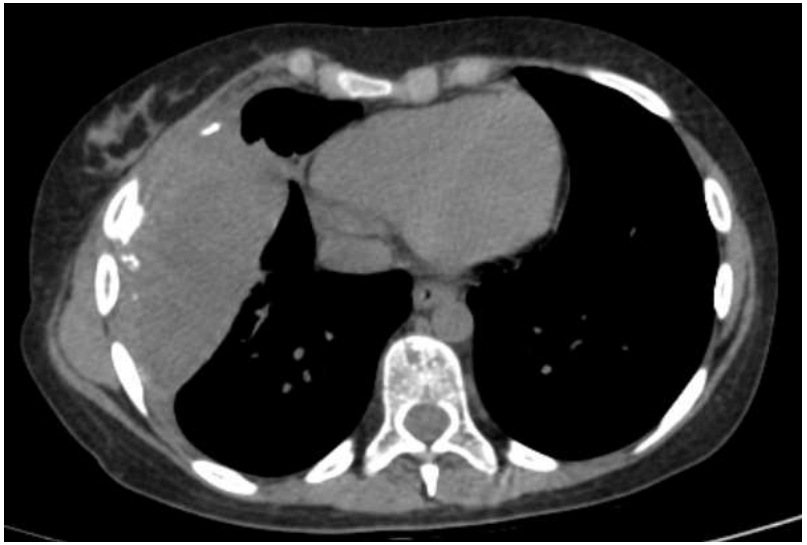


30.12.2015 7 kür KT ve RT sonu Toraks BT









Primer gecikmiş cerrahi rezeksiyon 12.2.2016

akciğer-cilt sınır kitle paryetal
sınırlarda tümör görülmedi,
eksizyon materyalinde seyrek

Histolojik yanıt değerlendirme

- **İyi yanıt: >%90 tümör nekrozu**
- **Orta derecede yanıt: %50-%90 nekroz**
- **Kötü yanıt: <%50 nekroz**

Table 8.1 Histologic response grading systems for treated osteosarcomas

Reference	Response grade	Response grade definition
Huvos (1988), Provisor et al. (1997)	I	Viable; little to no chemotherapeutic effect
	II	Partially necrotic
	III	Largely necrotic
	IV	Totally necrotic; no histologic evidence of viable tumor within specimen
Rosen et al. (1979)	I	Little to no chemotherapeutic effect
	II	Partial response, <50 % necrosis, some viable tumor remaining
	III	>90 % tumor necrosis, foci of viable tumor remaining
	IV	No viable-appearing tumor cells
Raymond et al. (1987)		Percentage of necrosis estimated
Picci et al. (1994)	Good	>90 % necrosis
	Fair	60–90 % necrosis
	Poor	<60 % necrosis
Wold (1998)** **Used in COG clinical trials	I	No chemotherapeutic effect
	II	Some necrosis
	A	50 % viable tumor remaining
	B	5–50 % viable tumor remaining
	III	Scattered foci; <5 % viable tumor remaining
	IV	No viable tumor remaining
Salzer-Kuntschik et al. (1983)	I	No viable-appearing tumor cells
	II	Single viable tumor cells or 1 viable cell cluster, <0.5 cm
	III	<10 % Viable tumor remaining
	IV	10–50 % Viable tumor remaining
	V	>50 % Viable tumor remaining
	VI	No chemotherapeutic effect

Adapted from Coffin et al. (2005), Lowichik et al. (2000)

BİYOPSİ: TUMOR GÖRÜLMEDİ.
BİYOPSİ: TUMOR GÖRÜLMEDİ.
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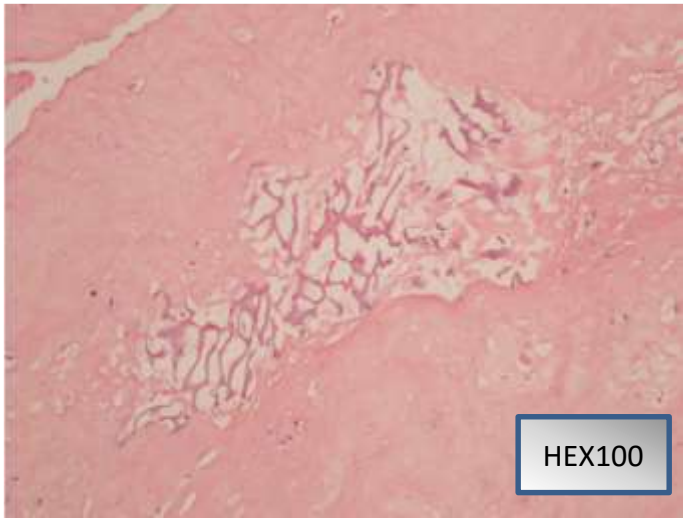
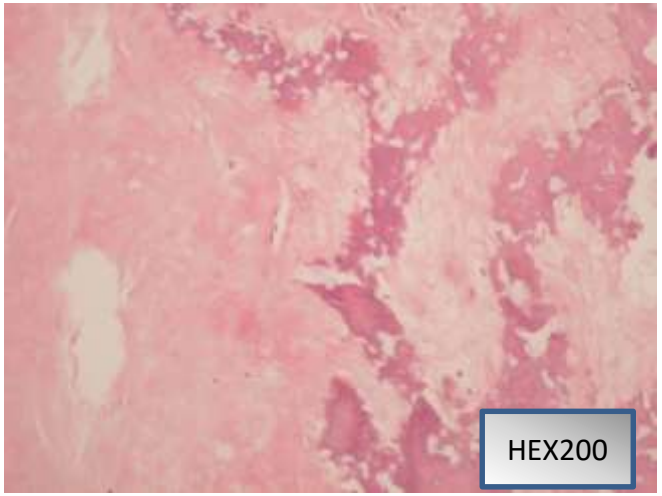
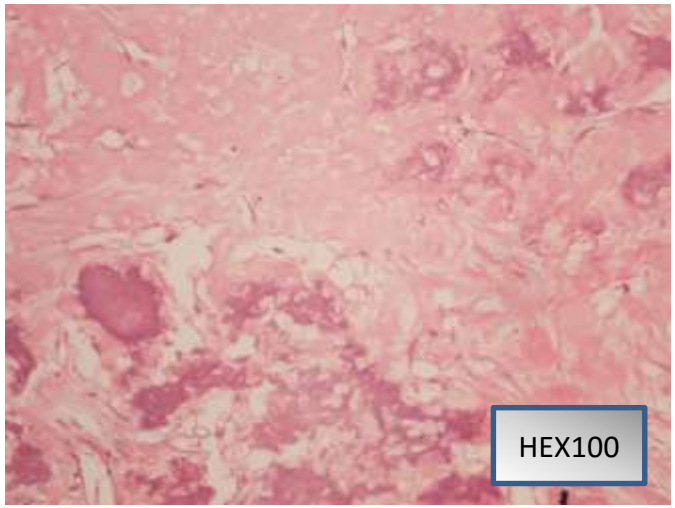
Tedavi sonrası patoloji





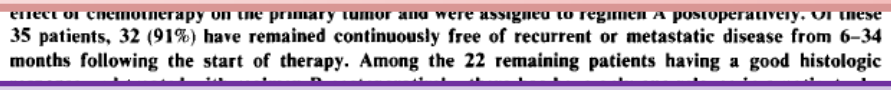


Cerrahi sonrası nekroz oranına göre kemoterapi azaltalım mı? Yoğunlaştıralım mı?

- Olaysız sağkalım (5 yıllık) histolojik yanıtı iyi olanlarda %73, kötü olanlarda %59 ($p<0.001$)
- Genel sağkalım (5 yıllık) histolojik yanıtı iyi olanlarda %83, kötü olanlarda %71 ($p<0.001$)

Operasyon sonrası tedavi modifikasyonu ile ilgili erken dönemdeki çalışmalar

- Rozen ve ark, Cancer, 1982
- 57 hasta
- Hastalar 4-16 hafta yüksek doz MTX, adriamisin ve bleo/siklo/daktinomisin(BCD) ile tedavi
- Ardından cerrahi
- >%90 nekroz ise aynı rejime devam
- <%90 nekroz ise yüksek doz MTX yerine sisplatin, devamında adriamisin/BCD


effect of chemotherapy on the primary tumor and were assigned to regimen A postoperatively. Of these 35 patients, 32 (91%) have remained continuously free of recurrent or metastatic disease from 6–34 months following the start of therapy. Among the 22 remaining patients having a good histologic

Sonuç: Kötü histolojik yanıtlı olan hastaların %91'i hastalığın başlangıcından itibaren 6-35 ay hastalıksız yaşamış.

Operasyon sonrası tedavi modifikasyonu ile ilgili erken dönemdeki çalışmalar

Meyers ve ark, J Clin Onc, 1992
Yüsek doz MTX, adriamisin ve BCD (Bleomisin, siklofosfamid, daktinomisin) hepsi almış.
Kötü histolojik yanıtlı olan hastalara sisplatin randomizasyonu

DFS da farklılık yok

J Clin

Che

Meye

A

Abs

PUR

with C

our experience

of salvage

chemotherapy after poor initial response.

METHODS: From 1975 to 1984, we saw 279 patients with previously untreated OS without metastasis. All patients received intensive chemotherapy and underwent surgical resection of primary tumor. Chemotherapy included high-dose methotrexate; Adriamycin (doxorubicin; Adria Laboratories, Columbus, OH); and bleomycin, cyclophosphamide, and dactinomycin (BCD). Selected patients also received cisplatin.

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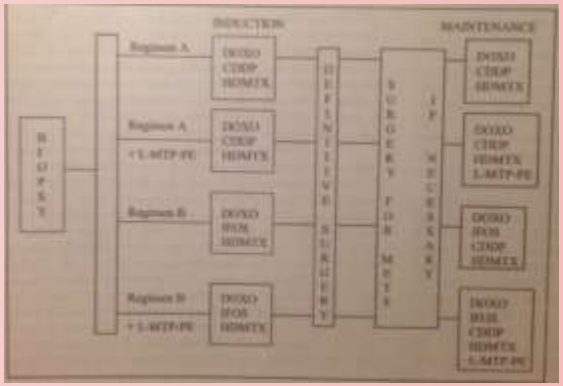
Sonuç: İyi histolojik yanıt veren hastaların oranını yükseltmek lazım

Operasyon sonrası tedavi modifikasyonu ile ilgili daha yeni çalışmalar

VOLUME 23 · NUMBER 9 · MARCH 20 2005
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Meyers ve ark, J Clin Onc, 2005
Randomize prospektif çalışma
Sisplatin/dokso
+/- Ifosfamid
+/- Muramil tripeptid
MTP ile ifosfamid arası etkileşim var, ileri analizler gerekli



A complete listing of grant support for research conducted by the Children's Cancer Group and the Pediatric Oncology Group before initiation of the Children's Oncology Group grant in 2003 is available online at http://www.childrensoncologygroup.org/admin/grantinfo.htm.

lated in liposomes to cisplatin, doxorubicin, and high-dose methotrexate (HDMTX) could improve the probability for event-free survival (EFS) in newly diagnosed patients with osteosarcoma (OS).

Patients and Methods

Six hundred seventy-seven patients with OS without clinically detectable metastatic disease were treated with one of four prospectively randomized treatments. All patients received identical cumulative doses of cisplatin, doxorubicin, and HDMTX and underwent definitive

Sonuç: İfosfamid ilavesi ile EFS artmadı
MTP; EFSyi arttırabilir.

ifosfamide and MTP.

OXFORD JOURNALS Annals of Oncology

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Published online 2014 Nov 24. doi: 10.1093/annonc/mdu526

EURAMOS-1, an international randomised study for osteosarcoma: results from pre-randomisation treatment†

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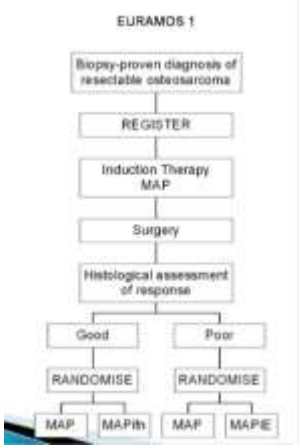
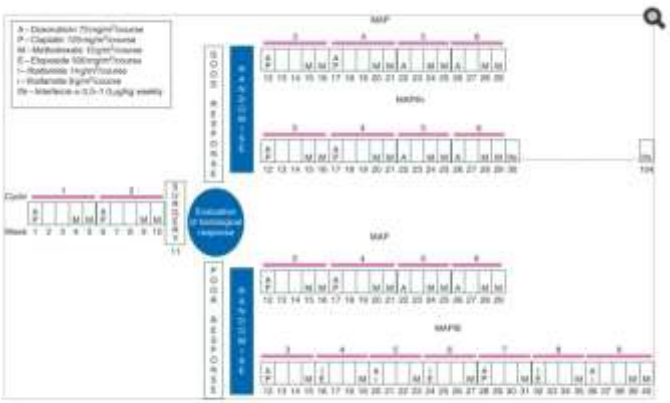


Figure 2.



EURAMOS-1 treatment schedule

Interventions

M Methotrexate 12 g/m²
A Doxorubicin 75 g/m²
P Cisplatin 120 g/m²

Pegylated IFN-α-2b

Dosing
Starting at 0.5 µg/kg/week (max. 50 µg) SC × 4 weeks
Escalation to 1.0 µg/kg/week (max. 100 µg) SC
if well tolerated

Timing
Once per week after chemotherapy until week 104

R Random assignment

VOLUME 33 · NUMBER 20 · JULY 10 2015

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Methotrexate, Doxorubicin, and Cisplatin (MAP) Plus Maintenance Pegylated Interferon Alfa-2b Versus MAP Alone in Patients With Resectable High-Grade Osteosarcoma and Good Histologic Response to Preoperative MAP: First Results of the EURAMOS-1 Good Response Randomized Controlled Trial

Stefan S. Bielack, Sigbjørn Smeland, Jeremy S. Whelan, Neyssa Marina, Gordana Jovic, Jane M. Hook, Mark D. Krailo, Mark Gebhardt, Zsuzsanna Papai, James Meyer, Helen Nadel, R. Lor Randall, Claudia Deffenbaugh, Rajaram Nagarajan, Bernadette Brennan, G. Douglas Letson, Lisa A. Teot, Allen Goorin, Daniel Baumhoer, Leo Kager, Mathias Werner, Ching C. Lau, Kirsten Sundby Hall, Hans Gelderblom, Paul Meyers, Richard Gorlick, Reinhard Windhager, Knut Helmke, Mikael Eriksson, Peter M. Hoogerbrugge, Paula Schomberg, Per-Ulf Tunn, Thomas Kühne, Heribert Jürgens, Henk van den Berg, Tom Böhling, Susan Picton, Marleen Renard, Peter Reichardt, Joachim Gerss, Trude Butterfass-Bahloul, Carol Morris, Pancras C.W. Hogendoorn, Beatrice Seddon, Gabriele Calaminus, Maria Michelagnoli, Catharina Dhooge, Matthew R. Sydes, and Mark Bernstein, on behalf of the EURAMOS-1 investigators

Author affiliations appear at the end of this article.

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Support information appears at the end of this article.

Terms in blue are defined in the glossary, found at the end of this article and online at www.jco.org.

M.R.S. and M.B. contributed equally to this work.

Trial unit staff at the Medical Research Council Clinical Trials Unit of University College London, Children's Oncology Group, Cooperative Osteosarcoma Study Group, Scandinavian Sarcoma Group, EURAMOS Intergroup Safety Desk, and Quality of Life Coordinating Centre were central to the trial design, trial conduct, data analysis, data interpretation, and development of this report. S.S.B., G.J., J.M.H., T.B.-B., and M.R.S. accessed raw data. The corresponding author had full access to the data and had final responsibility for the decision to submit for publication.

Authors' disclosures of potential conflicts of interest are found in the article online at www.jco.org. Author contributions are found at the end of this article.

Clinical trial information: NCT00134030; ISRCTN67613027.

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0732-183X/15/3320w-2279w/$20.00

DOI: 10.1200/JCO.2014.60.0734

ABSTRACT

Purpose

EURAMOS-1, an international randomized controlled trial, investigated maintenance therapy with pegylated interferon alfa-2b (IFN-α-2b) in patients whose osteosarcoma showed good histologic response (good response) to induction chemotherapy.

Patients and Methods

At diagnosis, patients age ≤ 40 years with resectable high-grade osteosarcoma were registered. Eligibility after surgery for good response random assignment included ≥ two cycles of preoperative MAP (methotrexate, doxorubicin, and cisplatin), macroscopically complete surgery of primary tumor, < 10% viable tumor, and no disease progression. These patients were randomly assigned to four additional cycles MAP with or without IFN-α-2b (0.5 to 1.0 μg/kg per week subcutaneously, after chemotherapy until 2 years postregistration). Outcome measures were event-free survival (EFS; primary) and overall survival and toxicity (secondary).

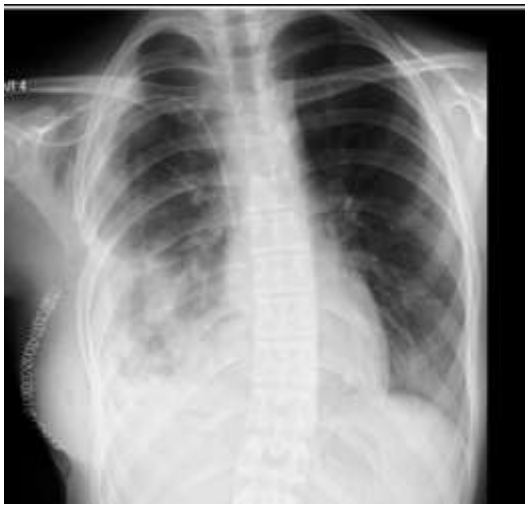
Results

Good response was reported in 1,041 of 2,260 registered patients; 716 consented to random assignment (MAP, n = 359; MAP plus IFN-α-2b, n = 357), with baseline characteristics balanced by arm. A total of 271 of 357 started IFN-α-2b; 105 stopped early, and 38 continued to receive treatment at data freeze. Refusal and toxicity were the main reasons for never starting IFN-α-2b and for stopping prematurely, respectively. Median IFN-α-2b duration, if started, was 67 weeks. A total of 133 of 268 patients who started IFN-α-2b and provided toxicity information reported grade ≥ 3 toxicity during IFN-α-2b treatment. With median follow-up of 44 months, 3-year EFS for all 716 randomly assigned patients was 76% (95% CI, 72% to 79%); 174 EFS events were reported (MAP, n = 93; MAP plus IFN-α-2b, n = 81). Hazard ratio was 0.83 (95% CI, 0.61 to 1.12; $P = .214$) from an adjusted Cox model.

Conclusion

At the preplanned analysis time, MAP plus IFN-α-2b was not statistically different from MAP alone. A considerable proportion of patients never started IFN-α-2b or stopped prematurely. Long-term follow-up for events and survival continues.

Operasyon sonrası izlem



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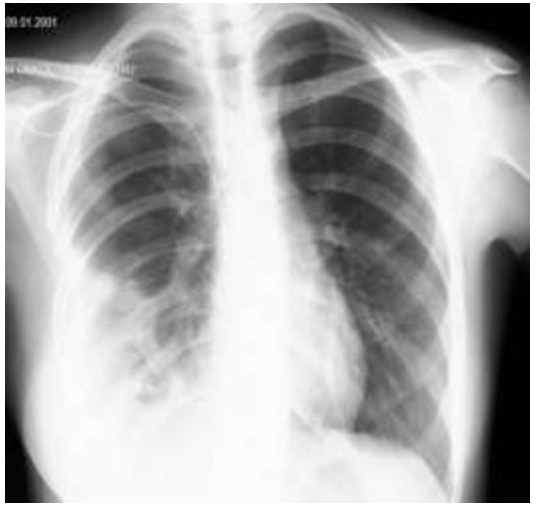

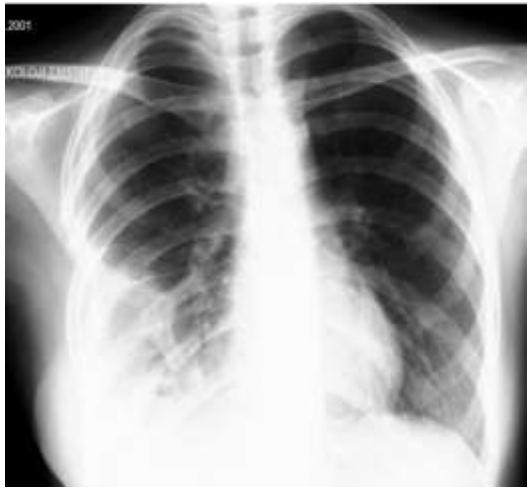

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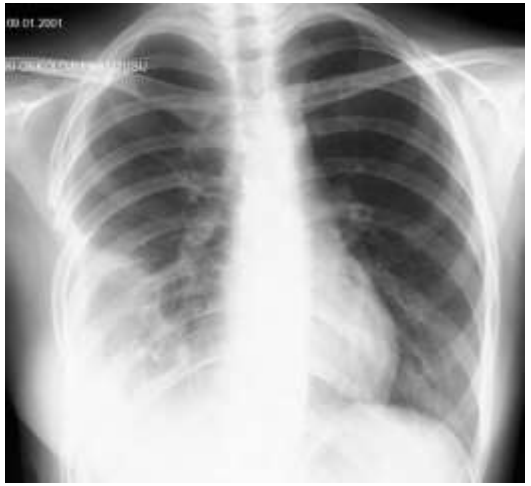

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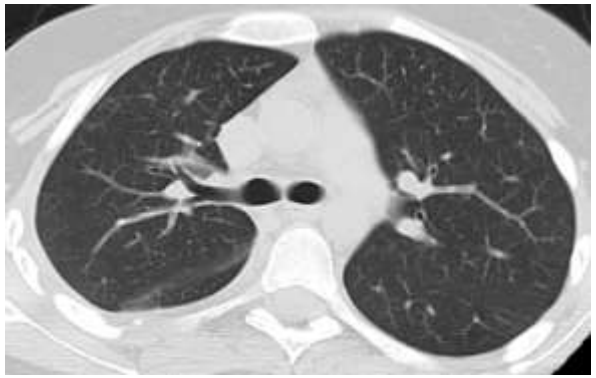
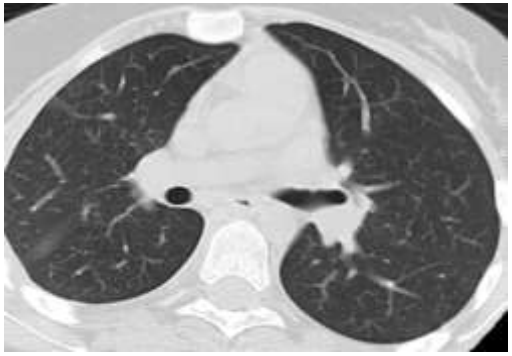
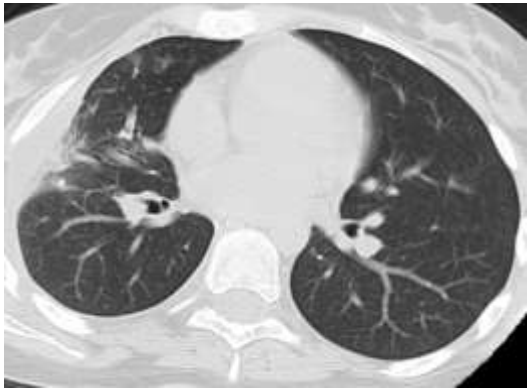
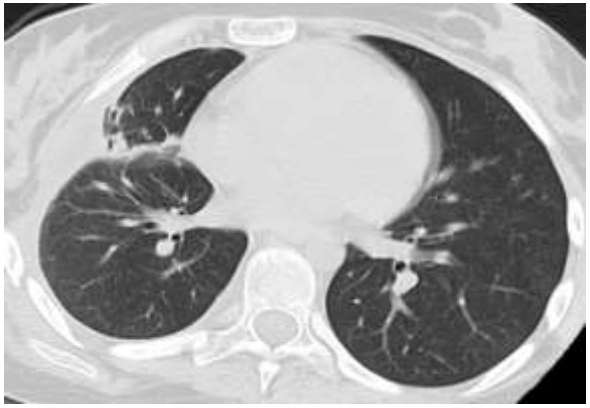
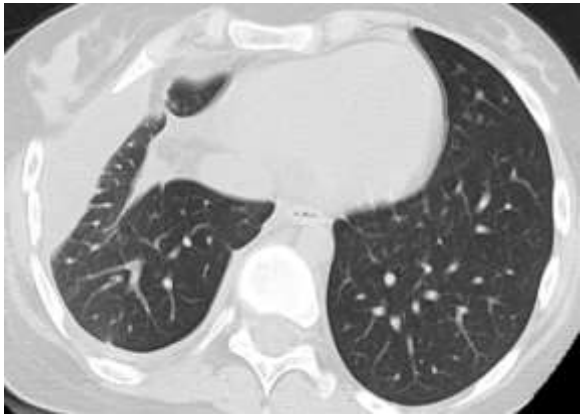
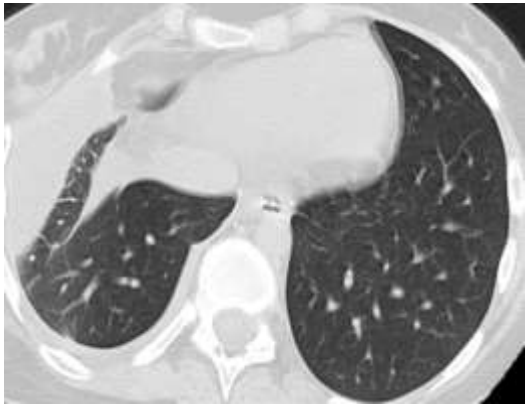







Metastatik Hastalıkta Tedavi

- Chemotherapy – metastatic disease
  - Active agents
    - Cisplatin
    - Doxorubicin
    - Methotrexate
    - Ifosfamide
    - ± Etoposide

5-year EFS 46.7% ± 9.3%
(Harris et al.)

2-year EFS 43% ± 9.3%
(Goorin et al.)

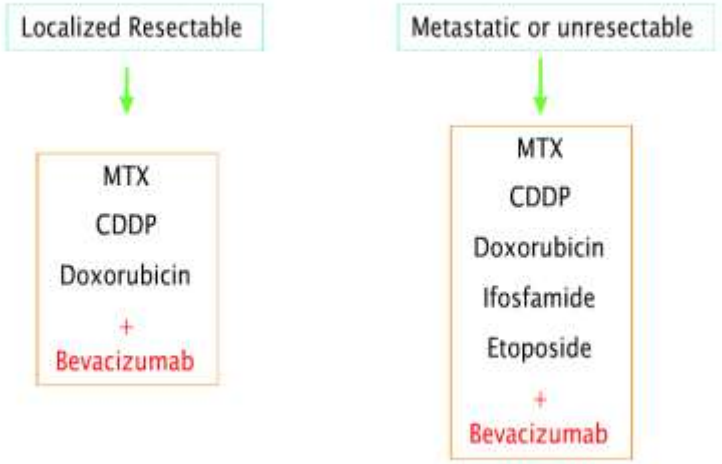
Authors	N	EFS	OS
Marina 1992 St. Jude	18		50% (3 years)
Meyers 1992 N.Y.	62		11% (5 years)
Pacquement 1996 France	73		15%
Harris 1998 POG	30	46.7% (5 years)	53.3% (5 years)
Ferguson 2001 COG	36	24% (3 years)	32% (3 years)
Goorin 2002 POG	41	43% (2 years)	55% (2 years)
Kager 2003 COSS	202		31% (5 years)
Petrilli 2006 Brazil	41	12.2% (5 years)	12.2% (5 years)
Daw 2006 St. Jude	29	6.9% (5 years)	24.1% (5 years)

Kötü Prognostik Faktörler

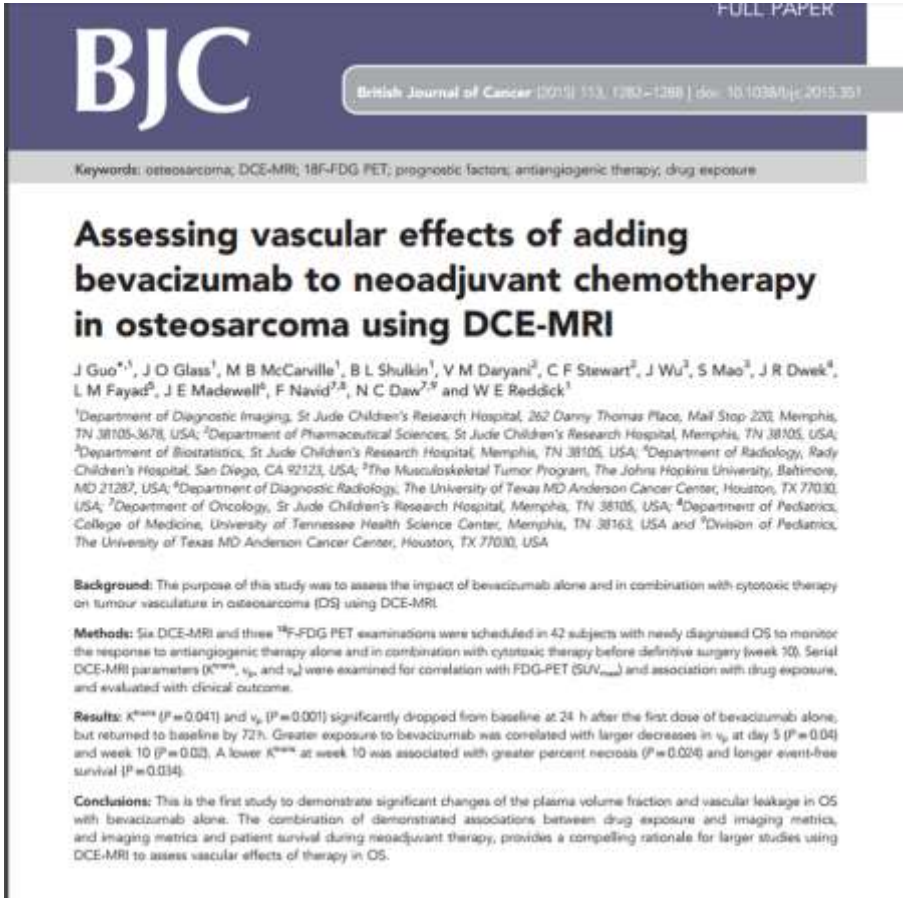
- Metastatik hastalık
- Kemoterapi sonucu tümör nekrozu
- Yaş (10 yaş altı), erkek cinsiyet
- Tümör çapı ve yayılımının büyük olması
- Skip lezyonların olması
- Patolojik kırık varlığı
- ALP ve LDH yüksekliği
- DNA içeriği (Hiperdiploidi)
- Moleküler belirteçler
  - RB gen lokusunda LOH,HER2 ve p glikoprotein aşırı üretimi

Diğer tedaviler

OS08



- Tedavi düzeyleri platoda
- Metastatik ve rezeke edilemeyenlerde prognoz kötü
- Antianjiojenik tedavi+sitotoksik KT ile survi artışı (Erişkinde)



FULL PAPER

BJC

British Journal of Cancer [2015] 113, 1282–1288 | doi: 10.1038/bjc.2015.351

Keywords: osteosarcoma; DCE-MRI; 18F-FDG PET; prognostic factors; antiangiogenic therapy; drug exposure

Assessing vascular effects of adding bevacizumab to neoadjuvant chemotherapy in osteosarcoma using DCE-MRI

J Guo*,[1], J O Glass[1], M B McCarville[1], B L Shulkin[1], V M Daryani[2], C F Stewart[2], J Wu[3], S Mao[3], J R Dwek[4], L M Fayad[5], J E Madewell[6], F Navid[7,8], N C Daw[7,9] and W E Reddick[1]

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Background: The purpose of this study was to assess the impact of bevacizumab alone and in combination with cytotoxic therapy on tumour vasculature in osteosarcoma (OS) using DCE-MRI.

Methods: Six DCE-MRI and three ^{18}F-FDG PET examinations were scheduled in 42 subjects with newly diagnosed OS to monitor the response to antiangiogenic therapy alone and in combination with cytotoxic therapy before definitive surgery (week 10). Serial DCE-MRI parameters (K^{trans}, v_p, and v_e) were examined for correlation with FDG-PET (SUV_{max}) and association with drug exposure, and evaluated with clinical outcome.

Results: K^{trans} ($P = 0.041$) and v_p ($P = 0.001$) significantly dropped from baseline at 24 h after the first dose of bevacizumab alone, but returned to baseline by 72 h. Greater exposure to bevacizumab was correlated with larger decreases in v_p at day 5 ($P = 0.04$) and week 10 ($P = 0.02$). A lower K^{trans} at week 10 was associated with greater percent necrosis ($P = 0.024$) and longer event-free survival ($P = 0.034$).

Conclusions: This is the first study to demonstrate significant changes of the plasma volume fraction and vascular leakage in OS with bevacizumab alone. The combination of demonstrated associations between drug exposure and imaging metrics, and imaging metrics and patient survival during neoadjuvant therapy, provides a compelling rationale for larger studies using DCE-MRI to assess vascular effects of therapy in OS.

Diğer potansiyel tedaviler

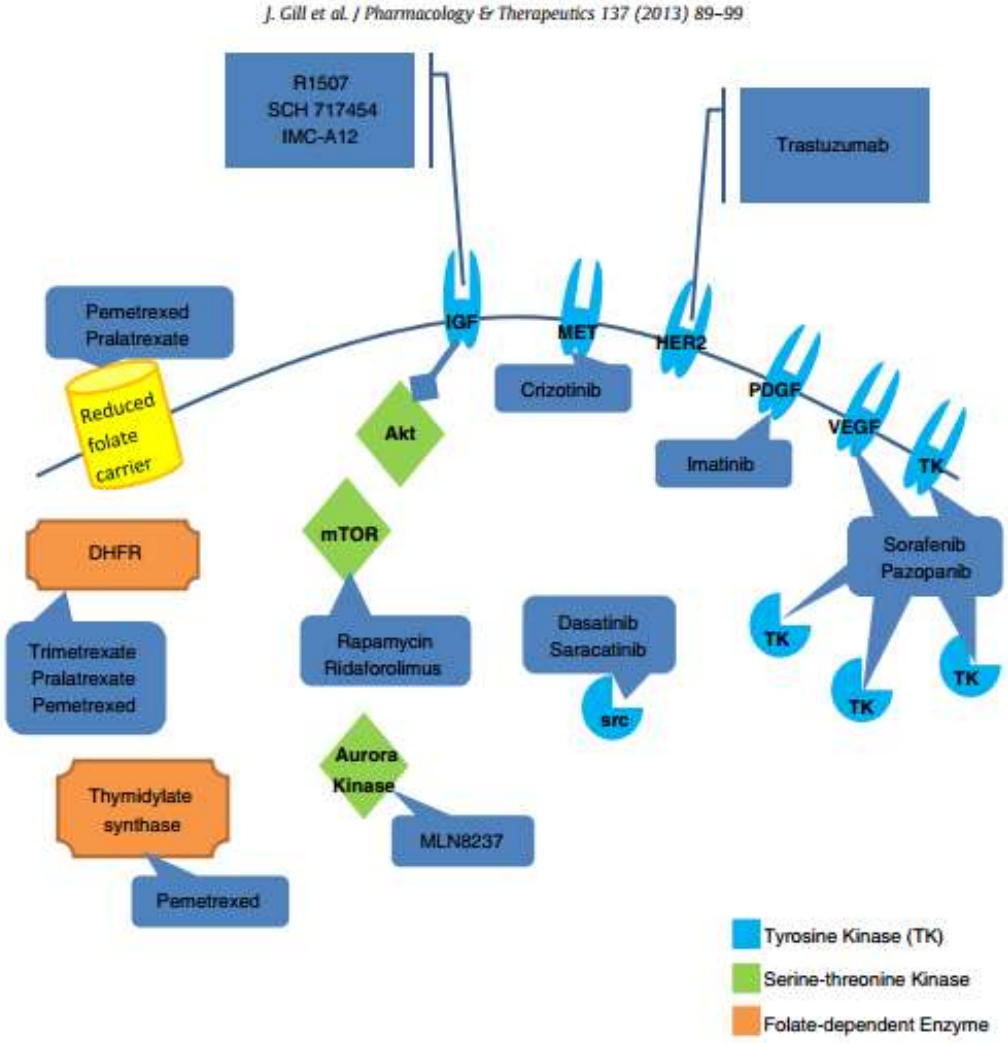

Fig. 1. Schematic of investigational agents and targets.

Pharmacology & Therapeutics 137 (2013) 89–99

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Associate editor: B. Teicher

New targets and approaches in osteosarcoma

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ARTICLE INFO

Keywords:
Osteosarcoma
Chemotherapy
Novel agents
Review

ABSTRACT

Osteosarcoma is the most common primary tumor of bone. Approximately 2/3 of patients who present with localized osteosarcoma can be expected to be cured of their disease with surgery and routine chemotherapy. Only 1/3 of patients with metastases detectable at presentation will be cured. These survival trends have stagnated over the past 20 years using conventional chemotherapy. New agents need to be rationally investigated to strive for improvement in the survival of patients diagnosed with osteosarcoma. This manuscript will review the rationale for conventional chemotherapy used in the treatment of osteosarcoma, as well as agents in varying stages of development that may have promise for treatment in the future.

Table 1
Trials leading to present day use of conventional chemotherapy.

Investigator (year)	Patients	Regimen	Outcome (follow-up)
Marcove (1970)	145 nonmetastatic		Event-free survival (5-year) 17.4%
Cortes (1972)	13 metastatic	Doxorubicin	Response rate (5-12 months) 31%
Jaffe (1974)	20 nonmetastatic	Vincristine Methotrexate	Event-free survival (2-23 months) 80%
Cortes (1974)	21 nonmetastatic	Doxorubicin	Event-free survival (18 months) 45%
Ochs (1978)	8 metastatic	Cisplatin	Response rate 63%
Marti (1985)	18 recurrent	Ifosfamide	Response rate 33%
Link (1986)	156 nonmetastatic 36 randomized 77 declined randomization (59 chemotherapy, 18 obervation)	No chemotherapy Bleomycin, cyclophosphamide, dactinomycin, methotrexate, doxorubicin, cisplatin	Event-free survival (2 years) Randomized 17% Non-randomized 9% Randomized 66% Non-randomized 67%
Winkler (1990)	109 metastatic and nonmetastatic	Doxorubicin, methotrexate, ifosfamide, IA cisplatin Doxorubicin, methotrexate, ifosfamide, IV cisplatin	>90% tumor necrosis 68% 69%
Goorin (2003)	100 nonmetastatic	Methotrexate, doxorubicin, cisplatin, bleomycin, cyclphosphamide, dactinomycin Neoadjuvant Adjuvant	Event-free survival (2-years) 61% 69%
Meyers (2008)	662 nonmetastatic Factorial (MTP-PE)	Methotrexate, doxorubicin, cisplatin Methotrexate, doxorubicin, cisplatin, ifosfamide	Event-free survival (4 years) 65% 66%

Investigator (year)	Patients	Regimen	Outcome (follow–up)
Meyers (2008) **Chou (2009)**	662 nonmetastatic 91 metastatic	MTP-PE Randomized factorial design (MAP/I)	Event-free survival (4-years/5-years) 70% → 78% 40% → 53%
Strander (1995)	19 nonmetastatic	Interferon α-2b Single-agent adjuvant	Disease-free survival (5 years) 63%
Arndt (2010)	43 lung metastases (recurrence)	Aersolized GM-CSF	Event-free survival (2 years) 12.9%
Meyers (2011)	29 nonmetastatic 11 metastatic	Pamidronate MAP backbone	Event-free survival (5 years) 72% 45%
Berger (2012)	22 relapsed metastatic (bone)	Samarium (^{153}SM-EDTMP)	Progression-free survival (60 days) 45%
Grignani (2012)	35 relapsed Unresectable	Sorafenib	Response rate /disease control rate 14%/49%
Bond (2008)	10 relapsed/refractory	Imatinib	Response rate 0%
Ebb (2012)	96 metastatic 41 HER2 positive 55 HER2 negative	Trastuzumab for HER2+ only MAPIE backbone	Event-free survival (30 months) 32% 32%
Bagatell (2011)	3 relapsed/refractory	IGF-1R (R1507) phase 1. 31 total patients	Response rate 2/3 stable disease
Chawla (2012)	54 metastatic/unresectable (Bone sarcomas)	Ridaforolimus	Response rate 2 patients PR
Trippett (1999)	7 relapsed/ refractory	Trimetrexate	Response rate 2 patients (1 CR, 1 PR)
Duffaud (2012)	32 relapsed/ refractory	Pemetrexed	Response rate 1 PR, 5 SD

Spine (Phila Pa 1976). 2003 Feb 15;28(4):E74-7.

Osteogenic sarcoma of the rib: a case presentation and literature review.

Deitch J[1], Crawford AH, Choudhury S.

Author information

Abstract

STUDY DESIGN: A case report is presented.

OBJECTIVES: Primary tumors of the rib are relatively uncommon in the adult population, and even more rare in children. A case of osteogenic sarcoma of the rib and a literature review are presented.

SUMMARY OF BACKGROUND DATA: Osteogenic sarcoma represents approximately 30% of all malignant sarcomas diagnosed in the United States. A single case of osteogenic sarcoma of the rib has been reported in the literature involving a 9-year-old child.

METHODS: Clinical data analysis.

RESULTS: A 9-year-old white boy presented with a mass of the left posterior thorax. The initial chest radiograph showed a nonhomogeneous mass with calcifications adjacent to the 11th rib. The final diagnosis was osteogenic sarcoma. Chemotherapy was initiated. The patient underwent radical excision of the mass. Given the extent of the patient's resection, it was thought that he would be at high risk for the development of spinal deformity He was placed in a TLSO brace (Bolt Systems, Orlando, FL) and followed closely. At 15 months after excision of his tumor, he was noted to have progression of a thoracolumbar scoliosis and significant kyphosis. At this writing, it has been 52 months since resection. The patient has no evidence of local recurrence or metastatic disease, and his spinal curvature remains stable.

CONCLUSIONS: The patient's short-term (4-year) disease-free survival illustrates the efficacy of neoadjuvant chemotherapy and radical surgical resection. Patients with osteogenic sarcoma of the rib should be monitored closely for the development of spinal deformity if the required resection includes the vertebral column. Casting and bracing may help to limit progression of the deformity.

biij
Biomedical Imaging and Intervention Journal
CASE REPORT

Osteosarcoma of the rib

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Received 29 April 2007; received in revised form 29 November 2007, accepted 9 December 2007

ABSTRACT

This case describes the radiological-surgical correlation of a rare case of osteosarcoma of the rib in a 15-year-old boy. Successful repair of his chest wall defect using a wire mesh following extensive surgical resection of the tumour is highlighted, such a procedure being the first instituted at our centre.

Keywords: Osteosarcoma, rib

INTRODUCTION

All chest wall tumours in the paediatric population must be assumed to be malignant. The differential diagnoses include Ewings sarcoma, rhabdomyosarcoma, chondrosarcoma, primitive neuroectodermal tumours (PNET) or Askin tumours, other sarcomas and metastatic lesions in the ribs. Osteosarcoma occurs principally in the long bones while Ewings sarcoma is frequently seen in flat bones like the ribs and pelvic bones. Osteosarcoma occurring as a primary tumour in the rib is rare [1, 2]. This paper describes a rare case of osteosarcoma of the rib in a 15-year-old boy, its imaging features and surgical management.

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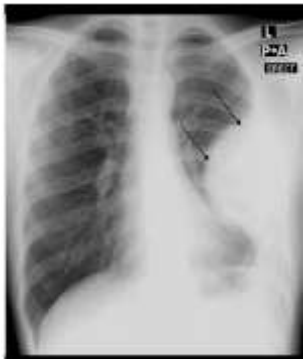
CASE REPORT

A 15-year-old Chinese boy presented with left-sided chest pain, loss of appetite and weight, and low grade fever for 6 weeks followed by cough and shortness of breath for a week prior to admission. On examination, he was pale and febrile with a temperature of 38.5°C. Examination of his chest revealed reduction of chest movement on the left side with reduced air entry into the left lung. There were no masses palpable. Haematological investigation revealed haemoglobin of 8.0 g/dL and a normal white cell count. Other blood investigations were unremarkable. A chest radiograph showed a large pleural mass in the left hemithorax, with rib destruction and a pleural effusion but no significant shift of midline structures (Figure 1). A CT examination of the chest showed a large heterogenously enhancing mass arising from left chest wall with lytic destruction of the fourth rib and coarse calcifications. There was a left pleural effusion with underlying lung collapse consolidation. There were no lung nodules in the right lung to suggest metastases (Figure 2). Due to the



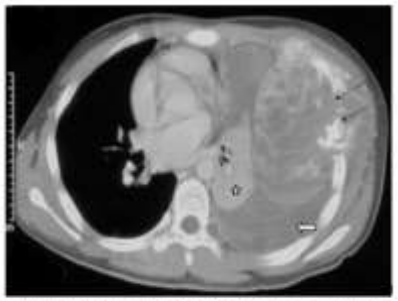
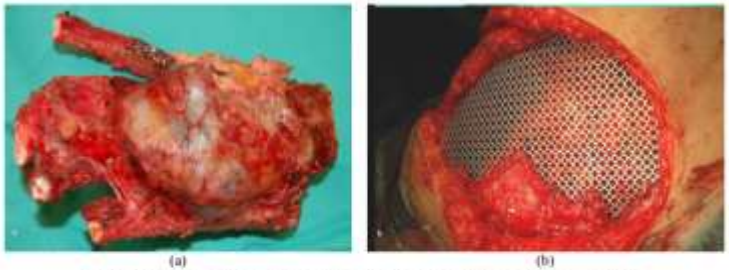


Figure 2 A contrast enhanced CT examination of the chest showing a large heterogeneously enhancing solid mass arising from the skeletal chest wall with lytic destruction of the rib and calcifications (arrows). There is a moderate-sized pleural effusion (black arrow) and underlying lung collapse and consolidation (star).



(a) (b)

Figure 3 (a) Gross appearance of the resected chest wall and the tumour (b) Appearance of the surgical site after resection of the tumour showing the titanium mesh covering the chest wall defect.

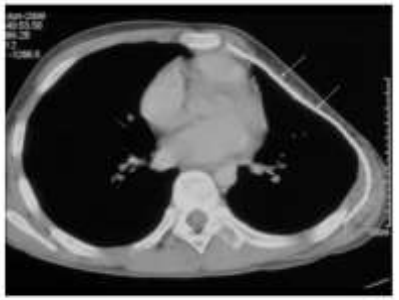
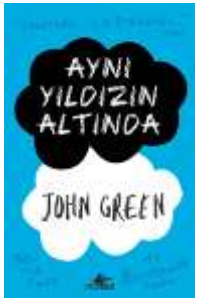


Figure 4 CT examination of the chest post-chemotherapy and chest wall surgery showing deformity of the left chest wall at site of extensive rib resection. The titanium mesh is seen in situ (arrows). There is no evidence of tumour recurrence.

Sonuç olarak OSTEOSARKOM



- Çocukluk çağında en sık görülen primer kemik tümörüdür
- Tedavide kemoterapi ve cerrahi gerekir.
- Cerrahi sırasındaki histolojik yanıt, önemli prognostik faktördür.
- EFS ve OS da son yıllarda pek belirgin iyileşme saptanamamıştır.
- Preoperatif histopatoloji sonucuna göre tedaviyi değiştirmenin sağkalım üzerine pek etkisi görülmemiştir.
- Tedavi etkinliğini arttırmak için pekçok yeni ajan denemektedir.

Teşekkürler