YUMUŞAK DOKU VE KEMİK SARKOMU: RADYOTERAPİDE GELİŞMELER

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2013-UKK

KONU AKIŞI

- YDS bilinenler
- YDS RT'de yenilikler
- Kemik-YD Sarkomlarında yeni enerjiler ile RT
- Retroperitoneal sarkomların radyoterapisinde güncel durum

SARKOM- GİRİŞ:

- Yağ, kas, kıkırdak ve kemik gibi bağ dokularından ortaya çıkan bir grup kanser.
- Tüm kanserlerin <% 3'ü
- %78'i yumuşak doku, geri kalanı kemik kaynaklı.
- YDS: ABD'de 2012 de 11260 vaka (çocuk ve erişkin) ve 3900 mortalite /yıl.(Siegel R, et al. Cancer statistics, 2013. CA Cancer J Clin 2013)
- %50 ekstremite, %25 gövde, %15 retroperitoneal, %10 baş-boyun.

SARKOM- GİRİŞ:

- 5 y hastalığa özgü sağkalım (SK) %83;

Bölgesel LN(+) ise %54; uzak metastaz(+) ise%16 (http://www.cancer.net/node/19610).

- Ekstremite yerleşiminde SK görece daha iyi.

- 5 hastadan 2'si sarkomdan ölüyor!..

- Sarkom konulu çalışmalar ve sağkalım arasında doğrudan etkileşim bulunmakta!...

% 90 ERIŞKINLERDE. GÖRECE GENÇ NUFUS:
ÇOCUK KANSERLERININ % 15-20'SI
ERIŞKIN KANSERLERININ %1'I
(GENÇ ERIŞKINLERDE % 10'A KADAR). DARLING, J (2007).

Diagnosis 0-19 yr	Diagnosis 15-29 yr	Diagnosis Adult
RMS	Kaposi	Kaposi
DFSP	DFSP	LMS
SS	LMS/Fibrosarcoma	MFH
Sarcoma NOS	RMS	LPS
MFH	SS	DFSP
Fibrosarcoma	Lipo	Carcinosarcoma
MPNST	MPNST	GIST

KEMIK SARKOMU-YAŞ

Annals of Oncology

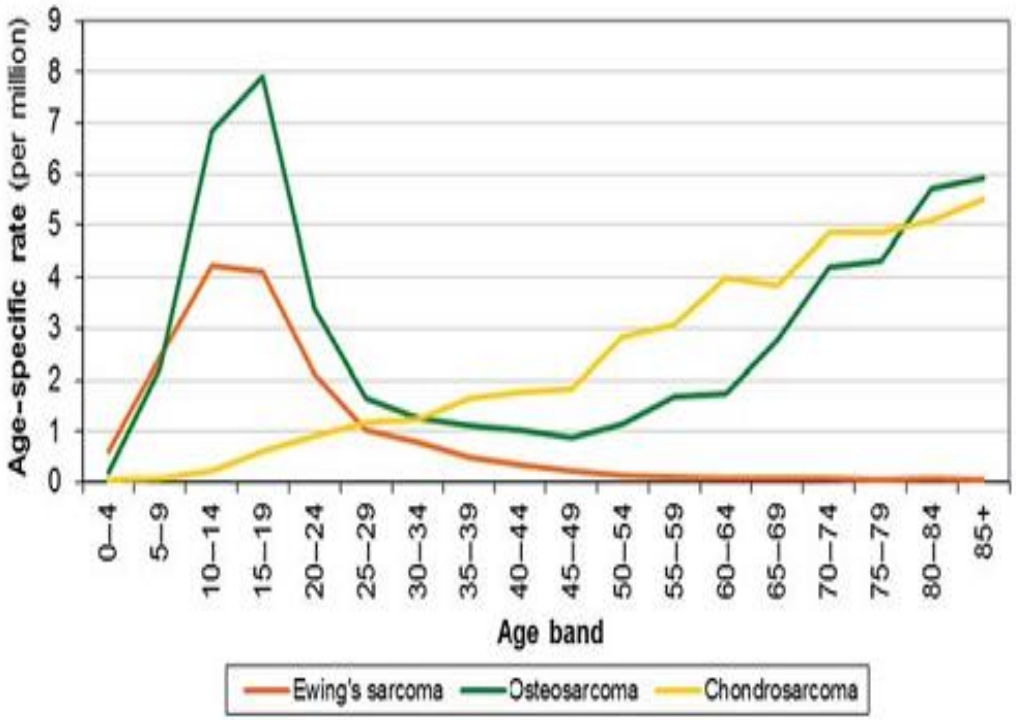

Figure 1 Age specific incidence rates by morphology, England, 1979–2004. Data from National Cancer Intelligence Unit, UK; http://www.ncin.org.uk/publications/data_briefings/bone_sarcomas_incidence_and_survival.aspx.

EVRELEME YDS
AJCC 7. Ed. (2009)

GRAD!....

- ***Primer Tümör:***

T1 - ≤ 5cm
T1a - yüzeyel
T1b - derin

T2 - ≥ 5cm
T2a - yüzeyel
T2b - derin

- ***Bölgesel Lenf Nodları:***

N0; N1

- ***Distant Metastaz:***

M0 ; M1

- ***Grad:***

AJCC 3 bölmeli FNCLCC (French) Fransız gradlama sistemini tercih eder

- Grad 3 parametre ile belirlenir:
  - Differensiasyon
  - Mitotik aktivite
  - Nekroz boyutu

Evre grupları:

IA - T1a/b N0 G1 - düşük grad, küçük
IB - T2a/b N0 G1 - düşük grad, büyük

IIA - T1a/b N0 G2-3 - orta/yüksek grad, küçük
IIB - T2a/b N0 G2 - orta grad, büyük

III - T2a/b G3, or N1 - yüksek grad, büyük; yada N(+)

IV - M1 - metastatik

"AJCC 6TH EDITION"DAN FARKı:

- 3'lü gradlama sistemi evrelemede (en azından Tm>5 cm için).
- N1 →Evre III (eski: Evre IV)
- Evre I: IA ve IB'ye ; Evre II: IIA ve IIB'ye bölündü.
- Derin yada yüzeyel* tümör lokalizasyonu genel evrelemeyi artık etkilemiyor.

*Yüzeyel : subkutanöz doku içinde (muskular fasya yada alttaki kas invazyonu yok)

Hariç: Kaposi sarcoma, fibromatosis (desmoid tm), infantil fibrosarkom; dura mater yada beyin, parenkimal organ kaynaklı,içiboş visseral organ sarkomları

Dahil : Dermatofibrosarkom protuberans (yeni), angiosarkom, and ekstraskeletal Ewing's sarkom"

Reprinted with permission from AJCC: Soft tissue sarcoma. In: Edge SB, Byrd DR, Compton CC, et al., eds.: AJCC Cancer Staging Manual. 7th ed. New York, NY: Springer, 2010, pp 291-8.

Pathologic types

Tissue	Sarcoma
Fibrous	Fibrosarcoma
Fibrohistiocytic	Malignant fibrous histiocytoma
Lipomatous	Liposarcoma
Smooth muscle	Leiomyosarcoma
Skeletal muscle	Rhabdomyosarcoma
Vascular/lymphatic	1) Angiosarcoma; 2) Lymphangiosarcoma; 3) Kaposi's sarcoma
Perivascular	1) Malignant Glomus Tumor; 2) Malignant hemangiopericytoma
Synovial	1) Synovial sarcoma; 2) Malignant giant cell tumor of tendon sheath
Mesothelial	1) Fibrous tumor of pleura/peritoneum; 2) Diffuse mesothelioma
Neural	1) Malignant peripheral nerve sheath tumor; 2) Malignant granular cell tumor; 3) Clear cell sarcoma; 4) Malignant melanocytic schwannoma; 5) Gastrointenstinal autonomous nerve tumor; 6) Primitive neuroectodermal tumors
Paraganglionic	Malignant paraganglioma
Extraskeletal cartilagenous/osseous	1) Extraskeletal chondrosarcoma; 2) Extraskeletal osteosarcoma
Pluripotent	Malignant mesenchymoma
Miscellaneous	1) Alveolar soft part sarcoma; 2) Epithelioid sarcoma; 3) Malignant extrarenal rhabdoid tumor; 4) Desmoplastic small cell tumor

MFH: kötü differansiye sarkom hali?

- Comment: MFH is the most heterogenous group of sarcomas. A hypothesis proposes that MFH, as a poorly differentiated sarcoma, may represent a common endpoint for various other sarcomas (PMID 11408500, PMID 11965276)

Diagnosis by immunostains

The following immunostains are useful in excluding or ruling in certain sarcomas (the stains listed are positive for the tumor type listed). Those listed below are not all sarcomas but some are useful diagnoses to exclude.

- Abdominal pelvic sarcoma: MART-1
- Desmoplastic small round cell tumor: WT1, perinuclear dot-like desmin
- Rhabdomyosarcoma: myogenin, myo-D1, myoglobin
- Leiomyosarcoma: Desmin, caldesmin
- Peripheral neuroectodermal tumor (PNET): CD-99, synaptophysin, chromogranin A
- Pleomorphic liposarcoma: S-100
- Neuroblastoma: neurofilament, chromogranin A, synaptophysin
- Angiosarcoma: CD31, CD34
- Follicular dendritic cell sarcoma: CD21, CD35
- GIST: CD117 (c-kit)
- Melanoma: S-100, MART-1
- Poorly differentiated carcinoma: pancytokeratin, EMA
- High grade lymphoma: CD45 (leukocyte common antigen), CD4, nuclear TdT
- Mesothelioma: WT1, pancytokeratin
- Poorly differentiated germ cell tumor: PLAP, pancytokeratin, CD117 (c-kit)
- Synovial sarcoma: translocation t(X;18)

Others to be classified: vimentin, CD56, CD57, collagen type 4 immunostaining -- peripheral nerve sheath tumor or synovial sarcoma

PROGNOSTİK FAKTÖRLER:

Artmış lokal rekürrens riski:

- Yaş : > 50[1]-60[2]
- Rekürrent hastalık
- (+) cerrahi sınır
- Fibrosarkom (desmoid dahil)
- Malign periferal sinir tümörü

Artmış uzak metastaz riski[3]

- Tm > 5cm
- Yüksek grad
- Derin yerleşim
- Rekürrent hastalık
- Leiomyosarkom

1Cahlon O, Cancer. Jun 15 2008;112(12):2774-9.
2Vraa Cancer 34 (12): 1876-82, 1998.
3French Federation, 2001 (1980-94) - Coindre JM et al. Cancer. 2001 May 15;91(10):1914-26.

TECRÜBELI MERKEZIN PROGNOZA KATKıSı!:

- Eur J Surg Oncol. 2012 Apr;38(4):346-51.

Inadvertent surgical resection of soft tissue sarcomas.

Venkatesan M, Richards CJ, McCulloch TA, Perks AG, Raurell A, Ashford RU; East Midlands Sarcoma Service.

Department of Orthopaedics, University Hospitals of Leicester,UK

CONCLUSION: **Unplanned excision of sarcoma by non-oncologic surgeons remains a problem**. It appears that it is equally prevalent in varied surgical community and general practitioners. Excision of large or deep solid soft tissue masses without tissue diagnosis is unacceptable.

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- Ann Surg Oncol. 2013 Jan 31. [Epub ahead of print]

Monitoring the Adequacy of Surgical Margins After Resection of Bone and Soft-Tissue Sarcoma.

Biau DJ, Weiss KR, Bhumbra RS, Davidson D, Brown C, Griffin A, Wunder JS, Ferguson PC.

Département de chirurgie orthopédique, Hôpital Cochin, Paris, France, .

CONCLUSIONS: With adequate preoperative planning and surgical technique, the risk of an inadequate resection can be limited. Implementation of a statistical process control method allows for ongoing performance monitoring and ensures that quality remains adequate over time.

- Acta Oncol. 2012 Jul;51(6):706-12. doi: 10.3109/0284186X.2011.643821. Epub 2012 Jan 10.

Soft tissue sarcoma - a population-based, nationwide study with special emphasis on local control.

Sampo MM, Rönty M, Tarkkanen M, Tukiainen EJ, Böhling TO, Blomqvist CP.

Department of Pathology, HUSLAB and University of Helsinki, Finland

RESULTS: Local control at five years was 82% at high-volume centres, 61% at intermediate-volume centres treating highest percentage of deep tumours and 69% at low-volume centres (p = 0.046). Local control improved as the number of patients operated (surgical volume of the centre) increased.

CONCLUSION: The present quality-control study is the first nationwide population-based study to assess diagnostics and treatment of STS. When referred to a specialised sarcoma centre even patients with inadequate surgery can achieve good local control. STS is a rare cancer and its treatment should be centralised in Finland, which has 5.4 million inhabitants and approximately 100 new STSs of extremities and trunk wall annually.

ÖLÜM RISKI-NOMOGRAM:

J Clin Oncol. 2013 Mar 25.

Outcome Prediction in Primary Resected Retroperitoneal Soft Tissue Sarcoma: Histology-Specific Overall Survival and Disease-Free Survival Nomograms Built on Major Sarcoma Center Data Sets.

Gronchi A, Miceli R, Shurell E, Eilber FC, Eilber FR, Anaya DA, Kattan MW, Honoré C, Lev DC, Colombo C, Bonvalot S, Mariani L, Pollock RE.

3 merkezin prospektif sarkom veri tabanı

Prognostik Değişkenler: Yaş, tm çapı, grad, histolojik tip, multifokalite, cerrahi kalite, RT.

SONUÇ:

Bu namogramlar GS ve hastalıksız sagkalımı predikte eder. Klinik pratikte ve çalışmalarda kullanılabilir.

GENEL TEDAVİ:

- Multidisipliner , **tecrübeli** merkezde tedavi.
- Cerrahi çoğu sarkom için temel.[3] **Organ koruyucu** yaklaşım ile≥%90 oranında ekstremite korunmakta.[3]
- Cerrahi öncesi / sonrası adjuvant tedaviler: KT ve RT uygulanabilir.[1]
- KT birçok vakada prognozu düzeltir (öz. kemik srk.).[4] Örn. Lokalize osteosarkomda uzun dönem sağkalım **%20 'den→ KT ile %60-70'e** yükseldi.[2]
- Yüksek gradlı tümörler **metastaz**a eğilimli → daha agresif tedavi.
- Liposarkom tedavisinde cerrahi rezeksiyon yeterli olabilir, KT araştırma bazında kullanılabilir. Postoperatif adjuvant RT kullanılabilir.[5]
- Rabdomiyosarkom cerrahi, RT ve/veya KT ile tedavi.[6] SK oranı % 50–85.[7]
- Osteosarkom rezektabl ise cerrahi ile tedavi, genellikle neoadjuvant KT ile .[8] RT çok etkin değil ama ikinci bir alternatif.

YDS TEDAVİ:

- Cerrahi +/- RT +/- KT.

- Lokal rekürrens:
  - **%90 basit eksizyon**, % 39 geniş eksizyon, %25 kompartmanal eksizyon, %7-18 amputasyon sonrası
  - **SK** üzerine LR minimal etkili, primer olarak **metastatik hastalık** belirler.

  - Geniş**(>=8 cm) ve HG** tümörlerde adjuvant RT ile iyi LK, ama **DM riski↑** (5-10 cm:%34, 10-15 cm: %43, 15-20 cm %58).

YDS:
1-) CERRAHI+RT ILE LK ORANLARı AMPUTASYONA BENZERDIR, SAĞKALıMı ETKILEMEZ

NCI randomize çlş.:

Yüksek gradlı ekstremite YDS'da +eş zamanlı KT/RT ilavesiyle amputasyon oranının **<%10 a** düşebilir.

- **NCI**(1975-1981) ; **1982** :

amputasyon vs koruyucu cerrahi + post-op Kemo-RT,

Medyan izlem 4.8 y. LR %**15 vs amputation %0 (p=0.06);**

4 LR'in : 1'i isole ve 3 LR+ DM.
5-y DFS (**NS)** ; 5-y GS **(NS)**

"The treatment of soft-tissue sarcomas of the extremities: prospective randomized evaluations of (1) limb-sparing surgery plus radiation therapy compared with amputation and (2) the role of adjuvant chemotherapy." (**Rosenberg** SA et al. Ann Surg. 1982) :

YDS :
2) POST-OP RT LOKAL YINELEMEYI ÖNLER:

Yüksek gradlı ekstremite YDS:

C vs C+ **EBRT** (63Gy, 1.8Gy/fr) ile

LK %70'→% 99'lara. GS'da fark yok.

- Yang et al , J Clin Oncol, 1998: NCI(1983-1991):

✓ **Yüksek grad, LR:**

adjuvant KT-**RT %0** vs adjuvant KT **%19 (SS)**; 10-yıllık DSS (NS), 10-year GS (NS)

✓ **Düşük grad, LR:**

adjuvant RT %4 vs **observasyon %33 (SS);** 10y GS (NS)

Int J Radiat Oncol Biol Phys. 2012 Mar 15;82(4):1528-34.

The relationship between local recurrence and radiotherapy treatment volume for soft tissue sarcomas treated with external beam radiotherapy and function preservation surgery.

Dickie CI, Griffin AM, Parent AL, Chung PW, Catton CN, Svensson J, Ferguson PC, Wunder JS, Bell RS, Sharpe
O'Sullivan B.SourceRadiation Medicine Program, Princess Margaret Hospital, Toronto, **Canada**.

Optimal RT volum IG-RT ile mümkün: marjinal relapslar düşük

RESULTS: Forty-nine tumors relapsed in field (**6.4%** overall). Nine were out of field (1.1% overall), and 2 were marginal (0.3% overall).

CONCLUSIONS: **The majority of STS tumors recur in field, indicating that the incidence of LR may be affected more by differences in biologic and molecular characteristics rather than aberrations in RT dose or target volume coverage.** In contrast, only two patients relapsed at the IRV boundary, suggesting that the risk of **a marginal relapse is low when** the TV is appropriately defined. **These data support the accurate delivery of optimal RT volumes in the most precise way using advanced technology and image guidance.**

STS-3)
SEÇILI DÜŞÜK RISKLI HASTADA ADJUVANT RT GEREKMEYEBILIR:

- **Pisters PW ve ark.** Ann Surg 2007. MDA (1996-2002).

N=88 **T1** hasta (60'ı ekstremite sarkomu, %68 yüzeyel T1a, %84 Ro.

Ekstremite ve gövde tümörü,
5 cm yada küçük, CS(-) Ro

LR 5 ve 10 y: **%7.9 ve %10.6**;

Sarkom spesifik sağkalım 5 ve 10 y: **%3.2 ve %3.2.**

Level of evidence: 3iiiDiv

" **Long-term results of prospective trial of surgery alone with selective use of radiation for patients with T1 extremity and trunk soft tissue sarcomas."**

MEMORIAL SLOAN KETTERING (1982-1992) ADJUVANT BRAKITERAPI VS İZLEM

"**Long-term results of a prospective randomized trial of adjuvant brachytherapy in soft tissue sarcoma."**
Pisters PW, J Clin Oncol. 1996 Mar.

Med. F/U 6.3 y . 162 hasta cerrahi rezeksiyon → brakiterapi **vs** takip.

5y GS, brakiterapi ↑ **(%82 vs. %69, p=0.04).**

Yüksek gradlıda, LK brakiterapi lehine **(%89 vs. %66, p=0.0025)**,

Düşük gradlıda brakiterapi ile LK'a anlamlı **katkı yok** (%83 vs. %76, **p=0.60**).

5y DSS için farklı gradlar arasında anlamlı fark yok.

SONUÇ; yüksek gradlı lezyonlarda brakiterapi *LK'u a*nlamlı ↑ ama bu artış, DM ve DFS'a anlamlı katkı yapmamakta.

4)RT'NIN SAĞKALıMA KATKıSı?:

- **Prospektif çalışmada henüz gösterilemedi??**
- **Retrospektif:**
- **U Maryland SEER Analysis** (1988-2005) — **"Improved Survival With Radiation Therapy in High-Grade Soft Tissue Sarcomas of the Extremities: a SEER Analysis" (Koshy** M, IJROBP. **2010** May)
  - 6,960 hasta, Organ koruyucu cerrahi, **%47'si RT** almış (Çoğu postop: %86).
  - **Düşük gradlıda RT ile GS'a fayda yok**
  - **Yüksek gradlıda GS, RT ile arttı: 3-yr GS (%73 vs %63,SS)**

Sonuç: Yüksek grad YDS'da +RT ile sağkalım yararı (+)

STS: 5) RT ZAMANLAMA: PRE- OR POST-OP RT?

Optimal zamanlama hala çok net değil:

Preop vs Postop RT

- **Pre-op RT ile akut yara komplikasyonu ↑ (çoğu alt ekstremite)**
- **Post-op ile uzun dönemde ekstremite fonksiyonu daha kötü (üst ekstremitede pre-op daha iyi?)**
- **Meta-analiz pre-op RT ile GS etkilenmeksizin LK↑'gösterir (Çalışmalar heterojen!..)**
- **Pre-op RT ile RT alanı daha küçük**

O'SULLIVAN ET AL;
FIVE YEAR RESULTS OF RANDOMISED PHASE III TRIAL OF PRE-OP VS. POST-OP RADIOTHERAPY IN EXTREMITY STS; JCO 2004;

Primer sonlanım major yara komplikasyonu!

- **3-years; 2002—**

  Yara komplikasyonu: preop RT %35 vs. postop RT %17 (SS); üst bacak↑ **(45% vs. 28%). Preop RT ile non-primer yara kapanması↑**

  LR, LRR, DMR(NS). **GS >2.5 y preop grup↑ (fakat çalışma dizaynı ilgili değil!)**

  RT alanı, medyan: **preop 333 cm2 vs. postop 416 cm2 (SS)**

Sonuç: Normal doku toksisitesi farklı, anatomik yerleşim dikkate alınmalı.

- **5-years; 2004** -

  5-y LK %93 vs %92 (NS), RFS %58 vs. %59 (NS), GS 73% vs. 67% **(NS).**

  Prediktör faktörler: CS+ ~ **LC, çap ve grad ~ RFS vs GS**

  Sonuç:Pre-op ve post-op RT etkisi benzer. ND toksisitesi farklı

- **Late effects; 2005**," (Davis AM, Radiother Oncol. 2005.)

  Post-op RT ile fibrosis ↑**, ödem** ve eklem kısıtlılığı ↑ **(NS olmasına karşın).**

  Geniş RTsahası~fibrozis ve eklem kısıtlılığı !

  Sonuç: Postop RT de hasta fonksiyonunu olumsuz etkileyen fibroziz eğilimi↑

PRE-OP RT ILE YENI BULGULAR VAR MI?

Ann Surg Oncol. 2010 May; **A SYSTEMATIC REVIEW AND META-ANALYSIS OF ONCOLOGIC OUTCOMES OF PRE- VERSUS POSTOPERATIVE RADIATION IN LOCALIZED RESECTABLE SOFT-TISSUE SARCOMA.**

Al-Absi E, Farrokhyar F, Sharma R, Whelan K, Corbett T, Patel M, Ghert M.
McMaster University and Hamilton Health Sciences, Hamilton, ON, Canada.

- ✓ 5 çalışma (1 RCT ve 4 retrospektif kohort), 1098 hasta. Heterojenite: 0.26
- ✓ **LK** preop grupta↑ (**HR 0.6, SS**). GS preop 76% vs postop 67% (NS)
- ✓ **Sonuç:**
  Preop RT için cerrahi rezeksiyondaki gecikme mortaliteyi arttırmaz.
  preop RT ile LR daha↓.

(Ama heterojenite nedeniyle sonuç temkinli yorumlanmalı!)

Int. J. Radiation Oncology Biol. Phys., Vol. 81, No. 2, pp. 498–505, 2011

0360-3016/$–see front matter

doi:10.1016/j.ijrobp.2010.06.034

CLINICAL INVESTIGATION **Sarcoma**

PREOPERATIVE VERSUS POSTOPERATIVE RADIOTHERAPY IN SOFT-TISSUE SARCOMA: MULTI-INSTITUTIONAL ANALYSIS OF 821 PATIENTS

Sagus Sampath, M.D.,* Timothy E. Schultheiss, Ph.D.,† Ying J. Hitchcock, M.D.,*
R. Lor Randall, M.D.,‡ Dennis C. Shrieve, M.D., Ph.D.,* and Jeffrey Y. C. Wong, M.D.†

Int J Radiat Oncol Biol Phys. **2011** Oct

- ✓ **Retrospektif 821 hasta**
- ✓ **5-y kansere özgü sağkalım %79 and %74 preop. RT lehine ($p < 0.05$)**
- ✓ **Lokal ve uzak relaps anlamlı düşük.**

Ann Surg Oncol. 2012 Feb;

Influence of specialty and clinical experience on treatment sequencing in the multimodal management of soft tissue extremity sarcoma

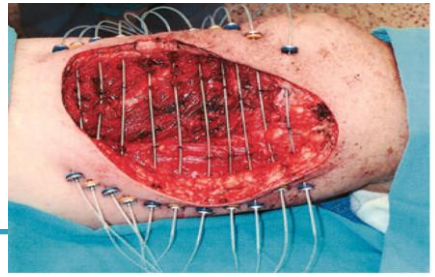
Wasif N, Tamurian RM, Christensen S, Do L, Martinez SR, Chen SL, Canter RJ.

Mayo Clinic, USA

" CONCLUSIONS:

Treatment sequencing in STS is influenced by specialty and clinical experience, with no clear consensus. These patterns may reflect the recent trend toward regionalization of STS care."

BRAKITERAPI:



Bilinen:

- **Yüksek gradlı YDS da LK ↑; ama düşük gradlı YDS da (ND). DSS ve GS' a katkı yok.***
- **Çevre dokulara daha az radyasyon**
- **EBRT ile Brakiterapiyi direkt karşılaştıran veri yok (Cerrahi ile var).**

- **Memorial Sloan Kettering (1982-1992)** *Pisters ve ark1996 ,
- **Alektiar 2000;**

  Morbidity of adjuvant brachytherapy in soft tissue sarcoma of the extremity and superficial trunk. IJROBP47 (5)

  Sonuç:

  Önemli yara komplikasyonu (revizyon gerektiren vd):

  %24 RT ve ve% 14% Kontrol kollarında (*P* = .13);

  yara reoperasyon oranı 10% and 0%, respectively (*P* = .006).

(Kateter yüklemesi :

1985'te 5. Günden itibaren yükleme ile komplikasyon farkı yok (%14% vs % 10))

Clin Orthop Relat Res. 2012 Mar;470(3):751-8.

Early complications of high-dose-rate brachytherapy in soft tissue sarcoma: a comparison with traditional external-beam radiotherapy.

Emory CL, Montgomery CO, Potter BK, Keisch ME, Conway SA.

Wake Forest University School of Medicine,, USA.

190 hasta (37 si brakiterapi),Retrospektif veri

SONUÇ:

- **HDR brakiterapi ile normal doku radyasyon maruziyeti düşük,**
- **RT süresi daha kısa,**
- **Yara komplikasyonu yüksek.**

(LEVEL OF EVIDENCE: Level III, therapeutic study)

CANCER. **2011** JUL 15;117(14):3229-34.

LOCAL CONTROL COMPARISON OF ADJUVANT BRACHYTHERAPY TO INTENSITY-MODULATED RADIOTHERAPY IN PRIMARY HIGH-GRADE SARCOMA OF THE EXTREMITY.

ALEKTIAR KM, BRENNAN MF, SINGER S.

Department of Radiation Oncology, Memorial Sloan-Kettering Cancer Ce
New York, New York, USA. alektiak@mskcc.org

Non randomize, 134 hasta (1995-2006) koruyucu cerrahi sonrası RT

LK:
%92 vs %81
(SS)

IMRT ile advers etki daha fazla olmasına karşın;

5 y LK daha iyi (SS).

Brachytherapy. 2013 Feb 20.

American Brachytherapy Society (ABS) consensus statement for sarcoma brachytherapy.

Holloway CL, Delaney TF, Alektiar KM, Devlin PM, O'Farrell DA, Demanes DJ.

Department of Radiation Oncology, BC Cancer Agency, Vancouver Island Centre, Victoria, BC, Canada. Electronic address: cholloway@bccancer.bc.ca.

RESULTS: The indications for adjuvant BT are discussed. There is no consensus on the use of BT alone or in combination with external beam radiation therapy (EBRT), but factors that influence the selection of this modality include tumor grade and size, prior surgeries, and tumor recurrence. Low-dose-rate, high-dose-rate, and pulsed-dose-rate radiation are all acceptable BT modalities to use for STS. Recommendations are made for patient selection, techniques, dose rates, and dosages. Outcome data and toxicity data are reviewed.

"CONCLUSIONS: BT is a useful component of the treatment of STS. The advantages of BT are the targeted dose distribution, low integral dose, and short treatment times. Ultimately the clinician should select the modality or combination of modalities that are most familiar to the treatment team and suitable to the patient."

BRAKITERAPI: C.SINIR(+) ISE YETERSIZ

Int. J. Radiation Oncology Biol. Phys., Vol. 81, No. 4, pp. e529–e539, 2011

DETERMINANTS OF TOXICITY, PATTERNS OF FAILURE, AND OUTCOME AMONG ADULT PATIENTS WITH SOFT TISSUE SARCOMAS OF THE EXTREMITY AND SUPERFICIAL TRUNK TREATED WITH GREATER THAN CONVENTIONAL DOSES OF PERIOPERATIVE HIGH-DOSE-RATE BRACHYTHERAPY AND EXTERNAL BEAM RADIOTHERAPY

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Purpose: The present study was undertaken to determine factors predictive of toxicity, patterns of failure, and survival in 60 adult patients with soft tissue sarcomas of the extremity and superficial trunk treated with combined perioperative high-dose-rate brachytherapy and external beam radiotherapy.

Methods and Materials: The patients were treated with surgical resection and perioperative high-dose-rate brachytherapy (16 or 24 Gy) for negative and close/microscopically positive resection margins, respectively. External beam radiotherapy (45 Gy) was added postoperatively to reach a 2-Gy equivalent dose of 62.9 and 72.3 Gy, respectively. Adjuvant chemotherapy with ifosfamide and doxorubicin was given to patients with advanced high-grade tumors.

Results: Grade 3 toxic events were observed in 18 patients (30%) and Grade 4 events in 6 patients (10%). No Grade 5 events were observed. A location in the lower limb was significant for Grade 3 or greater toxic events on multivariate analysis ($p = .013$), and the tissue volume encompassed by the 150% isodose line showed a trend toward statistical significance ($p = .086$). The local control, locoregional control, and distant control rate at 9 years was 77.4%, 69.5%, and 63.8%, respectively. On multivariate analysis, microscopically involved margins correlated with local control ($p = .036$) and locoregional control ($p = .007$) and tumor size correlated with distant metastases ($p = .004$). The 9-year disease-free survival and overall survival rate was 47.0% and 61.5%, respectively. Multivariate analysis showed poorer disease-free survival rates for patients with tumors >6 cm ($p = .005$) and microscopically involved margins ($p = .043$), and overall survival rates decreased with increasing tumor size ($p = .011$).

Conclusions: Grade 3 or greater wound complications can probably be decreased using meticulous treatment planning to decrease the tissue volume encompassed by the 150% isodose line, especially in lower limb locations. Microscopically involved margins remain a predictor of local and locoregional failure, despite radiation doses >70 Gy. Patients with tumors ≥6 cm and microscopically involved margins are at high risk of treatment failure and death from the development of distant metastases.

YART (IMRT)

- **LC iyi/yüksek,**
- **Öz. ekstremitede potansiyal YE azlığı,**
- **Ama üstünlüğü henüz spekulatif,**
- **Tek merkezli çalışmalar(1,2)**

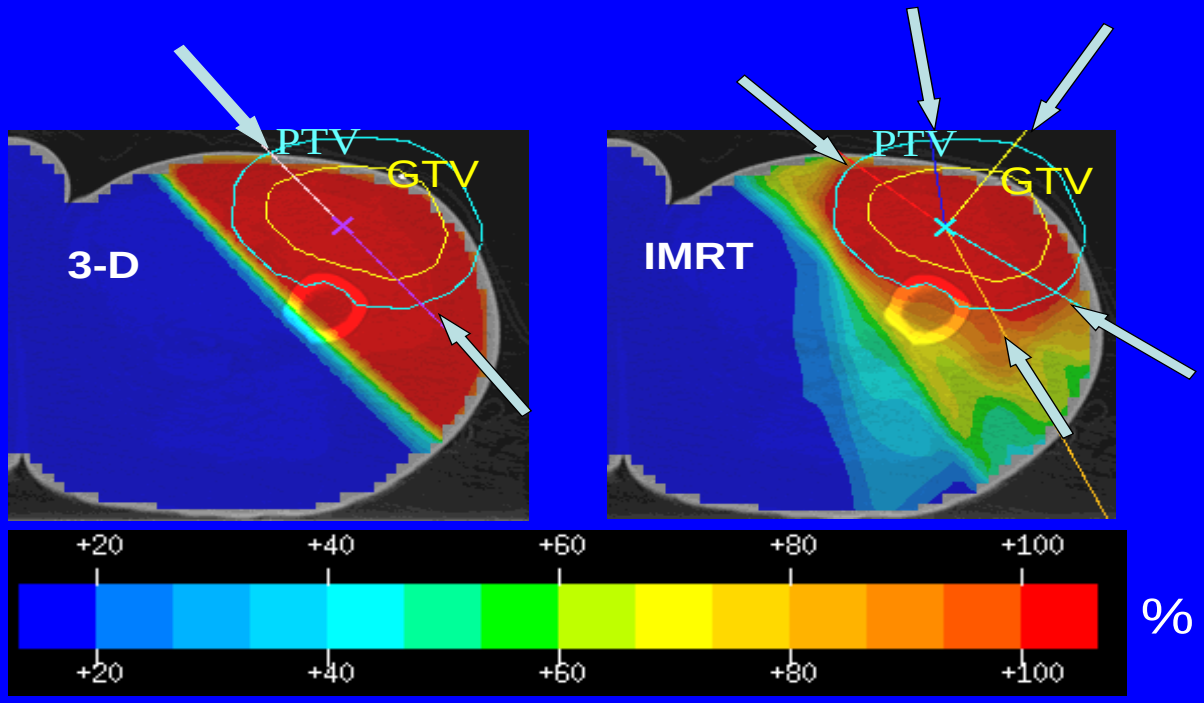
(1-Alektiar KM, Brennan MF, Healey JH, et al.: Impact of intensity-modulated radiation therapy on local control in primary soft-tissue sarcoma of the extremity. J Clin Oncol 26 (20): 3440-4, 2008.
2-Alektiar KM, Brennan MF, Singer S: Local control comparison of adjuvant brachytherapy to intensity-modulated radiotherapy in primary high-grade sarcoma of the extremity. Cancer 117 (14): 3229-34, 2011.)

YART

Intensity Modulated Radiation Therapy For Soft Tissue Sarcoma Of The Extremity: Preliminary Results

KM Alektiar, L Hong, MF Brennan, S Singer.
Memorial Sloan-Kettering Cancer Center

Introduction



Hong et al Int J Rad Oncol Biol Phys, 2004

J Clin Oncol. 2008 Jul 10;26(20):3440-4.

Impact of intensity-modulated radiation therapy on local control in primary soft-tissue sarcoma of the extremity.

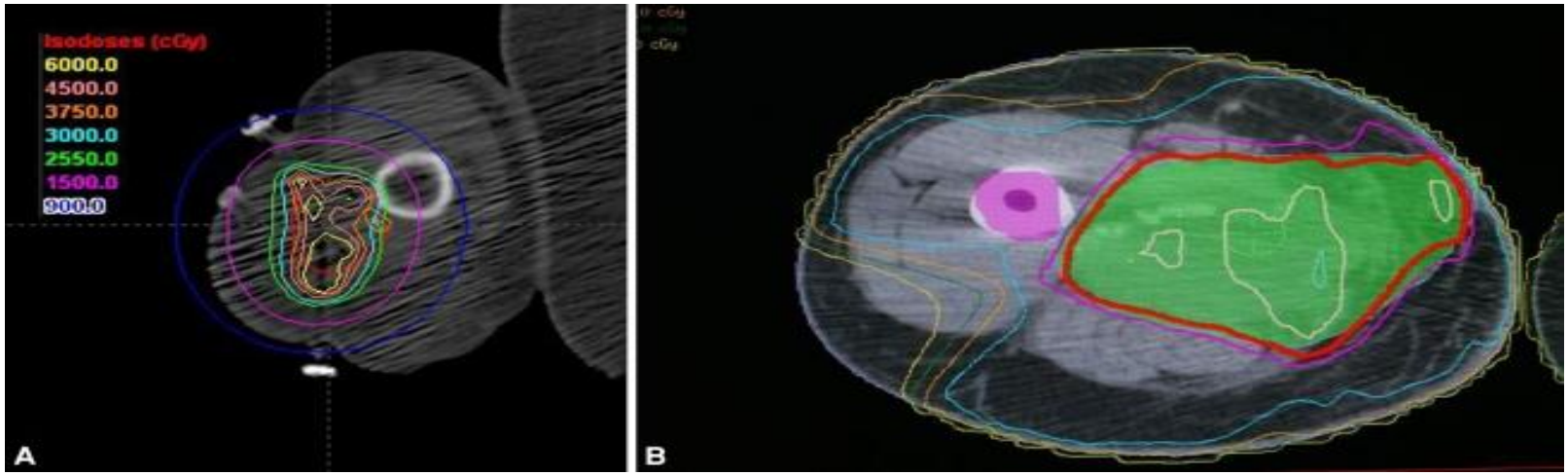
Alektiar KM, Brennan MF, Healey JH, Singer S.

5y LC %94 (negative or positive/close margin için de %94).

Diğer prognostik faktörler (yaş, boyut, grad : fark yok) .

"SONUÇ: Ekstremite YDS'da YART ile çok iyi LK.

Normal dokulara daha iyi koruma etkisi.



(**A**) Three-dimensional reconstruction of catheter position enables focused radiotherapy dose distribution, demonstrated in this dose-volume histogram of the arm with relative sparing of the radial nerve. (**B**) Typical Intensity Modulate Radiation Therapy (IMRT) dose distribution is shown for postoperative treatment of a thigh sarcoma.
Cynthia L. Emory, et al. Clin Orthop Relat Res. 2012 March;470(3):751-758.

GÜNCEL HEDEF:

ADJUVANT RT İLE LOKAL NÜKS <%10

RT YAN ETKİLERİ LK'u ETKİLEMEKSİZİN NASIL AZALTILABİLİR?

RT ŞEMALARı- ERKEN YARA KOMPLIKASYONU: %11-40 (ÇOĞU%30'LU ORANLAR)

Table 1 Wound complication probabilities with respect to RT schedule and timing in ESTS

		Preoperative		Postoperative			
Investigator	Patients (*n*)	RT (Gy)	WC (%)	RT (Gy)	WC (%)	*p*	Comment
O'Sullivan et al. (3)	182	25 × 2	35	33 × 2	17	.01	Excess in WC predominantly seen in thigh tumors
Cannon et al. (11)	412	50 (44-70)	34	60 (50-72)	16	<.001	
Virkus et al. (12)	209	28 × 1.8	22	-	-	-	
Pisters et al. (13)	26	25 × 2	23	-	-	-	Concurrent with continuous doxorubicin
Jakob et al. (14)	15	28 × 1.8	40	-	-	-	Concurrent with temozolomide
Tseng et al. (15)	173	25 × 2	32	-	-	-	Surgery performed with particular focus on reconstructive surgical techniques
Mack et al. (16)	75	10 × 3	15	-	-	-	3 days of preoperative doxorubicin (30 mg/d) and sequential RT of 10 × 3 Gy
Kraybill et al. (17)	61	22 × 2	11	-	-	-	RTOG 9514 phase II trial: 44 Gy split course interdigitated RT with mesna, doxorubicin, ifosfamide, and dacarbazine
Temple et al. (18)	53	10 × 3	11	-	-	-	Surgery performed with particular focus on reconstructive surgical techniques

Abbreviations: ESTS = extremity soft tissue sarcoma; RT = radiotherapy; WC = wound complications.

KOMPLİKASYONLAR NASIL AZALTILABİLİR?

- **Pre vs Post op RT: NCIC; O'Sullivan 2004 , Davis 2005;**

Primer sonlanım major yara komplikasyonu!:

- ✓ **Preop RT ile non-primer yara kapanması↑: %35 vs. %17 (SS);**
- ✓ Üst bacak↑ **(45% vs. 28%).**
- ✓ RT alanı, medyan**: preop 333 cm2 vs. postop 416 cm2 (SS)**
- ✓ Post-op RT ile fibrosis ↑**, ödem** ve eklem kısıtlılığı ↑ **(NS).**
- ✓ **Geniş RTsahası~fibrozis ve eklem kısıtlılığı**

❖ **Kemik fraktürü:**

- ✓ %3 /5y*, %4.5 /7y**
- ✓ RT Yüksek doz alanlarında fraktür var
- ✓ (Öneri :**V40 <%64. mean doz kemiğe <37 Gy** yada **maksimum** doz **<59 Gy**.)**

- Rosenberg 2013 Febr.; (Retrospektif) Plastik cerrahın yara komplikasyonu azalmasına katkısı (ND), 2.cil operasyon ihtiyacında azalma eğilimi??

- **(*Livi ve ark 2006, **Dickie ve ark 2009)**

LK'U DÜŞÜRMEDEN RT YAN ETKİSİ NASIL AZALTILABİLİR ?

ARAYIŞLAR:

- **Yeni RT teknikleri (IMRT, IGRT, vd)?**
- **Azaltılmış RT* volümleri?**
- **Yeni enerjiler (proton, ağır iyonlar vd)**
- **Yeni ajanlar (hedefe yönelik moleküller), yeni KT şemaları**

***süren 2 F2 çalışma:**
•RTOG-0630
•PMH

CANCER. 2013 FEB 19.

PHASE 2 STUDY OF PREOPERATIVE IMAGE-GUIDED INTENSITY-MODULATED RADIATION THERAPY TO REDUCE WOUND AND COMBINED MODALITY MORBIDITIES IN LOWER EXTREMITY SOFT TISSUE SARCOMA.

O'SULLIVAN B, GRIFFIN AM, DICKIE CI, SHARPE MB, CHUNG PW, CATTON CN, FERGUSON PC, WUNDER JS, DEHESHI BM, WHITE LM, KANDEL RA, JAFFRAY DA, BELL RS.

Department of Radiation Oncology, **Princess Margaret Hospital**, Toronto, Ontario, Canada; University of Toronto, Toronto, Ontario, Canada.

IG-RT: Yara kompl ⇩ %30.5

BACKGROUND: This study sought to determine if preoperative image-guided intensity-modulated radiotherapy **(IG-IMRT) can reduce morbidity**, including wound complications, by minimizing dose to uninvolved tissues in adults with lower extremity soft tissue sarcoma.

RESULTS: Eighteen **(30.5%)** patients developed **WCs.** This was not statistically significantly different from the result of the National Cancer Institute of Canada **SR2 trial** (P = .2); however, **primary closure** technique was possible more often (55 of 59 patients **[93.2%] versus** 50 of 70 **patients [71.4%]; P = .002**), and **secondary operations for WCs** were somewhat **reduced** (6 of 18 patients **[33%]** versus 13 of 30 patients **[43%]; P = .55). Moderate edema, skin, subcutaneous, and joint toxicity was present in 6 (11.1%)**, 1 (**1.9%**), 5 (9.3%), and 3 (**5.6%)** patients, respectively, **but there were no bone fractures**. **Four local recurrences (6.8%, none near the flaps**) occurred with median follow-up of 49 months.

CONCLUSIONS: The **30.5%** incidence of **WCs was numerically lower than the 43% risk derived from the National Cancer Institute of Canada SR2 trial, but did not reach statistical significance**. Preoperative IG-IMRT significantly diminished the need for tissue transfer**. RT chronic morbidities** and the need for subsequent secondary operations for WCs were **lowered, although not significantly**, **whereas good limb function** was maintained.

RTOG 0630: IG-RT

Target Accrual: 102
Current Accrual: 98
Status: Closed to Accrual
Date: 9/23/2010

234 **RTOG Phase II Trial of Preoperative Image Guided Radiotherapy (IG-RT) For Primary Soft Tissue Sarcoma of the Extremity: Acute Toxicity Report**

D. Wang[1], Q. Zhang[2], D. G. Kirsch[3], S. Okuno[4], J. Kane III[5], X. Li[1], D. Roberge[6], S. E. Finkelstein[7], T. DeLaney[8], B. Eisenberg[9]

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Purpose/Objective(s): To report acute toxicity results of the first reported multi-institutional prospective trial (RTOG 0630) using preoperative IG-RT (3D-CRT or IMRT) in primary extremity soft tissue sarcoma (STS) and compare the results to the preoperative arm of the NCIC sarcoma trial (O'Sullivan *et al.*, Lancet 2002).

Materials/Methods: Patients with primary extremity STS received IG-RT with chemotherapy (Cohort A) or without chemotherapy (Cohort B) followed by limb salvage surgery. Daily pretreatment images (2D or 3D) were required to be fused with Digitally Reconstructed Radiographs to allow adjustment of patient position. Cohort A was prematurely closed due to poor accrual and results are not presented. All patients in Cohort B were required to receive IG-RT to 50 Gy in 25 fractions. GTV and CTV were contoured according to strict guidelines (margin of 0.5 cm for PTV). Postoperative boost to positive margin was allowed. Adverse events were graded using CTCAE v3.0. Subcutaneous tissue fibrosis and joint stiffness were scored by RTOG/EORTC criteria, edema by Stern's scale and major acute wound complications (MAWC), defined in the previous NCIC protocol.

Results: A total of 98 patients were accrued (12 to Cohort A and 86 to Cohort B); 81 eligible Cohort B patients form the basis of this report. IMRT was used in 61 patients (75.3%), with the remainder receiving 3D-CRT. The most common histology was liposarcoma (30.9%), with proximal upper leg as the most common primary site (43.2%). Median tumor size was 10.2 cm. At a median follow-up of 9.3 months (range, 1.2-25.4), 4 (4.9%) experienced a Grade 4 CTCAE adverse event, and additional 16 (19.8%) experienced at least 1 Grade 3 event. By Stern's scale, 16 (19.8%) experienced Grade 2+ edema. By the RTOG/EORTC criteria, 7 (8.6%) experienced Grade 2+ joint stiffness and 6 (7.4%) had Grade 2+ subcutaneous tissue fibrosis. Of 54 patients with a wound assessment at median 110 (range, 21-281) days post surgery, 20 (37%) experienced at least one MAWC. This rate (37%) is similar to that in the preoperative arm of the NCIC trial (35%). MAWC occurred exclusively in lower extremity (20/43 lower extremity vs. 0/11 other sites, $p < 0.01$). 13 of 29 larger tumors (>10 cm) had MAWC while 7 of 25 others (≤10 cm) had MAWC ($p = 0.26$). There was no apparent difference in MAWC by T-Stage, grade, histology, or type of RT (3D-CRT vs. IMRT).

Conclusions: Acute toxicity profiles in patients with extremity STS treated with IGRT followed by limb salvage surgery are acceptable. Overall rate of MAWC is similar to the reported rate and MAWC occurred exclusively in the lower extremity. Longer follow-up results will be updated.

Acknowledgment: This project was supported by RTOG grant U10 CA21661, CCOP grant U10 CA37422, and ATC grant U24 CA81647 from the National Cancer Institute (NCI).

Author Disclosure: D. Wang: None. Q. Zhang: None. D.G. Kirsch: None. S. Okuno: None. J. Kane III: None. X. Li: None. D. Roberge: None. S.E. Finkelstein: None. T. DeLaney: None. B. Eisenberg: None.

GÜNCEL HEDEF:
LK ETKILEMEDEN RT'NIN YE'LERI NASIL AZALTILABİLİR?

- RT TEKNIK ve **RT VOLUM**

Study (Year) (Ref)	Margins (cm)		XRT schedule	Chemotherapy
	Longitudinal	Radial		
SR.2 NCI Canada (2002) (1)	5	≥2	50 Gy/ 25 fx	No
MSKCC* (2007) (5)	5	2	50 Gy/ 25 fx IMRT	Postoperative high-grade only
RTOG 9514 (2006) (6)	9	≥2	44 Gy/ 22 fx, split	Interdigitated MAID
MGH (2003) (7)	6–9	≥2	44 Gy/ 22 fx, split	Interdigitated MAID
MDACC (2004) (8)	5–7	≤1/3 of circumference	50 Gy/ 25 fx	Concurrent with Doxorubicin
Peter MacCallum (2006) (9)	6	-	50.4 Gy/ 28 fx	Selected cases
University of Florida (2002) (10)	5–10 (average 10)	Involved compartment	50.4 Gy/ 42 fx, 1.2 Gy *b.i.d*	Protocol based
Groningen University (1999) (11)	Entire tumor region		35 Gy/10 fx	Intra-arterial doxorubicin

3 PROSPEKTIF GÜNCEL ÇALıŞMA; AZALTıLMıŞ RT VOLÜM VE LK, TOKSISITE ILIŞKISINI ARAŞTıRıYOR:

- **RTOG 0630 F2 (ekstremite YDS, IG-RT: tamamlandı)**
- **UK-Vortex (sürüyor)**
- **COG ARST 0332 (Çocuk, genç erişkin ≤30y)**

0630: AZALTILMIŞ RT VOLUMU MODERN TEKNIK

http://atc.wustl.edu.

6.4 Treatment Planning/Target Volumes

6.4.1 *Target Definition*

The definition of volumes will be in accordance with the ICRU Report #62: Prescribing, recording and Reporting Photon Beam Therapy (supplement to ICRU Report #50).

6.4.1.1 Gross Target Volume (GTV): Gross tumor defined by MRI T1 plus contrast images (MRI with contrast is required). Fusion of MRI and CT is recommended to delineate the GTV for radiotherapy planning, but this is optional.

6.4.1.2 **(4/20/09)** Clinical Target Volume (CTV) for Intermediate-to-High Grade Tumors ≥ 8 cm: Include gross tumor and clinical microscopic margins. Typically CTV = GTV and suspicious edema (defined by MRI T2 images) plus 3 cm margins in the longitudinal (proximal and distal) directions. If this causes the field to extend beyond the compartment, the field can be shortened to include the end of a compartment. The radial margin from the lesion should be 1.5 cm including any portion of the tumor not confined by an intact fascial barrier or bone or skin surface.

6.4.1.3 **(4/20/09)** CTV For All Other Tumors: Include gross tumor and clinical microscopic margins. Typically CTV = GTV and suspicious edema (defined by MRI T2 images) plus 2 cm margins in the longitudinal (proximal and distal) directions. If this causes the field to extend beyond the compartment, the field can be shortened to include the end of compartment. The radial margin from the lesion should be 1 cm including any portion of the tumor not confined by an intact fascial barrier or bone or skin surface.

6.4.1.4 Planning Target Volume (PTV): Include CTV and error of setup and organ motion. Typically PTV includes CTV plus 5 mm.

Skin surfaces should not be conto
tumor. If the incisional biopsy sca
may not be contoured as CTV at t
bolus on the skin surfaces is not en

It is important to note that the above target definitions might not be suitable for sarcomas of specific histologies, including rhabdomyosarcoma, extraosseous primitive neuroectodermal tumor, or soft tissue Ewing's sarcoma, Kaposi's sarcoma, angiosarcoma, aggressive fibromatosis (desmoid tumor), dermatofibrosarcoma protuberans, or subcutaneous myxofibrosarcoma. Indeed, it may be challenging to identify

ELSEVIER
doi:10.1016/j.ijrobp.2011.04.038

RTOG SARCOMA RADIATION ONCOLOGISTS REACH CONSENSUS ON GROSS TUMOR VOLUME AND CLINICAL TARGET VOLUME ON COMPUTED TOMOGRAPHIC IMAGES FOR PREOPERATIVE RADIOTHERAPY OF PRIMARY SOFT TISSUE SARCOMA OF EXTREMITY IN RADIATION THERAPY ONCOLOGY GROUP STUDIES

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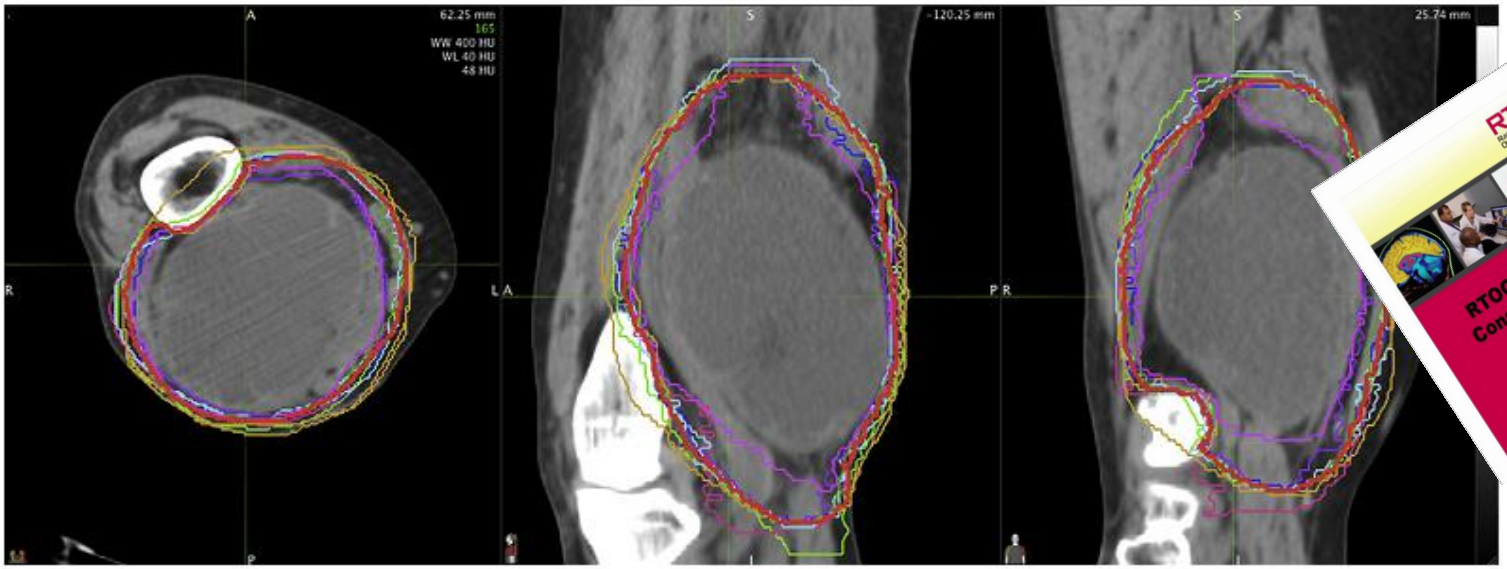

Fig. 2. Example of individual and consensus (red) contours of clinical target volume on axial computed tomography for patient with large high-grade sarcoma of distal aspect of right thigh.

contrast enhanced magnetic resonance images. Fusion of magnetic resonance and images is recommended to delineate the GTV. The CTV for high-grade large STS typically includes the GTV plus 3-cm margins in the longitudinal directions. If this causes the field to extend beyond the compartment, the field can be shortened to include the end of a compartment. The radial margin from the lesion should be 1.5 cm, including any portion of the tumor not confined by an intact fascial barrier, bone, or skin surface.

Conclusion: The consensus on GTV and CTV for preoperative radiotherapy of high-grade large extremity STS is available as web-based images and in a descriptive format through the RTOG. This is expected to improve target volume consistency and allow for rigorous evaluation of the benefits and risks of such treatment.

In regard to RTOG Sarcoma Radiation Oncologists Reach Consensus on Gross Tumor Volume and Clinical Target Volume on Computed Tomographic Images for Preoperative Radiotherapy of Primary Soft Tissue Sarcoma of Extremity in Radiation Therapy Oncology Group Studies: In regard to Wang et al (*Int J Radiat Oncol Biol Phys* 2011;81:e525–e528)

CTV düşürmek için henüz erken!...

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To date, the prospective randomized trial of preoperative RT in extremity sarcoma that utilized the smallest treatment volumes is the National Cancer Institute of Canada Clinical Trials Group SR2 trial. In SR2, target volumes comprised a 5-cm longitudinal field margin equating to 4-cm on GTV for the CTV volume delineation (3). The result was a local control rate exceeding 90% (4). Our recent phase II IMRT trial achieved a local control rate of 95% (mean follow-up: 33.4 months) (5) using the same CTV longitudinal margin definition as SR2 and which was influenced by our report on the significance of peritumoral edema, referred to by Wang et al. In that study, we found tumor cells up to 4-cm from the gross tumor in 4 of 15 cases. Disturbingly, the location of tumor cells beyond GTV did not actually correlate with the extent of peritumoral edema. Therefore, it may be prudent to remain conservative in defining longitudinal target volumes less than 4-cm even when peritumoral edema is not evident.

Recently, we also described 2 marginal recurrences at the edge of the target following preoperative RT with 4-cm longitudinal margin and 1.5-cm radial margin (6). One could speculate that we might have seen more than 2 marginal recurrences had we reduced the longitudinal CTV margin to less than 4-cm and a putative functional gain achieved through a 1-cm target volume reduction in the longitudinal dimension may not outweigh the adverse consequences of local disease recurrence. Perhaps it is premature to propose a CTV reduction without first waiting for the 0630 trial results that utilize 3-cm longitudinal margins.

The authors also indicate that their proposed definitions will be useful in future prospective trials. We would agree completely, once the outcome results become available, and congratulate them again for encouraging greater consistency to

e incorporation of new techniques and strategies in
t will evaluate whether smaller than standard CTV
e indeed beneficial.

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Preliminary Results from a Prospective Study using Limited Margin Radiotherapy in Pediatric and Young Adult High Grade Non-Rhabdomyosarcoma Soft Tissue Sarcoma

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2 cm CTV!..

Abstract

Purpose—To demonstrate the safety and efficacy of limited margin radiotherapy in the local control of pediatric and young adult patients with high grade non-rhabdomyosarcoma soft tissue sarcoma (NRSTS).

Methods and Materials—Pediatric patients with high-grade NRSTS requiring radiation were treated on an IRB approved prospective institutional study of conformal / intensity modulated / interstitial brachytherapy using a 2 cm anatomically constrained margin.

Results—Thirty-two patients (median age 15.3 years, range 2–22 years) received adjuvant (27 patients) or definitive (5 patients) irradiation. With a median follow-up of 32 months, the 3-year cumulative incidence of local failure was 3.7% for patients irradiated after surgical resection. In total four patients experienced local failure; the mean dose to the volume of recurrence was ≥ 97% of the prescribed dose.

Conclusions—Delivery of limited margin radiotherapy using external beam or brachytherapy provides a high rate of local tumor control without marginal failure. Further follow-up is required to determine if normal tissue effects are minimized using this approach.

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Critical Review

Radiotherapy for Management of Extremity Soft Tissue Sarcomas: Why, When, and Where?

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4 cm long.!.
CTV

Critical Review

Radiotherapy for Management of Extremity Soft Tissue Sarcomas: Why, When, and Where?

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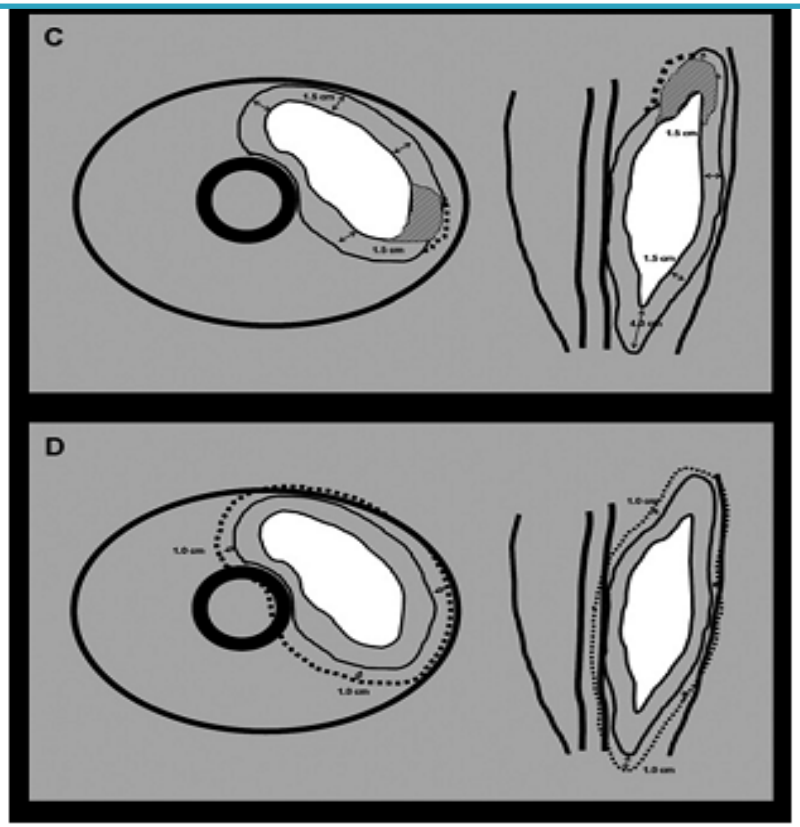


Fig. 1. Schematic descriptions of target definitions for preoperative radiotherapy (RT). (A) Patient to be treated with preoperative RT. Sarcoma delineated using T_1-weighted, postgadolinium magnetic resonance imaging (MRI) scan fused to planning computed tomography (CT) scan. This gross tumor volume (GTV) does not include peritumoral edema, generally best seen on T_2-weighted MRI scan. (B) GTV transversely expanded with 1.5 cm but constrained at surfaces of fascia and bones, unless invaded. Longitudinally, expansion was 4 cm. Note, this was a sarcoma case without peritumoral edema. (C) Sarcoma case with peritumoral edema, with GTV also transversely expanded with 1.5 cm and constrained at surfaces of fascia and bones, unless invaded. Longitudinally, expansion was 4 cm. Note, CTV has been manually edited (bold dashed line) to encompass edema zone in both transverse and coronal planes. Peritumoral edema indicated by striped zone. (D) Delineation of final preoperative planning target volume (PTV) by expansion of CTV with 1 cm in all directions, although PTV can vary by local institutional protocols, as described in text.

CTV should be manually edited to encompass any suspicious edema if the edema is not otherwise included by these margins.

PTV for preoperative RT

The PTV is generally produced by expanding the CTV approximately 1.0 cm isotropically in all directions (for additional remarks concerning the PTV, see above the remarks on immobilization, image guidance, and the reproducibility of the treatment setup).

Postoperative RT

In the case of postoperative RT, a portion of the dose is ordinarily applied to a larger volume encompassing the surgical bed with appropriately safe margins. This volume is generally referred to as the "elective" phase and is traditionally delivered first (phase 1). A careful review of the surgical and pathology reports is essential to optimally define the target volume and the dose level to be administered. Commonly applied doses are 45-50.4 Gy in once-daily 1.8-2-Gy fractions. This is followed by a smaller volume boost to the tumor bed (phase 2). Typically, doses of 10-16 Gy are applied, resulting in a total dose of 60-66 Gy.

PERITÜMÖRAL ÖDEM?- RT ALANı?

Int J Radiat Oncol Biol Phys. 2005 Apr 1;61(5):1439-45.

Histologic assessment of peritumoral edema in soft tissue sarcoma.

White LM, Wunder JS, Bell RS, O'Sullivan B, Catton C, Ferguson P, Blackstein M, Kandel RA.

Department of Medical Imaging, Mt. Sinai Hospital and **Princess Margaret Hospital,** University of Toronto, Toronto, ON, Canada. lwhite@mtsinai.on.ca

,"malignant cells were found at a distance >1 cm and up to a maximum of 4 cm. The location of tumor cells beyond the margin did not correlate with tumor size nor did it correlate with the location or extent of peritumoral changes."

Tümörden 1-4 cm Ötede tm hücreleri

Received Nov 18, 2012, and in revised form Jan 16, 2013. Accepted for publication Jan 29, 2013

Agreement Among RTOG Sarcoma Radiation Oncologist in Contouring Suspicious Peritumoral Edema for Preoperative Radiation Therapy of Soft Tissue Sarcoma of the Extremity

Houda Bahig, MD,* David Roberge, MD,* Walter Bosch, PhD,† William Levin, MD,‡ Ivy Petersen, MD,§ Michael Haddock, MD,§ Carolyn Freeman, MBBS,‖ Thomas F. DeLaney, MD,¶ Ross A. Abrams, MD,# Danny J. Indelicato, MD,** Elizabeth H. Baldini, MD, MPH,†† Ying Hitchcock, MD,‡‡ David G. Kirsch, MD, PhD,§§ Kevin R. Kozak, MD, PhD,‖‖ Aaron Wolfson, MD,¶¶ and Dian Wang, MD##

included in this margin (7), but the extent of inclusion remains subject to clinical judgment. Edema will typically already be included when 3-cm longitudinal margins are used, and the benefit of including edema >4 cm from the GTV is unclear.

VorteX

Randomised trial of Volume of post-operative radiotherapy given to adult patients with eXtremity soft tissue sarcoma

SÜRÜYOR.....

Aims/Objectives: The aim of this trial is to assess if a reduced volume of post-operative radiotherapy increases limb function without compromising local control

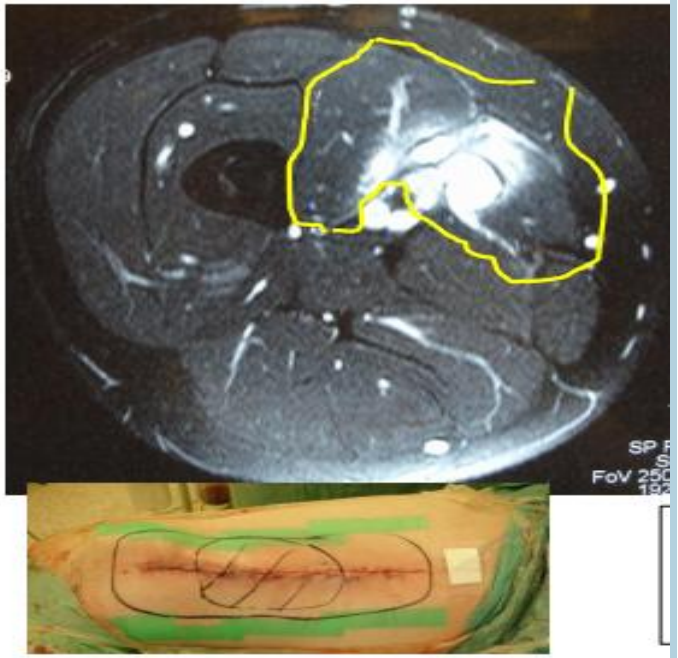
Stratified by: tumour grade, adequacy of definitive surgical clearance and centre

Radiotherapy planning

Control Arm Conventional two-phase treatment Total dose: 66Gy in 33#	
Weeks 1-5: 2Gy x 5 days Weekly	CTV_1: 5cm margin to GTV or 1cm to the scar, whichever is longer in the cranio-caudal direction and minimum margin of 2cm axially
Week 6 2Gy x 5 days	CTV_2 2 cm cranio-caudal margin to GTV and minimum margin of 2cm axially
Week 7 2Gy x 3 days	

Research Arm Single-phase treatment to CTV_2 only Total dose: 66Gy in 33#	
Weeks 1-6: 2Gy x 5 days Weekly	CTV_2 2 cm cranio-caudal margin to GTV and minimum margin of 2cm axially
Week 7 2Gy x 3 days	

VORTEX (POST-OP RT)



Appendix 1: Indications for radiotherapy

Staging:

Stage I
IA= low grade, small, superficial or deep (G1-2, T1a-b, N0, M0)

IB= low grade, large, superficial or deep (G1-2, T2a-b, N0, M0)

Stage II
IIA= high grade, small, superficial or deep (G3-4, T1a-b, N0, M0)

IIB= high grade, large, superficial (G3-4, T2a, N0, M0)

Stage III
High grade, large, deep (G3-4, T2b, N0, M0)

Stage	Surgical margin	Plan
IA & IB	<=10mm	Re-resection or radiotherapy depending on impact of surgery on function
	>10mm	Watch policy
IIA	superficial (rare)	Surgery alone
	deep	Surgery + XRT unless intramuscular tumour with 20mm margin
IIB	rare	Surgery alone if margin >10mm; else re- resection or XRT
III		Surgery + XRT

+/- ADJUVANT RT?: FRANSIZ ÇLŞ-08SARC01

Sürüyor.....

RNCT00870701 [RDF] Trial

Başlangıç:Mart 26, 2009 , Kapanış: Mart 2021

Sayı hedef: 570 , Kollar: 2

''Randomised Multicentric Phase III Study Comparing Observation Versus Post-Surgery Radiotherapy After Complete Exeresis With Margins Greater Than or Equal to 1 cm in Soft Tissues Members Sarcoma. ''

Randomize, sonlanım tipi: etkinlik,

primer amaç: tedavi

2CM VS 3 CM VS 4 CM CTV?

International Journal of Radiation Oncology biology • physics
www.redjournal

Critical Review

Radiotherapy for Management of Extremity Soft Tissu Sarcomas: Why, When, and Where?

Rick L.M. Haas, MD, PhD,* Thomas F. DeLaney, MD, PhD,† Brian O'Sullivan, MD

Çalışma sonuçları beklenmeli!

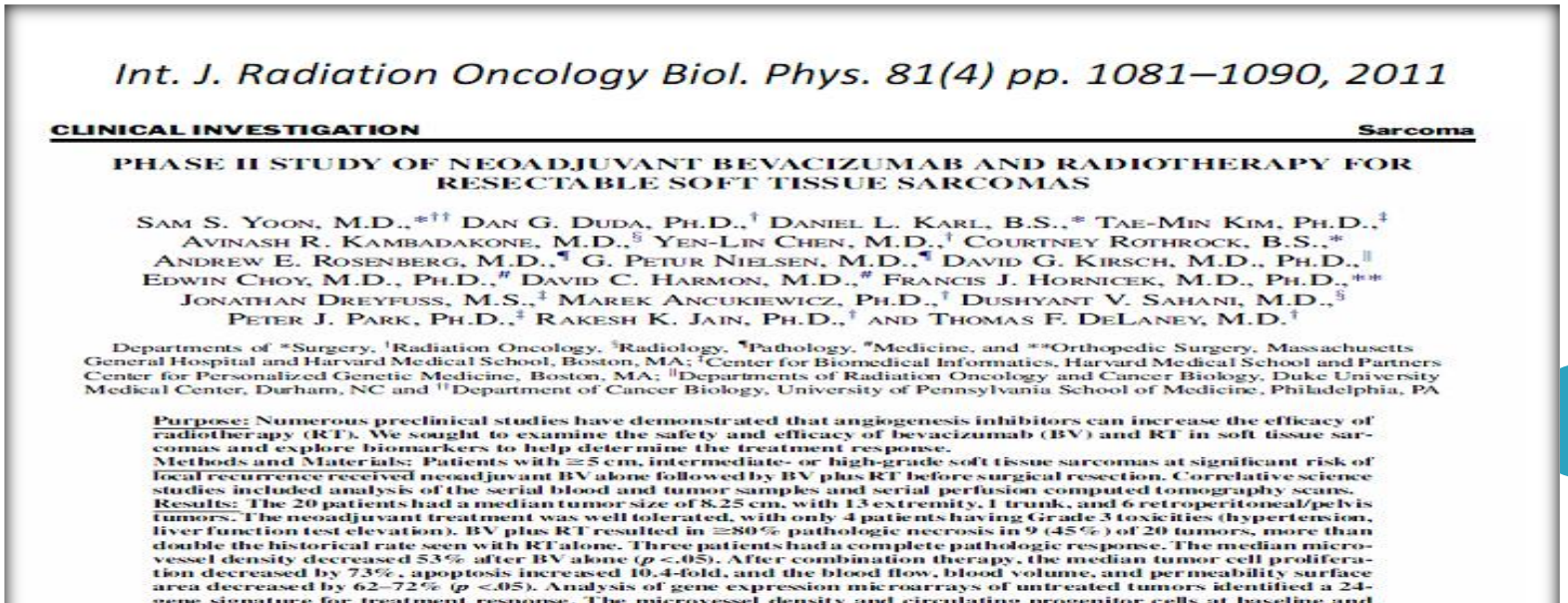
Conclusions

These target volume delineation recommendations have been generated mainly from retrospective data and clinical practice and should be re-evaluated using the results from ongoing and future studies. In addition, account should always be taken of individual patient factors that can only be appreciated by the treating physician. These recommendations are intended as an aid to individual radiation oncologists to facilitate the process of treatment planning, recognizing that prospective validation would be desirable but difficult to achieve with this rare disease.

SARKOMLARDA DİĞER FARKLI ÇALIŞMALAR:

HEDEFE YÖNELIK AJANLAR

- 2011, F2 (ABD: Bvz→Bvz+RT→Cerrahi: Tümör Nekrozu ≥%80 (x2 kat RT ye göre)



Int. J. Radiation Oncology Biol. Phys. 81(4) pp. 1081–1090, 2011

CLINICAL INVESTIGATION **Sarcoma**

PHASE II STUDY OF NEOADJUVANT BEVACIZUMAB AND RADIOTHERAPY FOR RESECTABLE SOFT TISSUE SARCOMAS

SAM S. YOON, M.D.,*†† DAN G. DUDA, PH.D.,† DANIEL L. KARL, B.S.,* TAE-MIN KIM, PH.D.,‡ AVINASH R. KAMBADAKONE, M.D.,§ YEN-LIN CHEN, M.D.,† COURTNEY ROTHROCK, B.S.,* ANDREW E. ROSENBERG, M.D.,¶ G. PETUR NIELSEN, M.D.,¶ DAVID G. KIRSCH, M.D., PH.D.,‖ EDWIN CHOY, M.D., PH.D.,# DAVID C. HARMON, M.D.,# FRANCIS J. HORNICEK, M.D., PH.D.,** JONATHAN DREYFUSS, M.S.,‡ MAREK ANCUKIEWICZ, PH.D.,† DUSHYANT V. SAHANI, M.D.,§ PETER J. PARK, PH.D.,‡ RAKESH K. JAIN, PH.D.,† AND THOMAS F. DELANEY, M.D.†

Departments of *Surgery, †Radiation Oncology, §Radiology, ¶Pathology, #Medicine, and **Orthopedic Surgery, Massachusetts General Hospital and Harvard Medical School, Boston, MA; ‡Center for Biomedical Informatics, Harvard Medical School and Partners Center for Personalized Genetic Medicine, Boston, MA; ‖Departments of Radiation Oncology and Cancer Biology, Duke University Medical Center, Durham, NC and ††Department of Cancer Biology, University of Pennsylvania School of Medicine, Philadelphia, PA

Purpose: Numerous preclinical studies have demonstrated that angiogenesis inhibitors can increase the efficacy of radiotherapy (RT). We sought to examine the safety and efficacy of bevacizumab (BV) and RT in soft tissue sarcomas and explore biomarkers to help determine the treatment response.

Methods and Materials: Patients with ≥5 cm, intermediate- or high-grade soft tissue sarcomas at significant risk of focal recurrence received neoadjuvant BV alone followed by BV plus RT before surgical resection. Correlative science studies included analysis of the serial blood and tumor samples and serial perfusion computed tomography scans.

Results: The 20 patients had a median tumor size of 8.25 cm, with 13 extremity, 1 trunk, and 6 retroperitoneal/pelvis tumors. The neoadjuvant treatment was well tolerated, with only 4 patients having Grade 3 toxicities (hypertension, liver function test elevation). BV plus RT resulted in ≥80% pathologic necrosis in 9 (45%) of 20 tumors, more than double the historical rate seen with RT alone. Three patients had a complete pathologic response. The median microvessel density decreased 53% after BV alone ($p < .05$). After combination therapy, the median tumor cell proliferation decreased by 73%, apoptosis increased 10.4-fold, and the blood flow, blood volume, and permeability surface area decreased by 62–72% ($p < .05$). Analysis of gene expression microarrays of untreated tumors identified a 24-

Int J Radiat Oncol Biol Phys. 2012 Feb 1;82(2):924-32.

Combination of external beam radiotherapy (EBRT) with intratumoral injection of dendritic cells as neo-adjuvant treatment of high-risk soft tissue sarcoma patients.

Finkelstein SE et al .H. Lee Moffitt Cancer Center, Tampa, FL 33612, USA.

PURPOSE:

The goal of this study was to determine the effect of combination of intratumoral administration of dendritic cells (DC) and fractionated external beam radiation (EBRT) on tumor-specific immune responses in patients with soft-tissue sarcoma (STS).

METHODS AND MATERIAL:

Seventeen patients with **large (>5 cm) high-grade STS** were enrolled in the study. They were treated in the **neoadjuvant setting with 5,040 cGy of EBRT**, split into 28 fractions and delivered 5 days per week, **combined with intratumoral injection of 10(7) DCs followed by complete resection**. DCs were injected on the second, third, and fourth Friday of the treatment cycle. Clinical evaluation and immunological assessments were performed.

RESULTS:

The treatment was well tolerated. No patient had tumor-specific immune responses before combined EBRT/DC therapy**; 9 patients (52.9%) developed tumor-specific immune responses**, which lasted from 11 to 42 weeks. Twelve of 17 patients **(70.6%) were progression free after 1 year.** Treatment caused a dramatic accumulation of T cells in the tumor. The presence of CD4(+) T cells in the tumor positively correlated with tumor-specific immune responses that developed following combined therapy. Accumulation of myeloid-derived suppressor cells but not regulatory T cells negatively correlated with the development of tumor-specific immune responses. **Experiments with (111)In labeled DCs demonstrated that these antigen presenting cells need at least 48 h to start migrating from tumor site.**

CONCLUSIONS:

Combination of intratumoral DC administration with EBRT was safe and resulted in induction of antitumor immune responses. **This suggests that this therapy is promising and needs further testing in clinical trials design to assess clinical efficacy.**

PROTON YADA DIĞER PARTIKÜLER RADYASYON

- Acta Oncol. **2013** Apr;52(3):545-52.

Dosimetric comparison between VMAT with different dose calculation algorithms and protons for soft-tissue sa

Fogliata A, Oncology Institute of Southern Switzerland

STS için benzer plan kalitesi

(orta/düşük doz alan Normal doku volümü proton ile ↓)

- Bull Cancer. 2010 Jun;97(6):657-72.

Radiotherapy for sarcoma: hadrontherapy, for whom and what for?.

Pommier P, Centre Léon-Bérard, France.

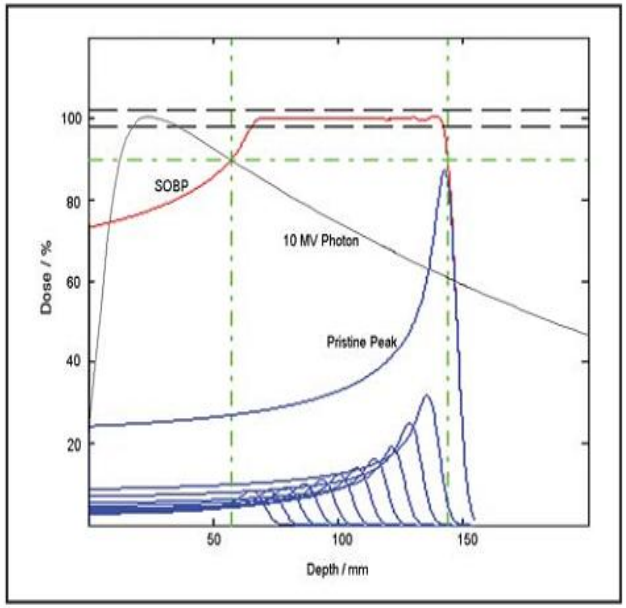
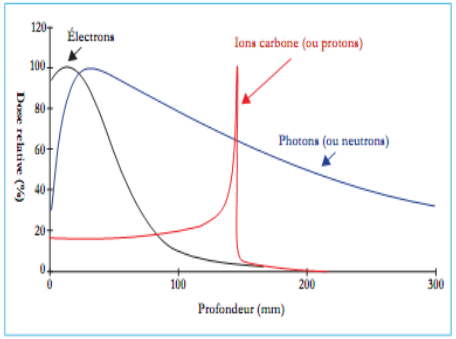


Fig 2. — Depth-dose distributions for a spread-out Bragg peak (SOBP, red), its constituent pristine Bragg peaks (blue), and a 10-MV photon beam (black). The SOBP dose distribution is created by adding the contributions

"**Thanks to** their physical properties (Bragg Peak), protons are characterized by a higher conformity index compared to photons (and neutrons) with optimal organs at risk preservation that permits a dose escalation. **Protontherapy is to date the standard of care for base of skull, spinal and paraspinal sarcomas.** Carbon ions combined both advantages from protons and neutrons"

KEMIK/YD SARKOMU- PROTON : %60-85 LK, CIDDI YE ↓



Cancer vol. 97 • N° 6 • juin 2010

Tableau 1. Sarcomes des tissus mous et ostéosarcomes : protons.

Étude	Patients	Tumeurs	Traitements	Contrôle local	Survie sans récidive Survie globale	Toxicité
Delaney *et al.*, 2005 MGH [8]	41 pts 1980-2002	Ostéosarcomes Localisation : ORL (17) ; extrémités (8) ; rachis (8) ; pelvis (7) ; tronc (1) Statut chirurgical : R0-1 : 27 pts ; R2 : 9 pts Biopsie seule : 5 pts	Dose médiane 66 Gy X seul : 18 pts ; P + X : 23 pts R0-R1 : 50-60 Gy R2 : 60-68 Gy Biopsie seule : > 68 Gy chimiothérapie : 35 pts (85,4 %)	(5 ans) 41 pts : 68 % R0-R1 : 78 % R2 : 78 % Biopsie seule : 40 %	SSR : ND SG (5 ans) : 41 pts : 65,5 % R0-R1 : 74,5 % R2 : 74 % Biopsie seule : 25 %	Complications tardives sévères 24 % (10 pts)
Hug *et al.*, 1995 MGH [9]	15 pts (issus d'une série de 47 pts) 1980-1992	Ostéosarcome-squelette axial Localisation : Base du crâne (47 %) ; Rachis (33 %) ; Sacrum (20 %) Statut chirurgical : ND	Proton + X 69,8 GyE (61,1-80 GyE) Chimiothérapie : 1 pt	59 % (5 ans)	SSR : ND SG : 44 % (5 ans)	NA
Weber *et al.*, 2007 PSI [16]	13 pts 1998-2005 (4 en situation de récidive)	Sarcome tissus mous Localisation : Paravertébral + pelvis (54 %) ; Rétropéritonéal (15 %) ; Tête et cou (15 %) ; épaule (15 %) Statut chirurgical : biopsie seule (2) ; R2 (4) ; R1 (7)	Proton (P) P seul (6 pts) : 69,4 GyE P + X (7 pts) : P : 28 GyE X : 41,4 Gy Chimiothérapie : ND	74,1 % (4 ans) (3 récidives locales)	ND	Grade 3 (nécrose cérébrale) : 1 pt
Timmermann *et al.*, 2007 PSI [17]	16 pts (enfants) 1997-2005	Sarcome tissus mous Rhabdomyosarcome (75 %) Localisation : parameningé (44 %) ; orbite (25 %) ; paraspinal (19 %) ; ORL (6 %) ; prostate (6 %) Statut chirurgical : R2 12 (75 %) ; autres (ND)	Proton (P) Dose médiane : 50 GyE, P seul (14 pts) ; P + X (2 pts) : Chimiothérapie (14 pts)	75 % (18 mois)	SSR : 71,6 % (2 ans) SG : 69,3 % (2 ans)	Pas de séquelles sévères
Truong *et al.*, 2008 MGH [18]	19 pts 1991-2006	Sarcome tissus mous Sinus de la face et cavités nasales Statut chirurgical : R0-R1 : 6 ; R2 : 8 pts Biopsie seule : 5	Protons (± X) Dose : 70 GyE [55-82 Gy] Chimiothérapie : pour les RMS	85 % (3 ans)	SSR : 47 % (3 ans) SG : 68 % (3 ans)	1 grade 4 (ostéomyélite)

KEMIK/YD SARKOMU-KARBON IYON: LK %60-80, CIDDI YE ↓

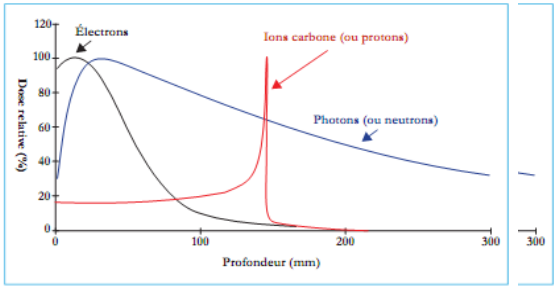


Tableau 3. Sarcomes des tissus mous, ostéosarcomes et chondrosarcomes : Ions carbone.

Étude	Patients	Tumeurs	Traitements	Contrôle local	Survie sans récidive Survie globale	Toxicité
Kamada *et al.*, 2002 NIRS [11]	57 pts (64 lésions) 1994–2000 phases I-II	Sarcome osseux : 72 % (41 pts) Ostéosarcome (15 pts) Chordome (11 pts) Chondrosarcome (6 pts) Sarcome tissus mous : 28 % (23 pts) Localisation : pelvis (56 %) ; Spinale/paraspinal (33 %) ; extrémités (11 %) Non résécable	Phase I (escalade de dose) Ions carbone seuls : 52,8–73,6 GyE (16 fractions)	73 % (3 ans) 63 % (5 ans)	SSR : ND SG : 46 % (3 ans) 37 % (5 ans)	Toxicité tardive Grade 3 (Peau, tissus mous) : 6 pts
Kamada *et al.*, 2008 NIRS [14]	26 pts 1996-2006	Sarcome osseux spinal Chondrosarcome (8 pts) Chordome (7 pts), Ostéosarcome (6 pts), Autres : 5 pts Non résécable	Phases I et II Ions carbone seuls : 52,8-64 GyE (17 pts) 70,4 GyE (9 pts)	86 % (3 ans)	SG : 52 % (5 ans)	Toxicité cutanée : 2 pts Fracture (chir.) : 3 pts
Kamada *et al.*, 2009 NIRS [13]	388 pts (414 lésions) 2000-2008 Phase II	Sarcome osseux : 73 % (304 pts) Ostéosarcome (66 pts) Chordome (126 pts) Chondrosarcome (63 pts) Sarcome tissus mous : 27 % (84 pts) Localisation : pelvis (72 %) ; spinale/ paraspinale (21 %) ; extrémités (7 %) Non résécable	Phase II Ions carbone seuls : 64–73,6 GyE (16 fractions)	(5 ans) Ensemble : 79 % Chordomes : 89 % ChondroS. : 65 % Ostéosarcome du tronc : 62 %	SSR : ND SG (5 ans) : Ensemble : 57 % Chordomes : 85 % ChondroS. : 59 % Ostéosarcome du tronc : 28 %	≥ grade 3 Toxicité tardive (peau) : 7 pts.
Serizawa *et al.*, 2009 NIRS [22]	24 pts (récidive : 8 pts) 1997-2006	Sarcome rétropéritonéal Non résécable	Ions carbone seuls : 52,8-73,6 GyE 16 fractions)	69 % (5 ans)	SSR : ND SG : 50 % (5 ans)	Pas de toxicité Grade ≥ 3
Schulz-Ertner *et al.*, 2007 GSI [30]	54 pts (récidives : 21 pts) 1998-2005 Phase I/II	Chondrosarcome de la base du crâne Statut chirurgical : R2 100 %	Carbon Ions RT 60 GyE (57-70)	ChondroS : 89,8 % (4 ans)	SSR : ND SG : 98,2 % (5 ans)	Toxicité tardive grade 3 : 1 pt
Combs *et al.*, 2009 GSI [31]	17 pts 1997-2007 Âge médian 18 ans [5-21] (récidive : 3 pts)	Histologie : Chordome : 7 pts Chondrosarcome : 10 pts Base du crâne : 100 % Statut chirurgical : R2 ou non résécable	Ions carbone 60 GyE (60–66,6 GyE) (3 GyE 7 j/7)	1 récidive (chordome) à 5 ans (suivi médian 49 mois)	ND	Pas de toxicité sévère > grade 3

The British Journal of Radiology, 84 (2011), S35–S47

Review of clinical experience with ion beam radiotherapy

A D JENSEN, MD, MSc, M W MÜNTER, MD and J DEBUS, MD, PhD

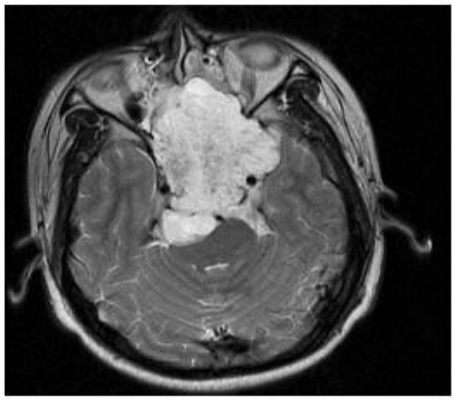
Department of Radiation Oncology, University of Heidelberg, Heidelberg, Germany

Table 2. Chordoma

Author	Year	Patient number	Radiotherapy	Local control rate
Romero et al [22]	1993	18	Conventional radiotherapy	17% at 5 years
Debus et al [21]	2000	45	FSRT	50% at 5 years
Munzenrider and Liebsch [23]	1999	519	Protons/photons	73% at 5 years
Castro et al [2]	1994	223	Helium ions	63% at 5 years
Noel et al [24]	2001	67	Protons/photons	71% at 3 years
Weber et al [25]	2005	11	Protons	87.5% at 3 years
Schulz-Ertner et al [6]	2007	67	^{12}C	70% at 5 years

FSRT, fractionated stereotactic radiotherapy.

BAŞLAYAN ÇALIŞMALAR



- BMC Cancer. 2010 Nov 5;10:606.

Randomised trial of proton vs. carbon ion radiation therapy in patients with low and intermediate grade chondrosarcoma of the skull base, clinical phase III study.

Nikoghosyan AV, Rauch G, Münter MW, Jensen AD, Combs SE, Kieser M, Debus J.

Dept of Clinical Radiology, University of Heidelberg, Germany.

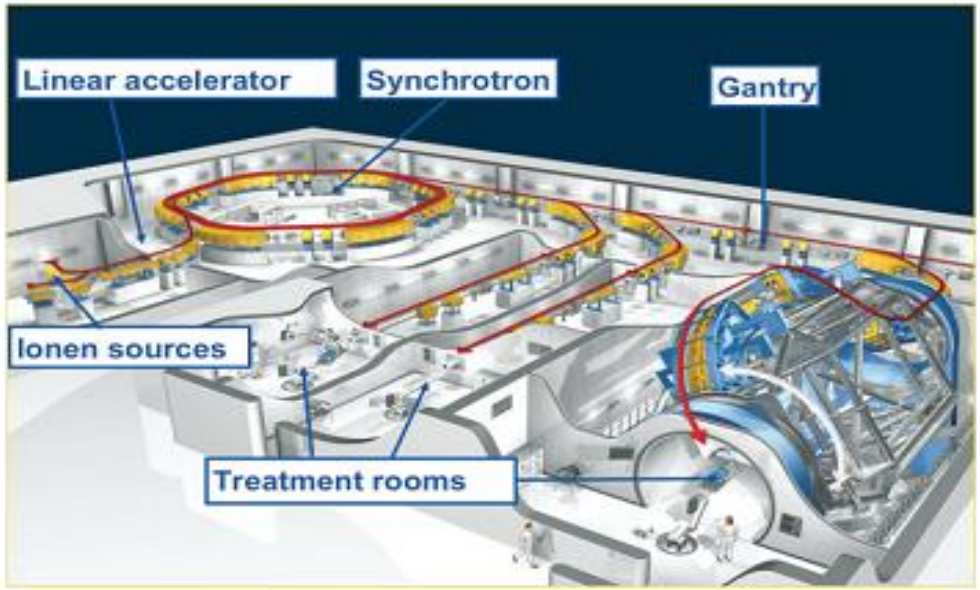


Figure 1. The Heidelberg Heavy Ion Centre facility, Germany (copyright Stern).

RT ILE 2. MALIGNITE RISKI :

- Phys Med Biol. 2012 Oct

Assessment of radiation-induced second cancer risks in proton therapy and IMRT for organs inside the primary radiation field.

Paganetti H (MGH)

- ✓ **Sarkom riski <%1.2**

- **İkinci malignite: %3-5**

Cancer. 2012 Mar 13. doi: 10.1002/cncr.27493. [Epub ahead of print]

Original Article

Late Effects of Chemotherapy and Radiotherapy in Osteosarcoma and Ewing Sarcoma Patients

The Italian Sarcoma Group Experience (1983-2006)

Alessandra Longhi, MD[1]; Stefano Ferrari, MD[1]; Angela Tamburini, MD[2]; Roberto Luksch, MD[3]; Franca Fagioli, MD[4]; Gaetano Bacci, MD[1]; and Cristina Ferrari, BA[1]

BACKGROUND: Patients with osteosarcoma and Ewing sarcoma have achieved longer survival over the past decades, but late side effects of chemotherapy and radiotherapy have become important concerns. **METHODS:** The authors reviewed all patients with localized osteosarcoma or Ewing sarcoma who had been enrolled in the Italian Sarcoma Group neoadjuvant protocols from 1983 through 2006. Data were updated in December 2010 to determine 3 endpoints: the incidence of a secondary primary cancer (designated as "second malignant neoplasm" [SMN]), infertility, and cardiotoxicity. **RESULTS:** Data were available on 883 patients with osteosarcoma and 543 patients with Ewing sarcoma. In the osteosarcoma group, there were 39 SMNs (4.4%) in 36 patients; in the Ewing sarcoma group, 15 patients (2.8%) experienced a single SMN each. The cumulative 10-year and 20-year incidence of an SMN (±standard error) was 4.9% ± 0.9% and 6.1% ± 1.2%, respectively, in the osteosarcoma group and 3.4% ± 0.9% and 4.7% ± 1.6%, respectively, in the Ewing sarcoma group. The most common SMN in the osteosarcoma group was breast cancer (n = 11), and the most common SMN in the Ewing sarcoma group was radiotherapy-induced osteosarcoma (n = 6). After 20 years, the risk of developing an SMN increased, whereas the risk of a recurrence of the primary tumor decreased. Permanent sterility was more common in males than in females. Doxorubicin cardiotoxicity occurred in 18 patients with osteosarcoma (2%) and in 7 patients with Ewing sarcoma (1.3%). **CONCLUSIONS:** The awareness of late side effects in long-term survivors of primary bone cancers should encourage longer follow-up. *Cancer* 2012;000:000–000. © *2012 American Cancer Society.*

RETROPERITONEAL YDS-RT

- **YDS'nın %10-15% i.**
- **<%70 komplet cerrahi rezeksiyon. (+) CS →yüksek LR, düşük GS.**
- **GTR (R0 , R1) ile ~50% LR!...(Uzun takip ile %95 !).**
- **Nükslerin çoğu LOKAL → RT'nin artan rolü (retospektif , tek merkezli veriler):**
  Cerrahi ile 5-y LK <%50 vs +RT ile>50%
- **Pre-op RT daha iyi (vs post-op RT) : iyi tümör lokalizasyonu, daha küçük RT volümü, potansiyal radyobiyolojik avantaj**
- **ACOSOG : Randomize çalışma pre-op RT:**

"A randomized trial of preoperative radiation plus surgery versus surgery alone for localized primary retroperitoneal soft tissue sarcoma"

SEER -2010: RETROPERITONEAL SARKOM: 2504 HST . 1901 (%75.9) LR HASTALIK. 1547 (%81.8) CERRAHI REZEKSIYON VE % 23.5 ILAVE RT.

The JAMA Network

From: **Surgery and Radiotherapy for Retroperitoneal and Abdominal Sarcoma: Both Necessary and Sufficient**

Arch Surg. 2010;145(5):426-431. doi:10.1001/archsurg.2010.70

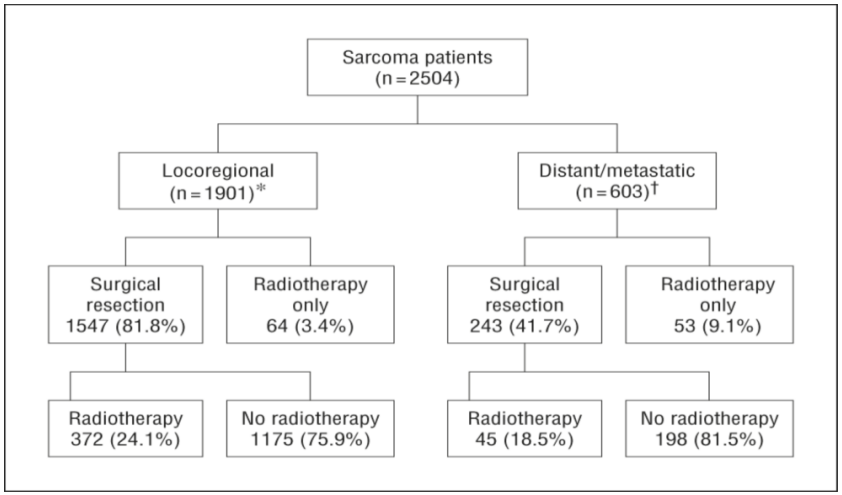
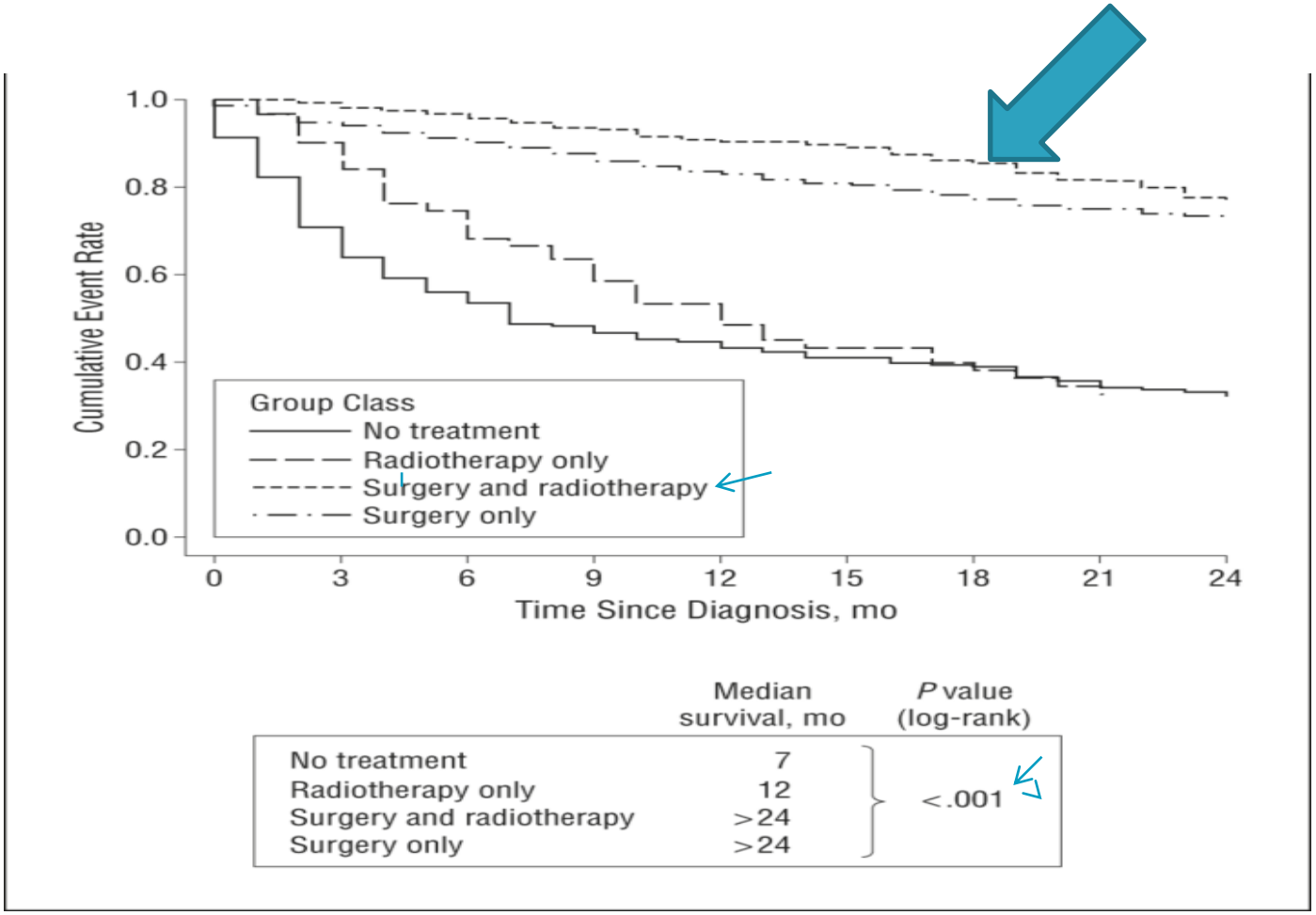


Figure Legend:

Patients with different disease stages and treatment received. *, Two hundred fifty seven patients had no treatment and 33 had missing resection data; †, 287 patients had no treatment and 20 had missing resection data.

SEER: SURGERY AND RADIOTHERAPY FOR RETROPERITONEAL AND ABDOMINAL SARCOMA: BOTH NECESSARY AND SUFFICIENT

ZHENG ZHOU, *ARCH SURG*. 2010



	Median survival, mo	*P* value (log-rank)
No treatment	7	<.001
Radiotherapy only	12	
Surgery and radiotherapy	>24	
Surgery only	>24	

SISTEMATIK REVIEW-2011: RT'NIN RETROPERITONEAL YDS'DA YERI.

Cancer. 2011 Oct 1;117(19):4355-64.

Radiotherapy and surgery-an indispensable duo in the treatment of retroperitoneal sarcoma.

Van De Voorde L, Department of Radiation Oncology, Ghent University Hospital, Ghent, Belgium.

Abstract

- ''..to designate the role that radiotherapy (RT) might play in the treatment of retroperitoneal sarcomas. ..... Furthermore**, this was a call for surgeons to talk to radiation oncologists before performing surgery.** The 2 objectives of this review were: **1) to determine the benefit of RT** in terms of local control and/or survival in the treatment of retroperitoneal sarcomas and 2**) to discover the optimal timing of RT i**n the treatment sequence. ''
- **reviewed a total of 1426 patients.** The **5-year LCR** varied from **27% to 62%,..** The **5-year OS** rate ranged from **12% to 90%, a**nd **complete resection and tumor grade were the most important prognostic** factors in most studies. This review resulted in 7 recommendations concerning the use of RT in the treatment of retroperitoneal sarcoma.
-

- The authors concluded that there is good evidence from multiple single-institutions studies that **RT improves the LCR** in patients with retroperitoneal sarcoma. Until now, there has not been a translation of this approach into survival benefit. The current results indicated that **preoperative external-beam RT followed by radical surgery seems to be the preferred sequence, and adding intraoperative RT is a safe procedure for dose escalation in the upper abdomen.**

RT'NIN RETROPERITONEAL YDS'DA YERI.

- BMC Cancer. 2012 Jul 12;12:287. **(çalışma duyurusu)**

A clinical phase I/II trial to investigate preoperative dose-escalated intensity-modulated radiation therapy (IMRT) and intraoperative radiation therapy (IORT) in patients with retroperitoneal soft tissue sarcoma.

Roeder F, Clinical Cooperation Unit Radiation Oncology, German Cancer Research Center

- **Retrospekif Çl.:**

Ann Oncol. **2013** Mar;24(3):832-7.

Should adjuvant radiotherapy be administered in addition to front-line aggressive surgery (FAS) in patients with primary retroperitoneal sarcoma?

Le Péchoux Gustave-Roussy, France

1994 -008, **110 RPS: N=62 yalnız cerrahi (gr S); 48'i C+ PORT (gr S + R).** Konformal PORT (%81%), 50 Gy.

SONUÇ: 5 y, S vs S + R grup, LR %36% vs % 22 (NS);

RFS % 47 vs %60% (P = 0.02), GS % 77 vs % 71 (NS).

Adjuvant konformal (FAS) RT randomize çalışma ile ele alınmalı.

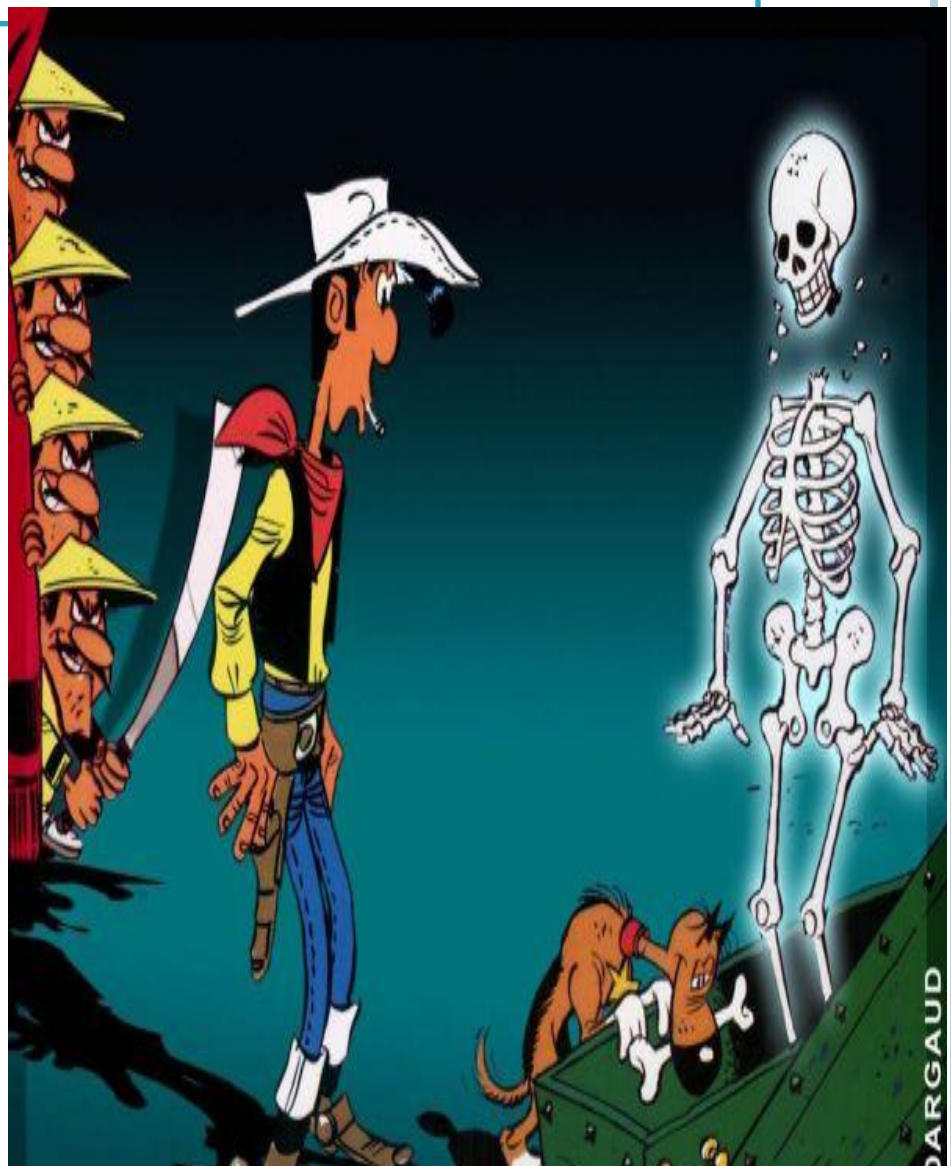
KEMIK SARKOMUNDA RT: SINIRLI ROL!

Ewing sarkomunda RT:
yakın CS, kötü histolojik cevapta

Osteosarkomda: temel tedavi C+KT.

RT:
cerrahiyi yapılmıyorsa, CS(+), yada palyasyonda

BONE SARCOMAS: A LIMITED ROLE FOR RADIATION
(lawrence 2010)



ÇALIŞMALAR -SARKOM

Sarcoma: RTOG OPEN TRIALS

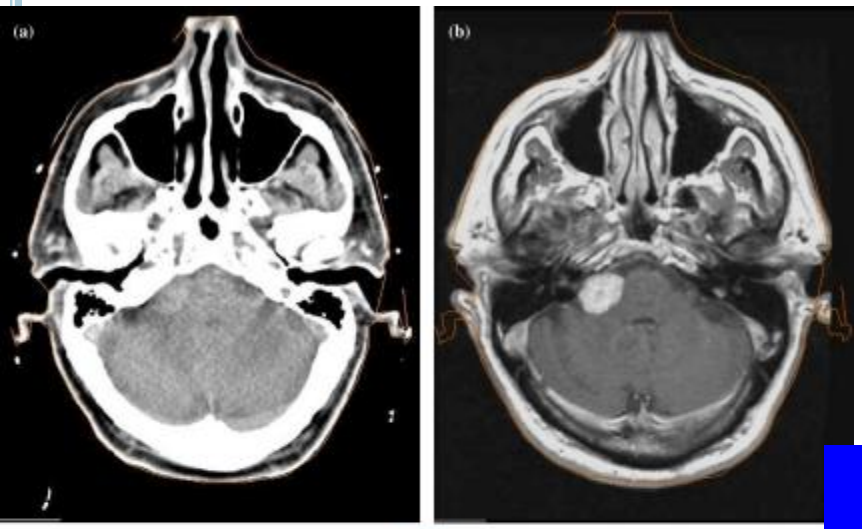
Number	*Title*
06-30 [2]	A Phase II Trial of Image Guided Preoperative Radiotherapy for Primary Soft Tissue Sarcomas of the Extremity

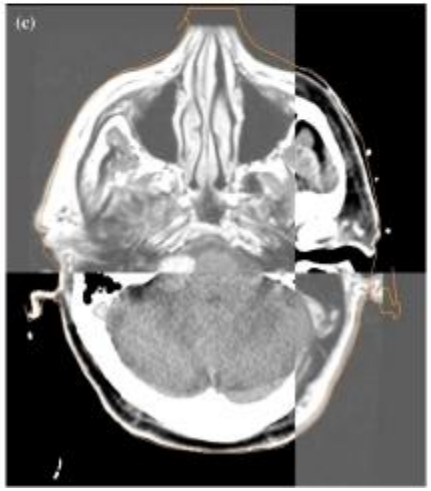
Sarcoma: RTOG CLOSED TRIALS

Number	*Title*	*Publication*
03-30 [3]	Phase II Pilot Study of Pre-Operative Thalidomide With Radiotherapy Alone in Patients With Low-Grade Primary Soft Tissue Sarcoma or With Radiotherapy and Doxorubicin, Ifosfamide, and Dacarbazine in Patients With High- or Intermediate-Grade Primary Soft Tissue Sarcoma of the Extremity or Body Wall	
01-32 [4]	Phase II Study of Neoadjuvant and Adjuvant Imatinib Mesylate in Patients With Primary or Recurrent Potentially Resectable Malignant Gastrointestinal Stromal Tumor	PMID 18942073
95-14 [1]	A Phase II Study of Neoadjuvant Chemotherapy and Radiation therapy in the Management of High-Risk, High-Grade, Soft Tissue Sarcomas of the Extremities and Body Wall	PMID 16446334
84-11 [5]	Phase III Randomized Comparison of Radiotherapy plus Hyperthermia vs Radiotherapy Alone in the Treatment of Patients with Head and Neck Carcinoma, Breast Cancer, or Soft Tissue Sarcoma Amenable to Potentially Curable Radiotherapy	

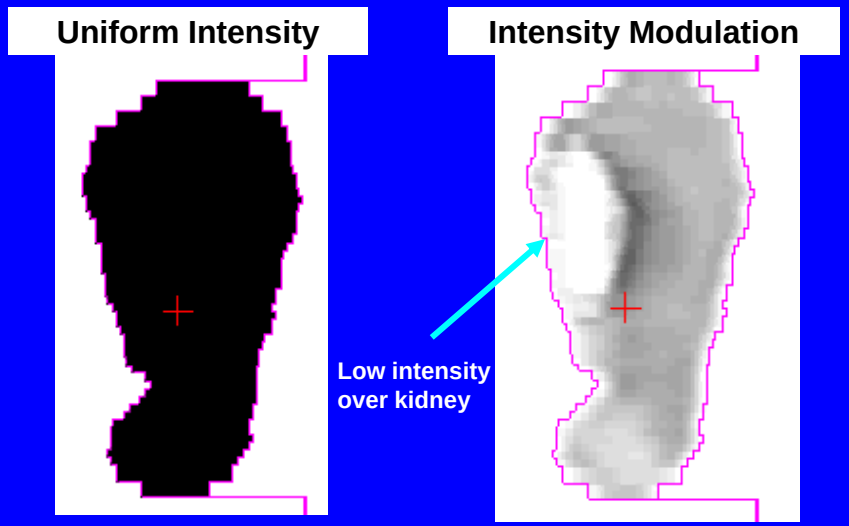
Sağlıklı, barış ve huzur dolu günler dileğiyle.....

TEŞEKKÜRLER.....





Conventional RT vs. IMRT



53. ASTRO

238 Quantitative Dosimetric Analysis of Patterns of Local Relapse after Adjuvant IMRT for Primary Extremity Sarcoma

K. M. Alektiar S. L. Berry

Memorial Sloan-Kettering Cancer Center, New York, NY

Purpose/Objective(s): To determine the failure patterns in patients with extremity STS treated with adjuvant IMRT using a quantitative method to calculate the dose received by the MRI-defined recurrence volume.

Materials/Methods: Between 2/2002 and 5/2008, 104 patients with primary non-metastatic STS of the extremity were treated with limb-sparing surgery and adjuvant IMRT. Preoperative IMRT to a median dose of 50 Gy was given to 17 (16%) patients and postoperatively to a median dose of 63 Gy to 87 (84%) patients. Age was >50 years in 69 (66%), tumors were deep in 96 (92%), size was >10 cm in 46 (44%), site was lower extremity in 75 (72%), and margin was positive or close (>1 mm) in 49 (47%). The MRI images obtained at the time of LR were fused with the original CT simulation dataset in order to determine the dose received by the recurrent tumor volumes during the course of the adjuvant IMRT.

Results: After delineation of recurrent tumor volume (*Vrecur*) from the fused MRI images was completed, dose volume histograms (DVH) were generated to calculate the dose received by the *Vrecur*. LR was divided into 3 categories relative to the D95%. It was central if ≥95% of the *Vrecur* was within the D95%, marginal if the *Vrecur* crossed the D95%, and distant if *Vrecur* was completely outside D95%. With a median follow-up of 40 months, 8/104 (8%) developed local recurrence. Of the 8 LR, 3 were central, 5 were marginal, and none were distant. Of the 5 marginal LRs, the *Vrecur* received 93% of prescription dose in 3 cases, 71% in 1, and 0.02% in 1. Median time to central LR was 17 months (range, 13-28), which didn't differ from that for marginal LR (median 16 months; range, 13-27). The overall 5-year actuarial rate for LR was 9% (95% CI, 3-15). The 5-year rate for central LR was 3% (95% CI, 0-7) and for marginal LR was 6% (95% CI, 1-10). On multivariate analysis, the only independent predictor of LR for the whole cohort was tumor size >10 cm (RR: 1.8; $p = 0.037$).

Conclusions: Based on this analysis a 3% rate of central recurrence at 5 years is unlikely to be altered by any modification in IMRT techniques. In contrast, when dealing with some of the marginal recurrences, perhaps there still some room for improvement in IMRT, especially for patients with large tumors.

Author Disclosure: K.M. Alektiar: None. S.L. Berry: None.

Int J Radiat Oncol Biol Phys. 2012 Mar 15;82(4):1528-34.

The relationship between local recurrence and radiotherapy treatment volume for soft tissue sarcomas treated with external beam radiotherapy and function preservation surgery.

Dickie CI, Griffin AM, Parent AL, Chung PW, Catton CN, Svensson J, Ferguson PC, Wunder JS, Bell RS, Sharpe
O'Sullivan B.SourceRadiation Medicine Program, Princess Margaret Hospital, Toronto**, Canada**.

Optimal RT volum IG-RT ile mümkün: marjinal relapslar düşük

PURPOSE: To examine the geometric relationship between local recurrence (LR) and external beam radiotherapy (RT) volumes for soft-tissue sarcoma (STS) patients treated with function-preserving surgery and RT.

METHODS AND MATERIALS: Sixty of 768 (7.8%) STS patients treated with combined therapy within our institution from 1990 through 2006 developed an **LR**. Thirty-two received preoperative RT, 16 postoperative RT, and 12 preoperative RT plus a postoperative boost. Treatment records, RT simulation images, and diagnostic MRI/CT data sets of the original and LR disease were retrospectively compared. For LR location analysis, three RT target volumes were defined according to the International Commission on Radiation Units and Measurements 29 as follows: (1) the gross tumor or operative bed; (2) the treatment volume **(TV) extending 5 cm longitudinally beyond the tumor or operative bed unless protected by intact barriers to spread and at least 1-2 cm axially** (the TV was enclosed by the isodose curve representing the prescribed target absorbed dose [TAD] and accounted for target/patient setup uncertainty and beam characteristics), and (3) the irradiated volume (IRV) that received at least 50% of the TAD, including the TV. LRs were categorized as developing in field within the TV, marginal (on the edge of the IRV), and out of field (occurring outside of the IRV).

RESULTS: Forty-nine tumors relapsed in field (6.4% overall). Nine were out of field (1.1% overall), and 2 were marginal (0.3% overall).

CONCLUSIONS: **The majority of STS tumors recur in field, indicating that the incidence of LR may be affected more by differences in biologic and molecular characteristics rather than aberrations in RT dose or target volume coverage.** In contrast, only two patients relapsed at the IRV boundary, suggesting that the risk of **a marginal relapse is low when** the TV is appropriately defined. **These data support the accurate delivery of optimal RT volumes in the most precise way using advanced technology and image guidance.**

O'SULLIVAN ET AL;
FIVE YEAR RESULTS OF RANDOMISED PHASE III TRIAL OF PRE-OP VS. POST-OP RADIOTHERAPY IN EXTREMITY STS; JCO 2004;

Primer sonlanım major yara komplikasyonu!

N=190 hasta(94 pre-op/96 post-op); 5yıllık LK %93 v %92, metastasız sağkalım %67% v %69, rekürrenssiz sağkalım; %58 v %59, genel sağkalım %73 v %67.

Pre-op ve post-op RT etkisi benzer. Normal doku toksisitesi farklı, anatomik lokalizasyonu dikkate almayı gerektirir.

3-years; 2002— "Preoperative versus postoperative radiotherapy in soft-tissue sarcoma of the limbs: a randomised trial." (O'Sullivan B, Lancet. 2002 Jun 29;359(9325):2235-41.) Median F/U 3.3 y :

Yara komplikasyonu: preop RT %35 vs. postop RT %17 (SS); üst bacak↑ **(45% vs. 28%). Preop RT ile non-primer yara kapanması**↑ LR, LRR, DMR(NS). **GS >2.5 y preop grup↑ (fakat çalışma dizaynı ilgili değil!)**

RT alanı, medyan: **preop 333 cm2 vs. postop 416 cm2 (SS)**

Sonuç: Normal doku toksisitesi farklı, anatomik lokalizasyonu dikkate almayı gerektirir.

5-years; 2004 - "Five-year results of a randomized phase III trial of pre-operative vs post-operative radiotherapy in extremity soft tissue sarcoma." (O'Sullivan B, Journal of Clinical Oncology, 2004 ASCO Annual Meeting Proceedings (Medyan F/U 6.9 y

5-year LK preop RT %93 vs. postop RT %92 (NS), RFS %58 vs. %59 (NS), GS 73% vs. 67% **(NS).** Prediktör faktörler: CS+ ~ **LC, çap ve grad ~ RFS vs GS**

:Pre-op ve post-op RT etkisi benzer. Normal doku toksisitesi farklı

Late effects; 2005, — "Late radiation morbidity following randomization to preoperative versus postoperative radiotherapy in extremity soft tissue sarcoma." (Davis AM, Radiother Oncol. 2005.

Post-op RT ile fibrosis ↑, **ödem** ve eklem kısıtlılığı ↑ **(NS olmasına karşın). Geniş RTsahası~fibrozis ve eklem kısıtlılığı**

Sonuç: Postop RT de hasta fonksiyonunu olumsuz etkileyen fibroziz eğilimi↑

International Journal of Radiation Oncology biology • physics
www.redjournal.org

Critical Review

Radiotherapy for Management of Extremity Soft Tissue Sarcomas: Why, When, and Where?

Rick L.M. Haas, MD, PhD,* Thomas F. DeLaney, MD, PhD,† Brian O'Sullivan, MD, PhD,‡

Is 4 cm longitudinal expansion of surgically manipulated tissues always necessary for postoperative elective CTV?

We are not aware of compelling data in support of the traditional expansion of the CTV beyond the surgical bed with a 4 cm margin craniocaudally, even in the case of an R0 resection. However, it is not known whether it is safe to reduce the expansion of the elective CTV to <4 cm if the surgical resection margins are negative (ie, an R0 resection), because of the possibility of tumor cells at distance from the dominant tumor mass (24). If the surgical resection margins are positive (ie, R1 resection), we strongly advise that re-excision should be performed whenever possible to achieve an R0 resection. In considering additional surgery, several aspects should be taken into account, including RT delay, early and late wound complications, functional outcome, and the normal tissues juxtaposed to the positive margin (eg, neurovascular bundles). If additional surgery is not possible, care should be taken to apply both wide CTV margins and a higher total radiation dose. It should be recognized that a difference in CTV margins between R0 and R1 resection scenarios has not been subjected to clinical trial