RABDOMYOSARKOM DIŞI YUMUŞAK DOKU SARKOMLARINDA RADYOTERAPİ

Dr Ayşe Hiçsönmez

ONKO Ankara Onkoloji Merkezi

07.05.2016

www.fppt.info


KOMPLET CERRAHİ REZEKSİYON
RT'den kim fayda görebilir?
Rezektabl hastalıkta kim nüks eder?
KÜRATİF TEDAVİ

- ✓ RT NRSTS'lerde multimodel tedaviler içinde önemli bir yeri vardır
- ✓ Ewing sarkom Rhabdomyosarkomların tersine inoperable yumuşak doku sarkomlarda tekbaşına RT kullanımı %25-30
- ✓ Çoğu bilgi erişkin çalışmalarından
- ✓ Standart yaklaşım

Yüksek dereceli sarkom

↓

Organ koruyucu cerrahi + RT

RDYDS; KİM RT'DEN FAYDA GÖRÜR?

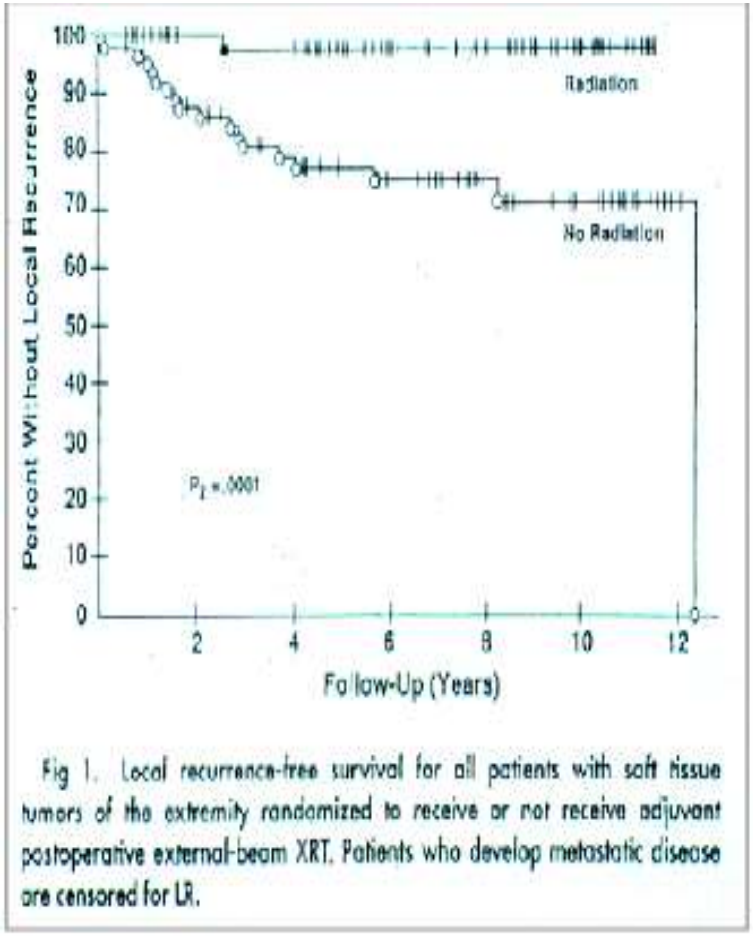


Fig 1. Local recurrence-free survival for all patients with soft tissue tumors of the extremity randomized to receive or not receive adjuvant postoperative external-beam XRT. Patients who develop metastatic disease are censored for LR.

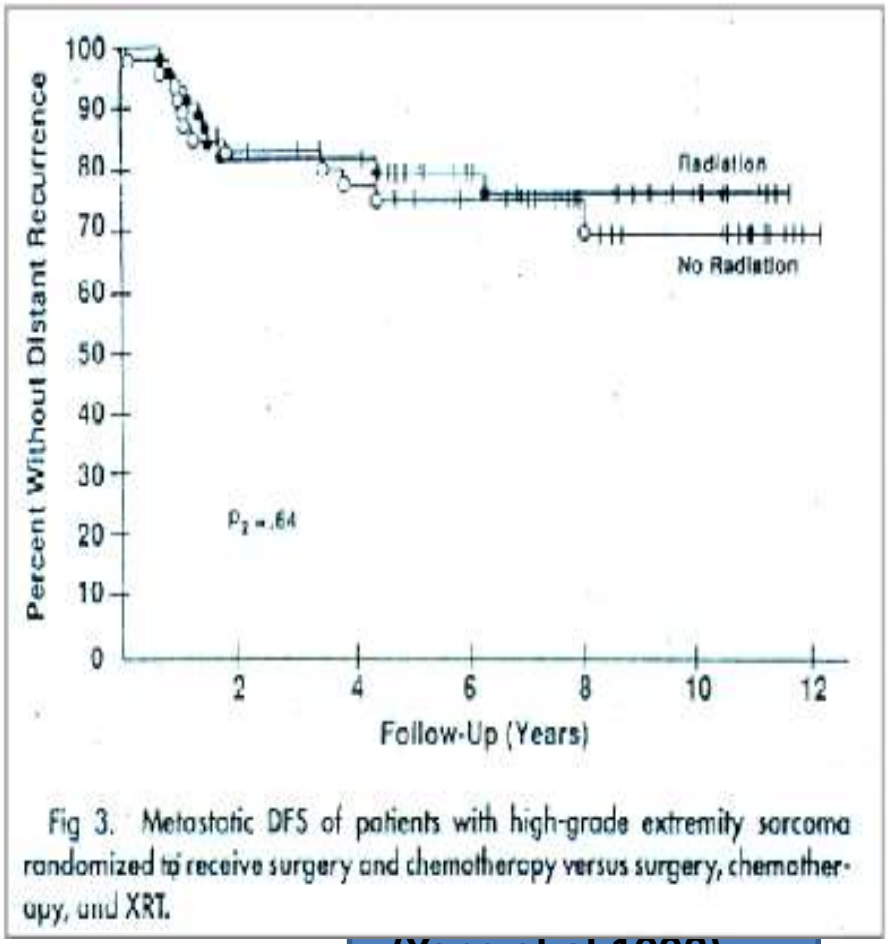


Fig 3. Metastatic DFS of patients with high-grade extremity sarcoma randomized to receive surgery and chemotherapy versus surgery, chemotherapy, and XRT.

(Yang et al.1998)

Pisters PWT, Long term results of a prospective randomized trial of adjuvant brachytherapy in soft tissue sarcoma. J Clin Oncol 1996

- 164 hasta randomizasyonda
- lokal kontrolun brakiterapi kolunda daha yüksek (p=0.04),
- uzak metastaz her iki kol arasında fark yok(p=0.60)

✓Yüksek dereceli < 5cm tümörlerde tekbaşına geniş cerrahi rezeksiyon iyi lokal kontrol

(Alektiar et al. 2002; Baldini et al. 1999)

✓Düşük derecelilerde RT tartışmalı

- ✓Birçok seride tek başına cerrahi ile sonuçlar iyi RT endikasyonu yok
- ✓Cerrahi sınır pozitifliği
- ✓> 5cm

(Baldini et al. 1999)

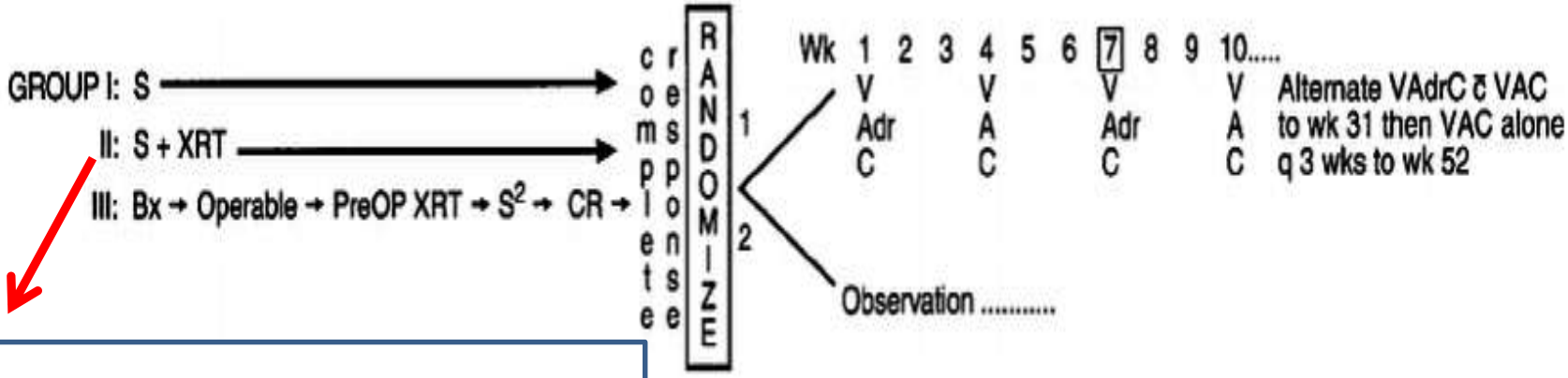
- ✓Snovyal sarkom RT'e daha sensitif olabilir
  - ✓KT cevabı iyi
  - ✓Maksimal cerrahi rezeksiyon istenir

- ✓Alveolar soft part sarkoma
  - ✓KT cevap yok
  - ✓RT sensitif

(Baldini et al. 1999)

POG 8653

Fig 1. Treatment schedule for POG protocol 8653. Abbreviations: S, surgery; XRT, radiotherapy; V, vincristine; ADR, doxorubicin; C, cyclophosphamide; A, dactinomycin.



<6 YAŞ 35 Gy + 10 Gy boost
> 6 YAŞ 45 Gy + 5 Gy boost

TABLE 12-5. *POG Protocol 8653: local control by surgical margins and radiotherapy*

		Low grade		High grade	
Surgery margins	IRS group	Surgery alone *n* (%)	Surgery + radiotherapy *n* (%)	Surgery alone *n* (%)	Surgery + radiotherapy *n* (%)
Marginal	II	2/2 (100%)	10/11 (91%)	1/4 (25%)	10/11 (91%)
Wide	I	18/18 (100%)	3/3 (100%)	14/16 (88%)	2/2 (100%)
				6/6 (100%)	No data

POG grade 3; 5 yıllık sağkalım%52 vs Grade 1-2 %92 GRADE

Modified from Marcus RJ. Current controversies in pediatric radiation oncology. *Orthop Clin North Am* 1996;27:551-557, with permission.

Toplam 8 hasta LR (%12.5)

4 retrospektif St Jude (1 002)

GROUP	GRADE	MARGIN	R		
I	LOW	<1C			-0,37
	HIGH			5 % 20 %	
II	A		S NO	DNG/21 DNG/19	P=0,001
I - II	ALL		E IVE	YES NO	DNG/31 : 3% DNG/16 : 16%	P=0,043

Yüksek grade
<1cm marjin
RT

S. L. Spunt, C. A. Poquette, Y. S.Hurt et al., "Prognostic factors for children and adolescents with surgically resected nonrhabdomyosarcoma soft tissue sarcoma: an analysis of 121 patients treated at St Jude Children's Research Hospital," *Journal of Clinical Oncology, vol. 17, no. 12, pp. 3697–3705, 1999.*

- 121 hasta
- 1969-1996
  - 81 hasta grup I
    - 61 hasta grup 1 >/=1cm
    - 20 hasta < 1cm
    - 10 hasta adj RT
    - LR için marjin ve RT etkisi yok
    - %60 grup 1 hasta low grade
  - Grup II 40 hasta
    - 21 hasta adj RT
    - 5 yıllık LR %12.8

- LR etkileyen faktörler
  - Rezidüel hastalık
  - Büyük tümör
  - İntraabdominal
  - RT lokal kontrolü iyileştiriyor

Grup I marjin genişliği önemli değil
Grup II RT LR azaltıyor

K. B. Smith, D. J. Indelicato, J. A. Knapik et al., “Adjuvant radiotherapy for pediatric and young adult nonrhabdomyosarcoma soft-tissue s… v…

Karşılaştırmalı değil !
Geniş negatif marjin RT’den yarar görecek hasta için önemli!
Çocuk yaş grubunda 1 cm marjin zor olabilir!
Özelikle bazı lokalizasyonlarda
Daha az marjin kabuledilebilir
COG çalışması 0.5 marjin test ediliyor

- (-) marjin LR %6
- (+) marjin LR %27

- Grade ile LR arası ilişki görülmemiş

ADJUVANT RT İÇİN PROGNOSTİK FAKTÖRLER

- Histolojik grade

Table 3. Fédération Nationale des Centres de Lutte Contre le Cancer Grading System

Tumor differentiation	
Score 1	Sarcomas closely resembling normal adult mesenchymal tissue (eg, well-differentiated liposarcoma)
Score 2	Sarcomas for which histologic typing is certain (eg, myxoid liposarcoma)
Score 3	Embryonal and undifferentiated sarcomas, sarcomas of doubtful type, synovial sarcomas
Mitotic count	
Score 1	0-9 mitoses per 10 HPF
Score 2	10-19 mitoses per 10 HPF
Score 3	≥20 mitoses per 10 HPF
Tumor necrosis	
Score 0	No necrosis
Score 1	<50% tumor necrosis
Score 2	≥50% tumor necrosis
Histologic grade	
Grade 1	Total score 2, 3
Grade 2	Total score 4, 5
Grade 3	Total score 6, 7, 8

Table 2. Pediatric Oncology Group Grading System[a]

Grade 1
- Myxoid and well-differentiated liposarcoma
- Well-differentiated or infantile (≤4 years old) fibrosarcoma
- Well-differentiated or infantile (≤4 years old) hemangiopericytoma
- Well-differentiated malignant peripheral nerve sheath tumor
- Angiomatoid malignant fibrous histiocytoma[b]
- Deep-seated dermatofibrosarcoma protuberans[b]
- Myxoid chondrosarcoma

Grade 2
- ≤15% of the surface area shows necrosis
- The mitotic count is <5 mitotic figures per 10 high-power fields using a ×40 objective
- Nuclear atypia is not marked
- The tumor is not markedly cellular

Grade 3
- Pleomorphic or round-cell liposarcoma
- Mesenchymal chondrosarcoma
- Extraskeletal osteogenic sarcoma
- Malignant triton tumor
- Alveolar soft part sarcoma
- Any other sarcoma not in grade 1 with >15% necrosis and/or ≥5 mitotic figures per10 high-power fields using a ×40 objective

S. L. Spunt, C. A. Poquette, Y. S.Hurt et al., "Prognostic factors for children and adolescents with surgically resected nonrhabdomyosarcoma soft tissue sarcoma: an analysis of 121 patients treated at St Jude Children's Research Hospital," *Journal of Clinical Oncology, vol. 17, no. 12, pp. 3697–3705, 1999.*

- POG grade 1-2 low grade
- POG 3 high grade
  - Grup 1-2 , grade 1-2 RT yok
  - Ölüm yok
  - Düşük grade tümörlerde uzak metastaz az
  - Düşük grade tümörlerde lokal rekürrensin sağkalım etkisi az
  - RT yok veya salvage
  - Nüksde reeksizyon + RT

M. L.Blakely, *Journal of Pediatric Surgery,*1999.

K. B. Smith, *International Journal of Radiation Oncology Biology Physics,*2011

M. F. Okcu *Journal of Clinical Oncology*, 2003.

T. M. Dantonello *Journal of Clinical Oncology*,2009.

- Yüksek grade lokal rekürrens ve uzak met riski yüksek
- yüksek grade +grup 2 RT ile lokal rekürrens düşük
- Lokal kontrol sağkalımı iyileştiriyormu??

M. F. Okcu, M. Munsell, J. Treuner et al., “Synovial sarcoma of childhood and adolescence: a multicenter, multivariate analysis of outcome,” *Journal of Clinical Oncology, vol. 21, no.*8, pp. 1602–1611, 2003.

- Grup 1 high grade
  - Marjin
  - Tümör boyutu
  - İnvazif özellik
- İnvazif ve >5cm sonuçlar kötü
  - Grup 1-2, >5cm, invazif tümör EFS ve OS kötü
  - Univaryan analizde invazif tümör LR için risk faktörü
  - +RT LRFS 5 yılda %96 vs %87 etki yok

D. Orbach, H.McDowell, A. Rey, N. Bouvet, A. Kelsey, andM. C. Stevens, “Sparing strategy does not compromise prognosis in pediatric localized synovial sarcoma: experience of the International Society of pediatric oncology, malignant mesenchymal tumors (SIOP-MMT) Working Group,” *Pediatric Blood and Cancer, vol. 57, no. 7, pp. 1130–1136, 2011.*

- Lokalize snovyal sarkom RT’den kaçılabilir mi?
  - 3 prospektif çalışma 1984-2003
  - 21 IRS grup 1 hasta
  - Sadece 2 hasta 45 Gy RT alıyor
  - LR %15 (3 hasta RT almayan , hayatta)
  - 2 hasta (RT alan)
    - Metastaz ve Ex
  - 5 yıllık EFS grup I %69
- Komplet rezeke sinovyal sarkomda lokal nüks sonuçları kötü etkilemiyor

M. Carli, A. Ferrari, A. Mattke et al., “Pediatric malignant peripheral nerve sheath tumor: the Italian and German Soft Tissue Sarcoma Cooperative Group,” Journal of Clinical Oncology, vol. 23, no. 33, pp. 8422–8430, 2005.

- Malign periferik sinir kılıfı tümörleri
- LR , DM yüksek; OS kötü
- NF 1 ile birlikte ise prognoz kötü prognoz
- Grup I PFS %61; OS %82
  - %25 adj RT; LR %17
  - RT yok LR %36
- Grup II PFS %37; OS %62
  - RT ile LR %45 vs RT siz %68
- Komplet rezeke hastalıkta dahi lokal kontrol kritik problem

YAŞ

Yaş;
RT endikasyonu için bir faktör

- Küçük yaş iyi prognostik faktör
- Küçük düşük grade tümör daha az invazif
- Erken evre

- Büyük yaş
- Yüksek grade
- Daha invazif
- İleri evre

F. Okcu, M. Munsell, J. Treuner et al., “Synovial sarcoma of childhood and adolescence: a multicenter, multivariateanalysis of outcome,” *Journal of Clinical Oncology, vol. 21, no.* 8, pp. 1602–1611, 2003.

A. A. Hayes-Jordan, S. L. Spunt, C. A. Poquette et al., “Nonrhabdomyosarcoma soft tissue sarcomas in children: is age at diagnosis an important variable?” *Journal of Pediatric Surgery,* vol. 35, no. 6, pp. 948–954, 2000, discussion 953–944.

GRUP I

Paulino *(Pediatr Blood Cancer 04)*

	RT	Local control rate 2 y	Local control rate 5 y	comments
Low grade & T< 5 cm	No RT	100 %	100 %	No RT
Low grade & T > 5 cm or high grade	No RT	69 %	44 %	RT necessary
	RT 57 Gy	83 %	63 %	

GRUP II

- Paulino *(Pediatr Blood Cancer 04)*

	RT	Local control rate 2 y	Local control rate 5 y	comments
- Low grade - High grade & T< 5 cm	No RT	51 %	43 %	RT necessary
	RT 64 Gy	92 %	82 %	
High grade & T > 5 cm	No RT	47 %	16 %	
	RT 64 gy	81 %	55 %	

- Okcu- MDACC Study *(JCO 03)* and Ferrari – INT Milan *(cancer 04)*

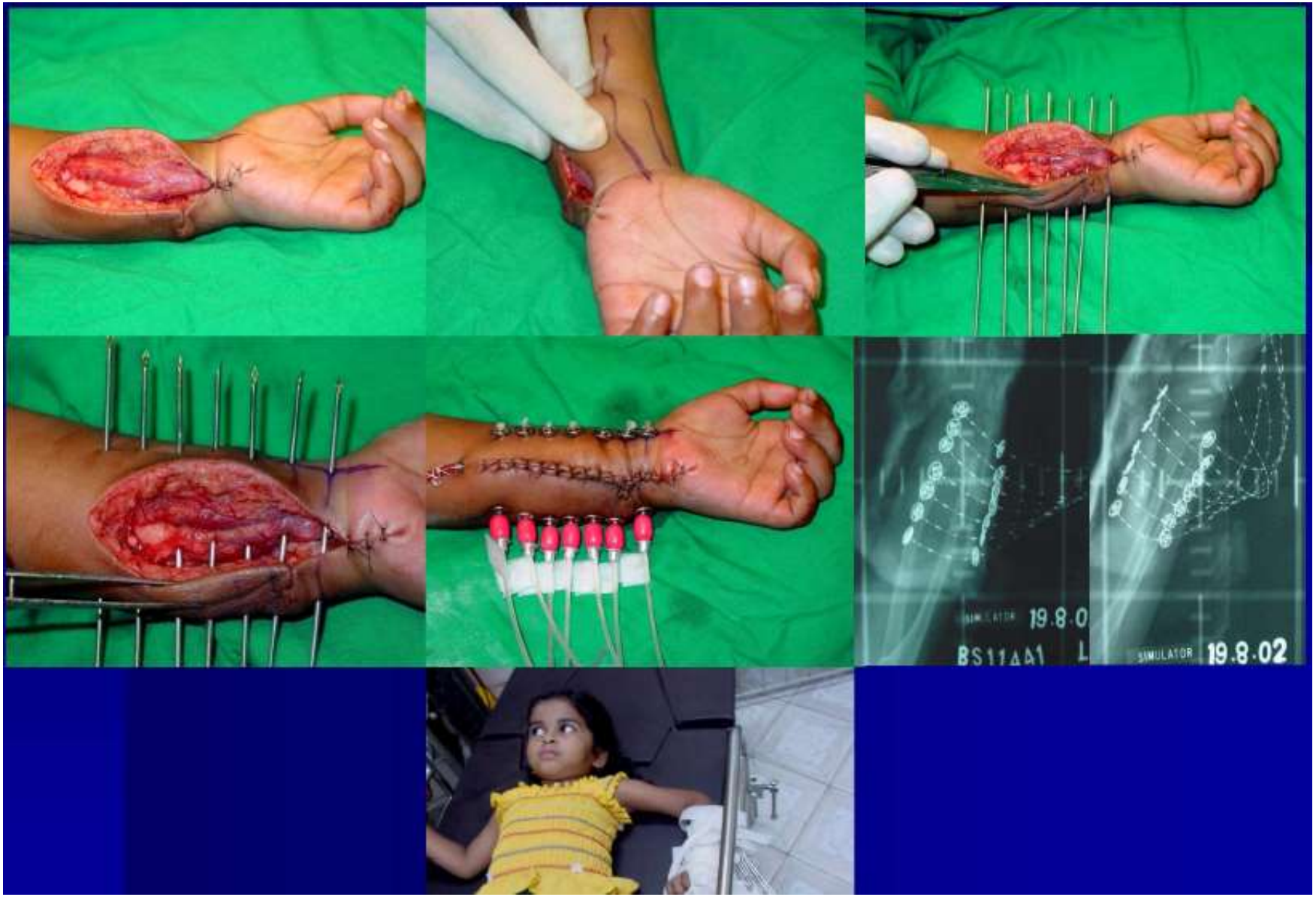
PREOP vs POSTOP

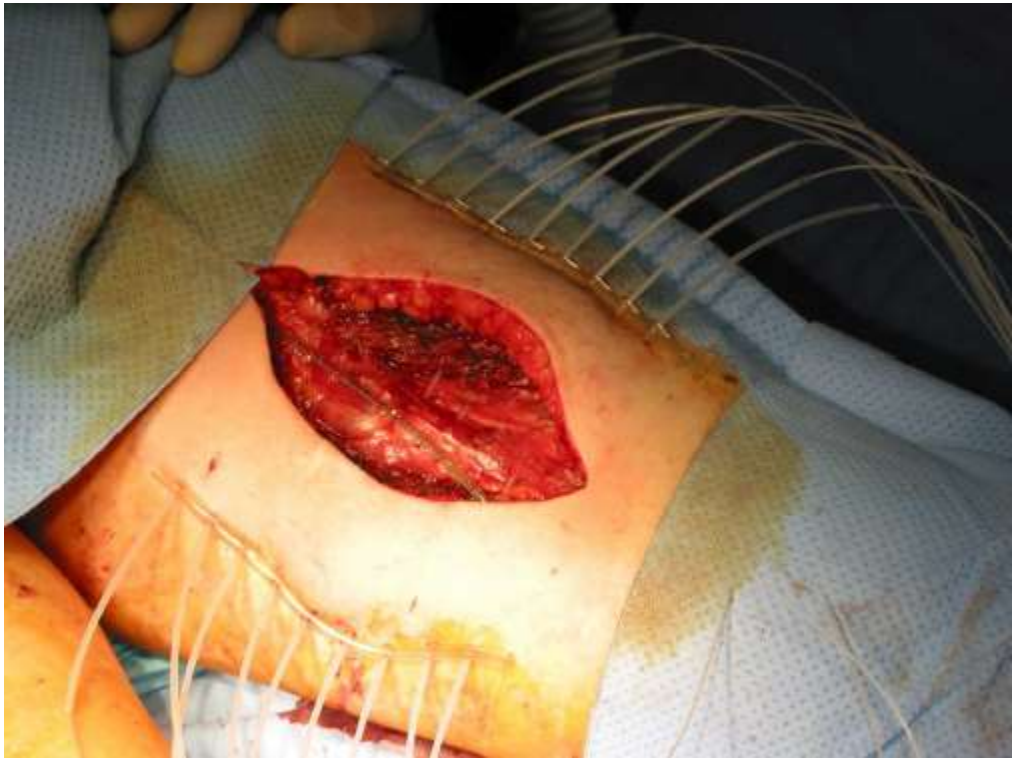
Center	No. of patients	% local failure
Postoperative Radiation		
MGH	176	14
MDAH	300	22
IGR 89	14	
RPMI	53	14
NCI 128	10	
Toronto	23	9
St Louis	35	14
Amsterdam	64	8
Penn / Fox Chase	67	13
Chicago	50	24
Preoperative Radiation		
MGH	181	10
MDAH	110	10
Toronto	39	3
Florida	58	9
Brachytherapy		
Memorial	55	18
Mayo	63	8
IA / IV Adriamycin + Radiation		
UCLA	371	~10
U. Virginia	55	2

BRAKİTERAPİ

Centre	Pts	Brachy	LCR%	tox
IGR	127	Ldr	81	22
Tata memorial	50	Ldr/hdr	82	
St jude	46	Ldr	86	26
University of california	8	Ldr	63	38
Mskcc	10	IO-HDr	80	20

Nag IJROBP 2001


19.8.0
SIMULATOR 19.8.02



DOZ

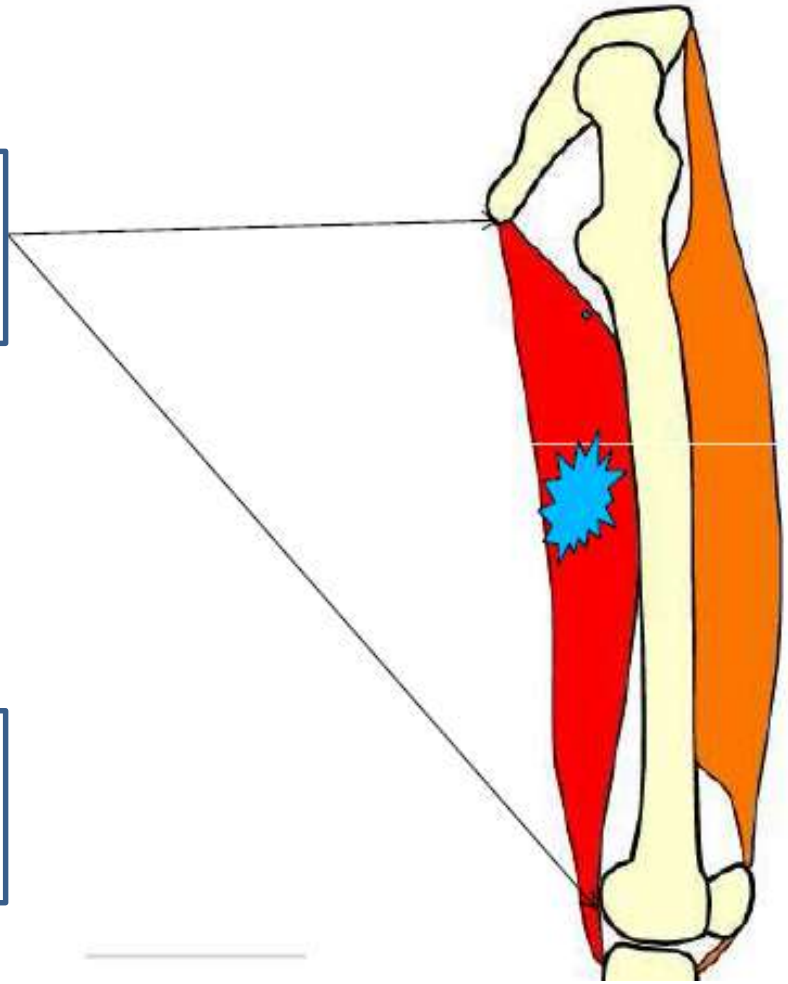
		IRS Gp I	IRS Gp II	IRS Gp III	comments
Paulino 04	1.8 Gy /d	54 Gy	64 Gy		
Cecchetto 00	HART 1.6 x 2/d		40 Gy HART		Less late effects?
CWS 86	1.8 Gy /d SynovialoS	54.4 Gy			Same Local Control Rate
CWS 91	1.8 Gy /d SynovialoS	48 Gy			
Trial IRS IV				54.4 HFRT vs 50.4 convent	Same LC and survival rate
EpSSG trial	1.8 Gy /d SynovialoS		50.4 Gy (T < 5 cm) 54 Gy (T > 5 cm)	50.4 if pre-op 54.4 to 59.5 Gy	(Current)

VOLÜM

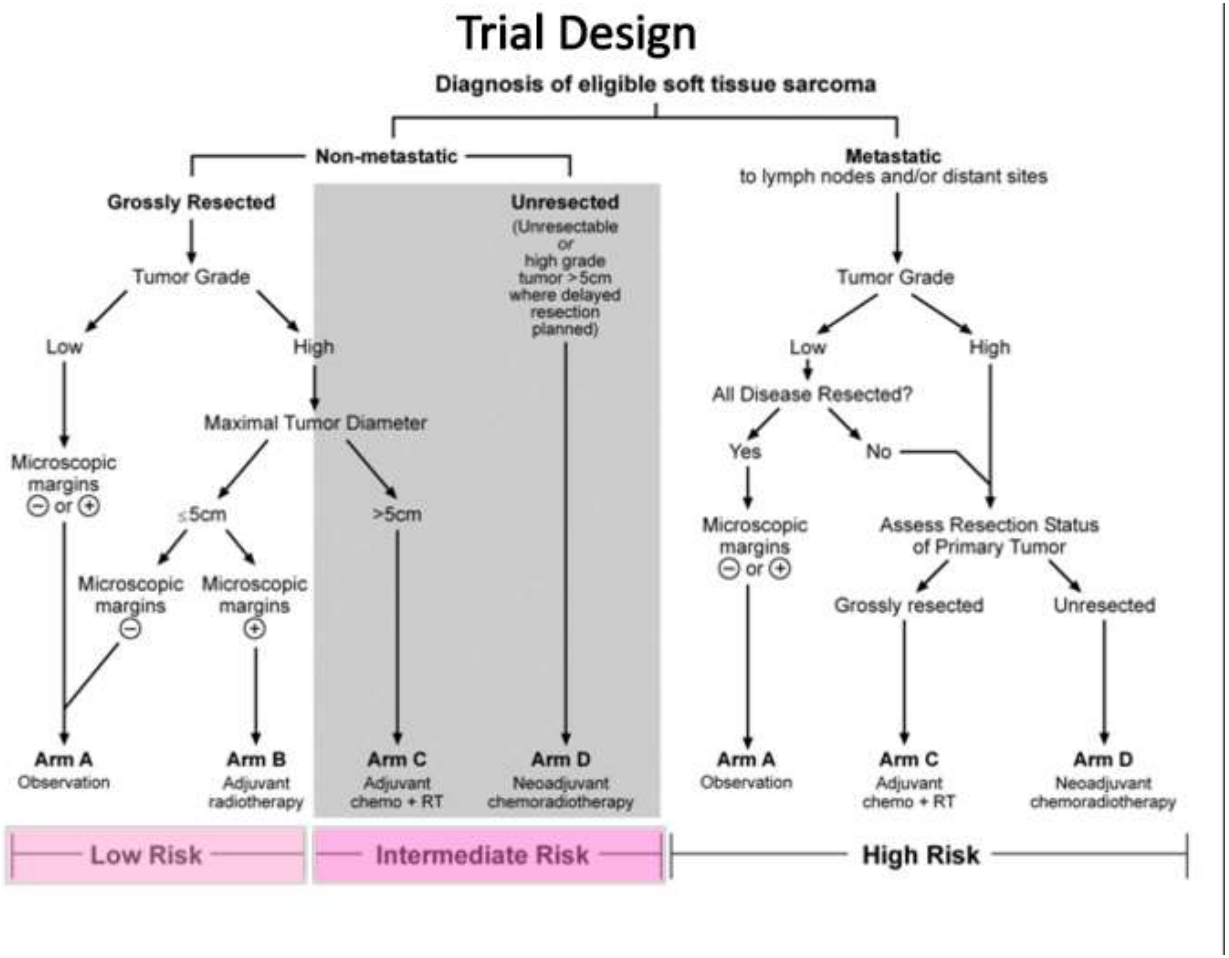
1970-1980 ekleme kadar
tüm kas kompartmanı

1990 5-10 cm marjin veya
kompartman

2000 4cm marjin

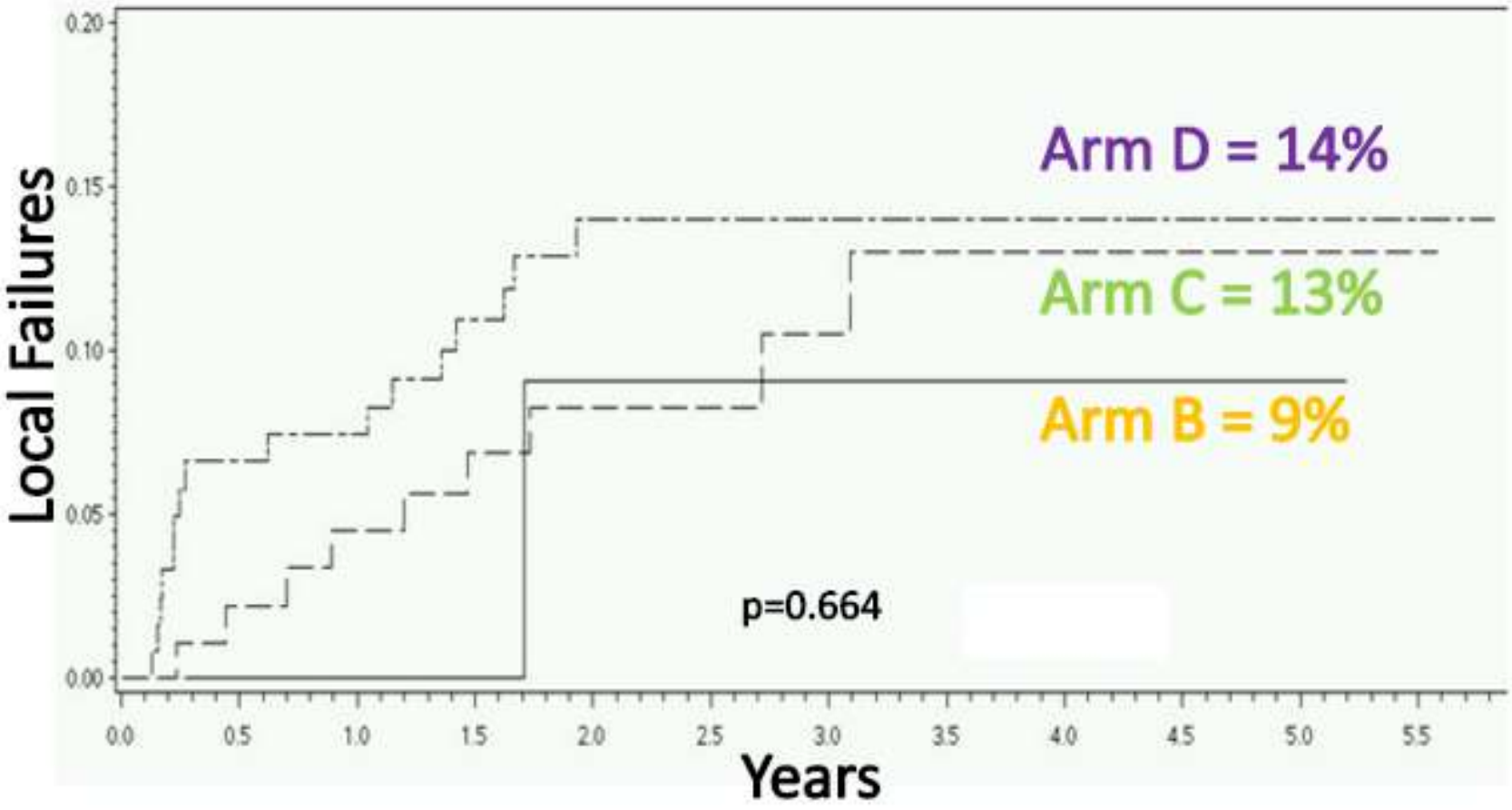


Risk-based treatment for nonrhabdomyosarcoma soft tissue sarcomas (NRSTS) in patients under 30 years of age: Children's Oncology Group study ARST0332



2014 ASCO Annual Meeting

Results: 4 yr Cumulative Incidence of Local Failure



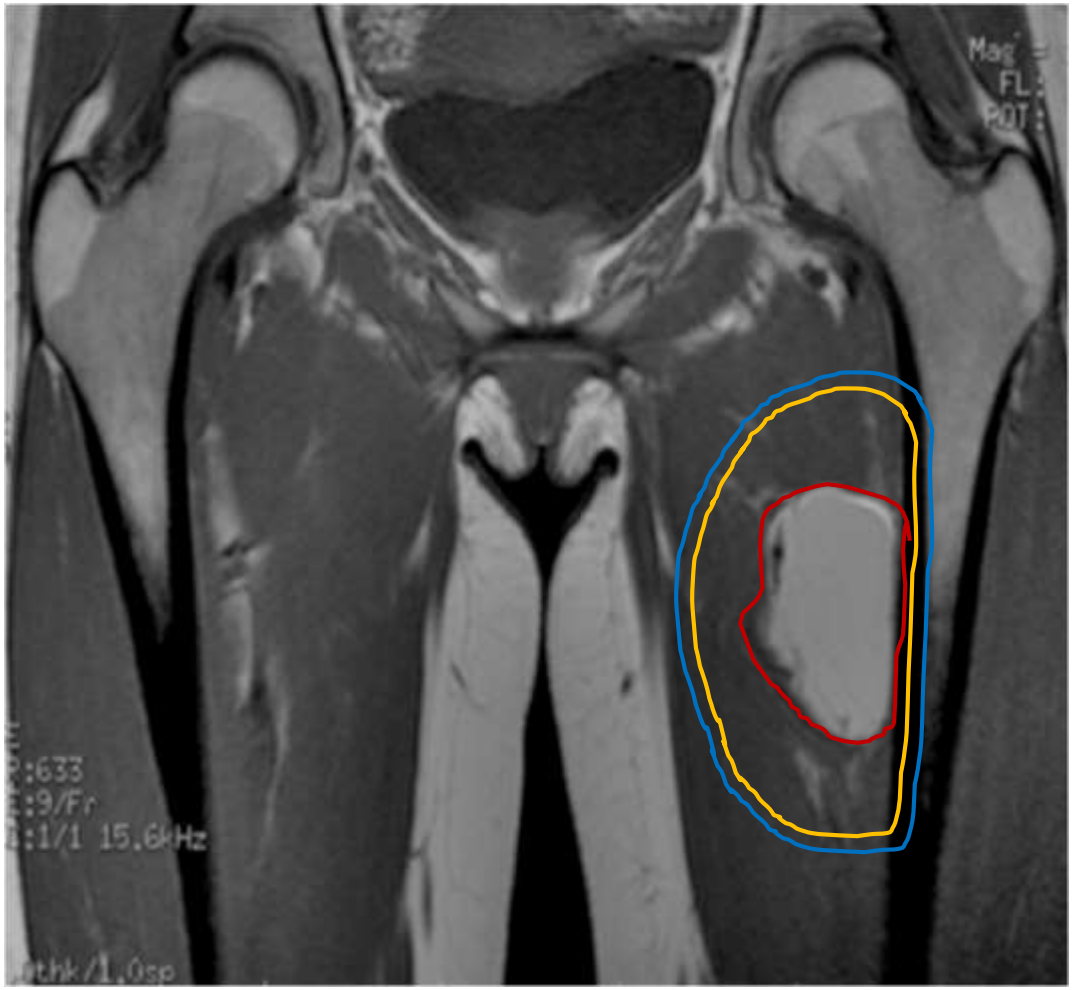
Results: Potential prognostic factors for LF (Cox model)

Prognostic factor	Categories	P-value
Age	0-14; 15+ years	.61
Sex	male; female	.08
Race	white; black; other	.17
Tumor characteristics		
Site	body wall; head and neck; lower extremity; upper extremity; viscera	.49
Type	SS; MPNST; ES liver; UDS; Unclassified; "other NRSTS"	.16
Size	<5; ≥ 5cm	.89
Depth	superficial; deep	.94
Invasiveness	non-invasive; invasive	.21
Status of surgical margins (arm B/C only)	negative; positive	.02

Radiation Therapy: Dose

	Total dose	PTV	PTV boost
Arm B: Post-operative RT Microscopic margin	55.8 Gy	45 Gy	10.8 Gy
Arm C: Post-operative RT Negative margin/or Microscopic margin	55.8 Gy	45 Gy	10.8 Gy
Arm D: Pre-operative RT Negative margin Microscopic margin Macroscopic margin	45 Gy 55.8 Gy 64.8 Gy	45 Gy 45 Gy 45 Gy	0 10.8 Gy (week 16) 19.8 Gy (week 16)

Radiation Therapy: Conformal Target Volumes



Gross tumor volume (GTV)

Clinical Target volume (CTV) = GTV + 1.5 cm

Planning Target Volume (PTV) = CTV + .5 cm

Conclusions

- Overall cumulative incidence of LF for non-metastatic high grade NRSTS: <15%

- Surgical margins status is predictive of LF for initially resected high grade NRSTS:
  - > 5cm; margin negative = 3% vs. microscopic positive = 29%
  - 55.8 Gy in combination with chemotherapy is effective for > 5cm margin negative tumors
  - The reasons for higher LF rate in >5 cm microscopic positive margin requires further analysis

- After neoadjuvant chemo/RT over 80% high grade NRSTS underwent surgical resection:
  - >90% had R0/R1 resection
  - Local failure rates are low regardless of margin status:

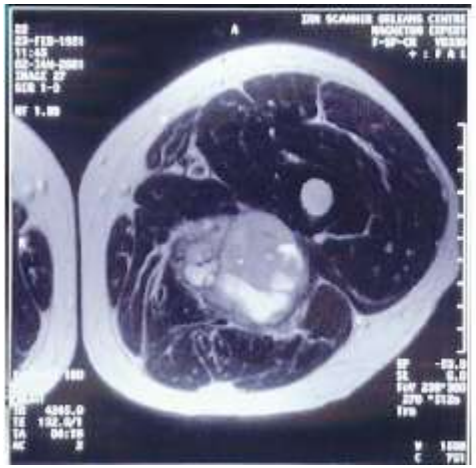
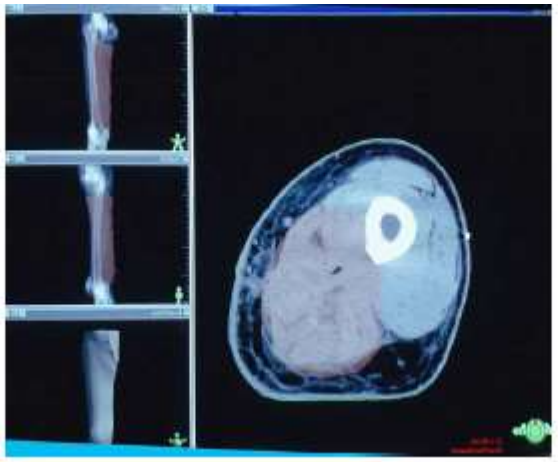
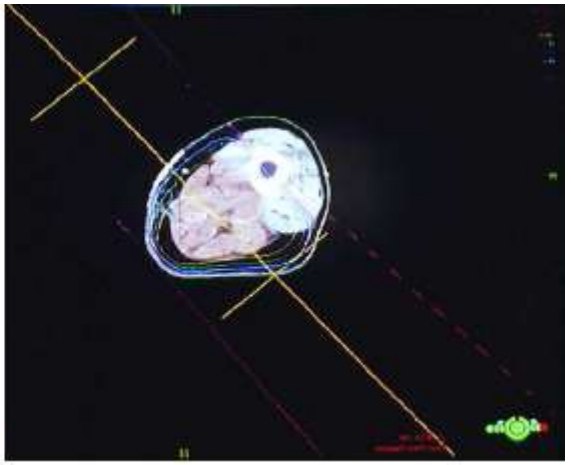
    negative = 3% vs microscopic positive = 7%
  - Lower dose (45 Gy) and PTV (2 cm) is effective in the neoadjuvant setting in combination with chemotherapy
  - Whether boost for microscopic positive margin (total dose 55.8 Gy) is necessary requires further analysis

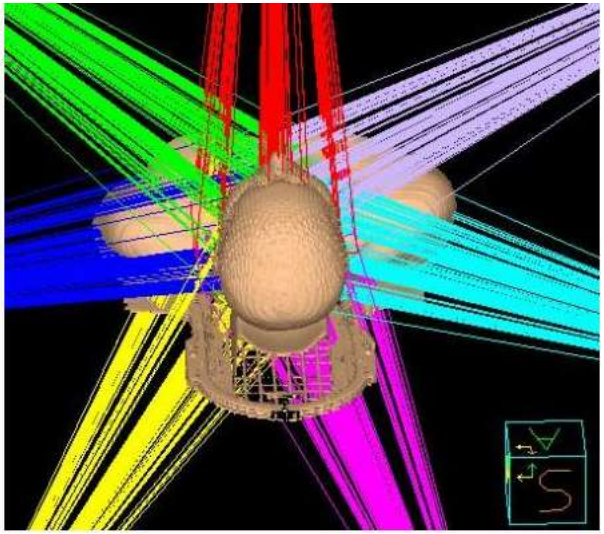
▪Stinson SF, Dellancy TF, Greenberg J, et al. Acute and long-term effects on limb function of combined modality limb sparing therapy for extremity soft tissue sarcoma. Int J Radiat Oncol Biol Phys 1991;21:1493–1499.

Bertucio CS, Wara WM, Matthay KK, et al. Functional and clinical outcomes of limb-sparing therapy for pediatric extremity sarcomas. Int J Radiat Oncol Biol Phys 2001;49(3):763–769.

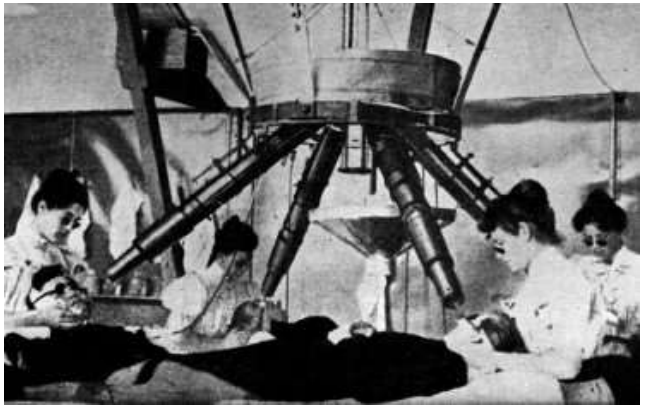
- ✓ Ekstremite koruyucu + RT
- ✓ Uzun dönem komplikasyonlar
  - ✓ Kontraktür
  - ✓ Ödem
  - ✓ Hareket kısıtlılığı
  - ✓ Kas kaybı

- Eklemin >%50'inden fazlası tedavi alanına girmesin
- 63 Gy/1.8Gy geçme
- Ekstremite çevresinin >%75 alma



SONUÇ



- RT
  - Rezeke hastalarda
    - Negatif marjin genişliğine,
    - Histolojik grade,
    - Tümör boyutuna,
    - İnvazyon özelliğine
    - Histolojik subtipe,
    - Genetik duruma

- RT DOZ
  - Yaş,
  - Subklinik hastalık genişliği
  - İnvazyon özelliği
  - Histoloji
  - Boyut

Sınırlı Alan RT

TEŞEKKÜRLER