HITRI plus
Heavy Ion Therapy Research Integration

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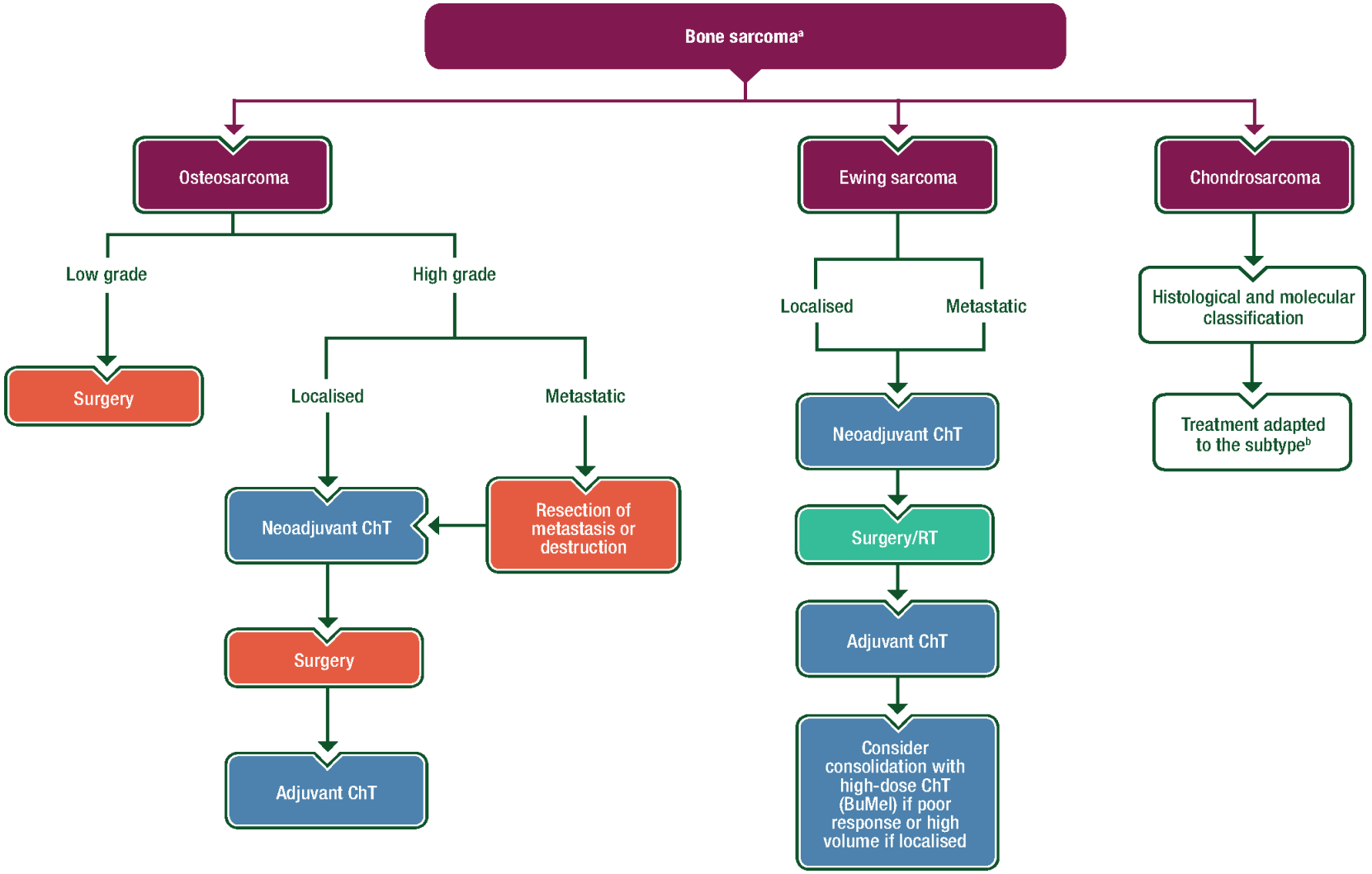
Session 5 – Indications for Hadron Therapy: Sarcomas

Anastasios Kyriazoglou MD,PhD

General therapeutic strategy for the three most frequent bone sarcomas.



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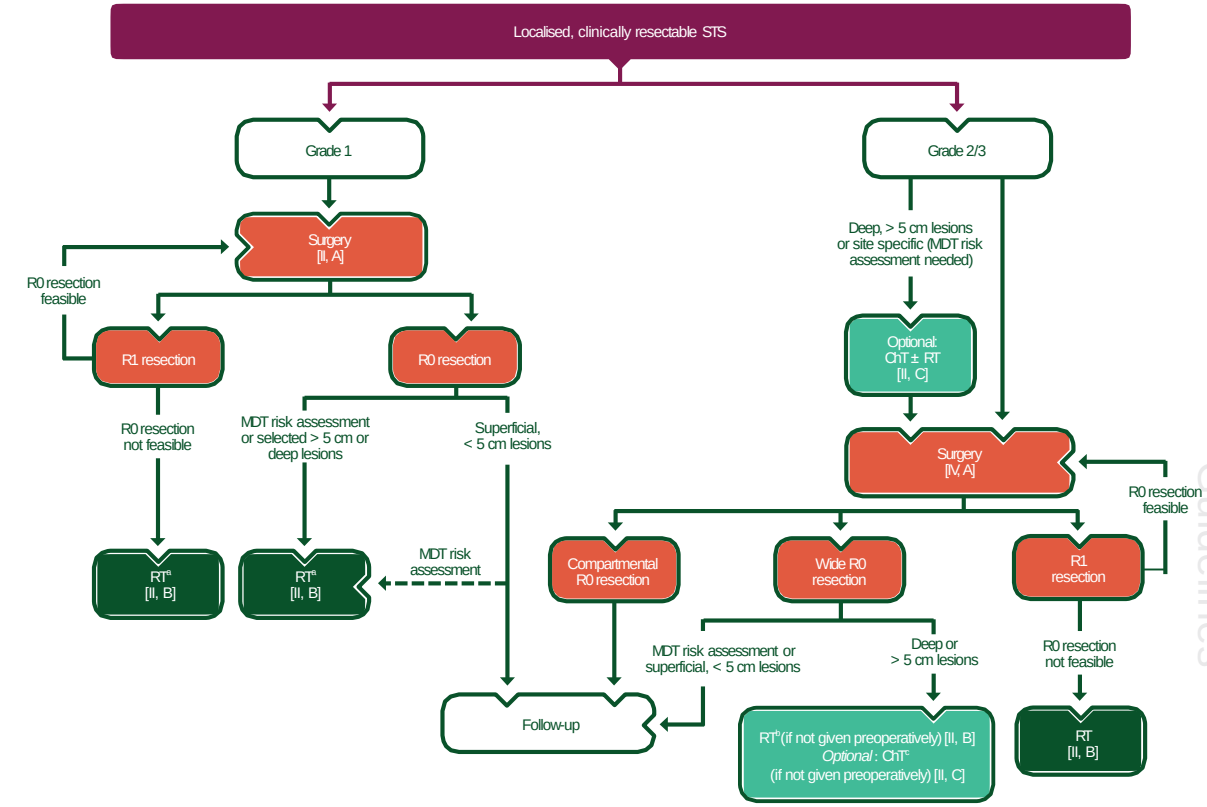

Figure 1. Management of localised, clinically resectable STS.
[a]RT can be omitted in selected cases; *optional*: isolated limb perfusion in highly selected cases.
[b]RT can be omitted in selected deep cases and added in selected superficial cases; to be administered preoperatively if problematic postoperatively.
[c]Extremity and superficial trunk, G3, deep, > 5 cm.
ChT, chemotherapy; MDT, multidisciplinary team; R0, no tumour at the margin; R1, microscopic tumour at the margin; RT, radiotherapy; STS, soft tissue sarcoma.

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doi:10.1093/annonc/mdy096 | iv55

Clinical Practice Guidelines

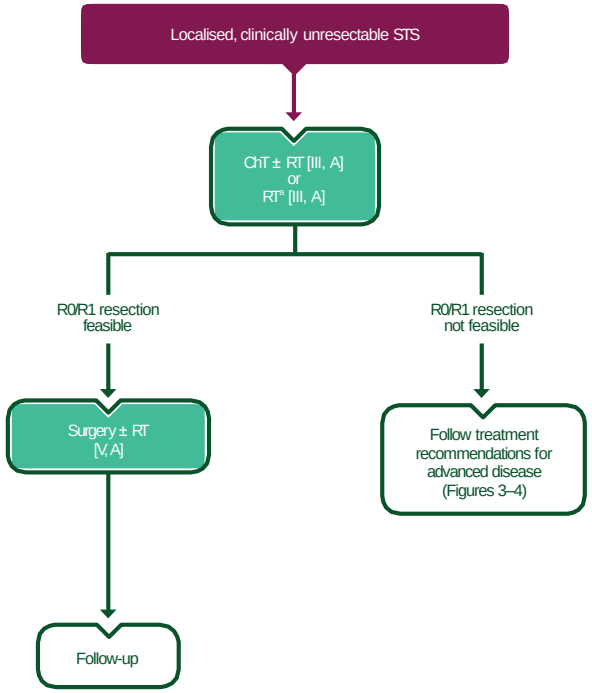


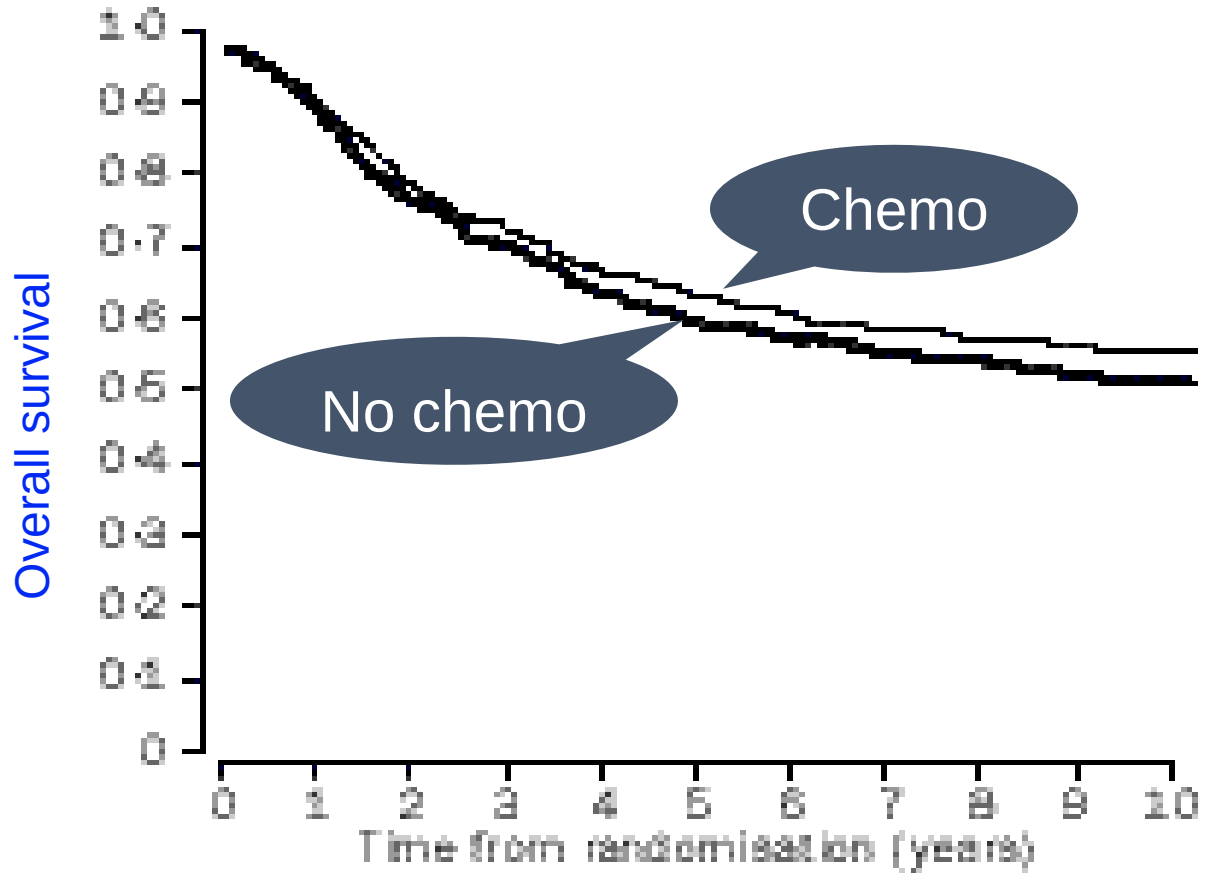
Figure 2. Management of localised, clinically unresectable STS.
[a]Optional: isolated limb perfusion in selected cases.
ChT, chemotherapy; R0, no tumour at the margin; R1, microscopic tumour at the margin; RT, radiotherapy; STS, soft tissue sarcoma.

published data on adjuvant RT after lymph node dissections in regional metastatic STS, the indication should probably be reserved for patients with a relatively large number of tumour-positive lymph nodes and/or extranodal spread in the absence of haematogenic metastases. The increase in local control should be balanced against toxicity (especially peripheral lymphoedema). These treatment modalities added to surgery should not be viewed as truly 'adjuvant', the context being, in fact, that of a likely systemic disease. In one large, randomised phase III study (in patients with G2–3, deep, > 5 cm STSs), regional hyperthermia in addition to systemic ChT was associated with a local control and disease-free survival (DFS) advantage when compared with ChT alone [I, B]. Isolated limb perfusion may be an option in this patient population. This modality obviously has no impact on systemic control (but it can be combined with other modalities) [III, A] [17].

There is no consensus on the current role of adjuvant ChT. Study results are conflicting, in the presence of negative results from the largest studies, though data are available from smaller studies suggesting that adjuvant ChT might improve, or at least delay, distant and local recurrence in high-risk patients [18, 19]. A meta-analysis on published data found a statistically significant limited benefit in terms of both relapse-free survival (RFS) and overall survival (OS) [20]. Gain in OS was not significant on the only meta-analysis using source data [21]. Given the conflicting results of trials included in the meta-analyses, adjuvant ChT is not standard treatment in adult-type STS. It can be proposed as an option to the high-risk individual patient (high-grade, deep, > 5 cm tumour) for a shared decision making with the patient [II, C]. ChT was used as neoadjuvant treatment, aiming at a local benefit facilitating surgery, in addition to the systemic one. A randomised trial showed no differences between three (preoperative) and five (pre- and postoperative) courses of full-dose ChT in high-risk STS patients [22]. A subsequent trial compared preoperative ChT with full-dose epirubicin plus ifosfamide versus a histology-driven ChT. This trial was closed slightly in advance because three interim analyses showed a statistically significant benefit in terms of both RFS and OS in favour of neoadjuvant therapy with epirubicin and ifosfamide. Since there is no obvious evidence that histology-driven ChT could be detrimental, this may be viewed as providing randomised evidence of the efficacy of neoadjuvant therapy with full-dose anthracyclines plus ifosfamide in high-risk extremity and superficial trunk STS 'fit' patients (i.e. with

SMAC Meta-analysis

1568 patients



Increase in local and distant RFS, trend for OS (few trials with ifo)

EORTC 62931: Randomized Phase III Study of AI vs Observation in Resected STS

- The largest randomized study of adjuvant AI in STS.
- 351 patients recruited, 1995-2003.
- Treated patients received five cycles of doxorubicin (Dox) 75 mg/m^2 + ifosfamide (Ifos) 5 gm/m^2 every 21 days.
- Survival in the observation arm was better than expected, leading to an interim analysis for futility.

	Estimated 5-year RFS	Estimated 5-year OS
Treatment	52%	64%
Observation	52%	69%

The hypothesis that adjuvant chemotherapy improves relapse-free survival (RFS) and overall survival (with a HR of 0.621) was rejected.

Supplemental Reference:
Woll ASCO Abstract

Audio

Dr. Maki

Histotype-tailored neoadjuvant chemotherapy versus standard chemotherapy in patients with high-risk soft-tissue sarcomas (ISG-STS 1001): an international, open-label, randomised, controlled, phase 3, multicentre trial

Alessandro Gronchi, Stefano Ferrari, Vittorio Quagliuolo, Javier Martin Broto, Antonio Lopez Pousa, Giovanni Grignani, Umberto Basso, Jean-Yves Blay, Oscar Tendero, Robert Diaz Beveridge, Virginia Ferraresi, Iwona Lugowska, Domenico Franco Merlo, Valeria Fontana, Emanuela Marchesi, Davide Maria Donati, Elena Palassini, Emanuela Palmerini, Rita De Sanctis, Carlo Morosi, Silvia Stacchiotti, Silvia Bagué, Jean Michelle Coindre, Angelo Paolo Dei Tos, Piero Picci, Paolo Bruzzi, Paolo Giovanni Casali

Standard versus histotype-tailored CT

Homogeneous group of STS

Grade III, adult type STS
Extremities and trunk wall
Size ≥ 5 cm

R → **EI x 3 → Surg ± RT**

R → **ht-CT x 3 → Surg ± RT**

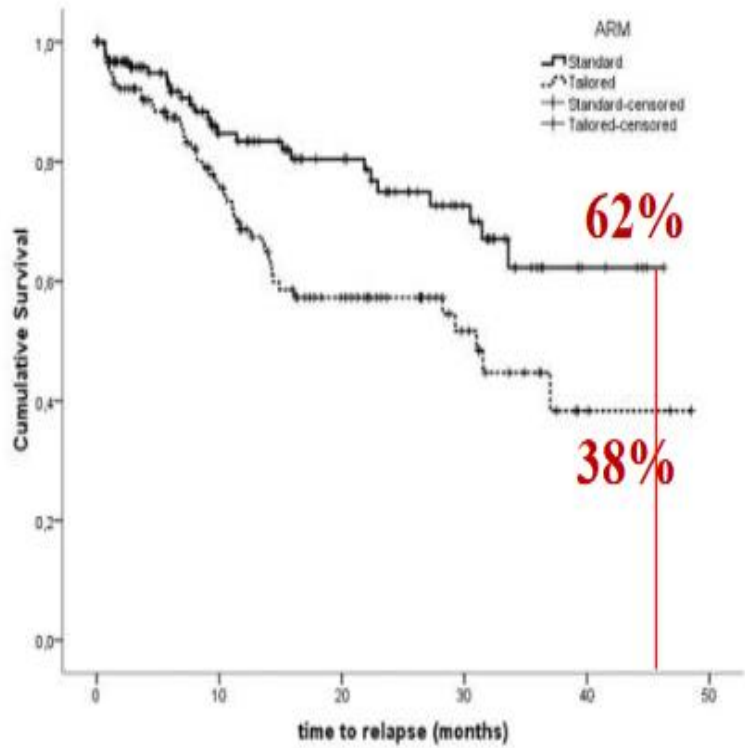
MRC LipoS	**→ Trabectedin**
Synovial S	**→ HD-IFX**
LeiomioS	**→ GEM - DTIC**
UPS	**→ GEM – TAX**
MPNST	**→ IFX + Etoposide**

Hypothesis: HT CT reduces by 30% the risk of relapse (40 to 27%, HR: 0.66)

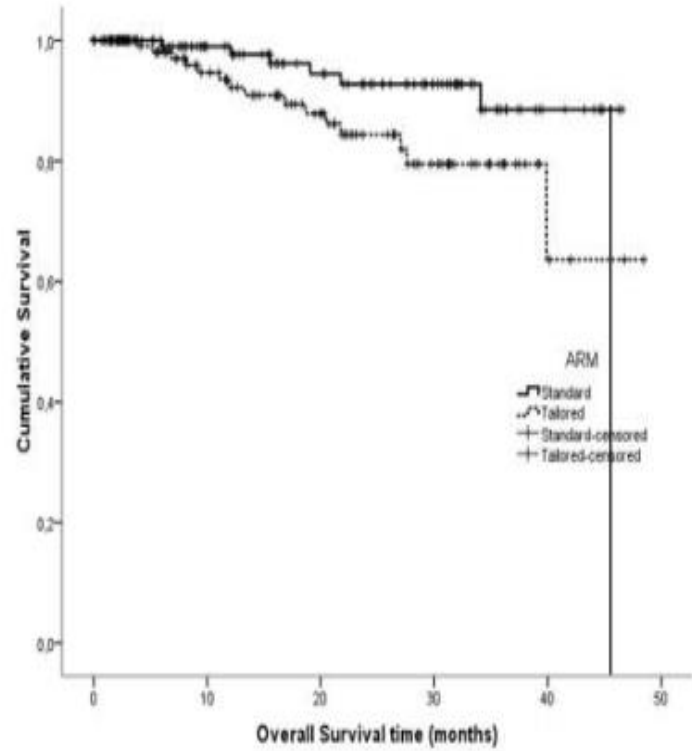
N random = 350, 500 registered

Analysis: 150 events (relapses or deaths) with interim analysis for futility (IDMC)

ISG-STS 1001 - Results



RFS



OS

JAMA Oncology | Original Investigation

Pathologic Complete Response and Clinical Outcomes in Patients With Localized Soft Tissue Sarcoma Treated With Neoadjuvant Chemoradiotherapy or Radiotherapy

The NRG/RTOG 9514 and 0630 Nonrandomized Clinical Trials

Dian Wang, MD; Jonathan Harris, MS; William G. Kraybill, MD; Burt Eisenberg, MD; David G. Kirsch, MD, PhD; David S. Ettinger, MD; John M. Kane III, MD; Parul N. Barry, MD; Arash Naghavi, MD; Carolyn R. Freeman, MD; Yen-Lin Chen, MD; Ying J. Hitchcock, MD; Manpreet Bedi, MD; Kilian E. Salerno, MD; Diane Severin, MD; Karen D. Godette, MD; Nicole A. Larrier, MD; Walter J. Curran Jr, MD; Pedro A. Torres-Saavedra, PhD; David R. Lucas, MD

IMPORTANCE Pathologic complete response (pCR) may be associated with prognosis in patients with soft tissue sarcoma (STS).

OBJECTIVE We sought to determine the prognostic significance of pCR on survival outcomes in STS for patients receiving neoadjuvant chemoradiotherapy (CT-RT) (Radiation Therapy Oncology Group [RTOG] 9514) or preoperative image-guided radiotherapy alone (RT, RTOG 0630) and provide a long-term update of RTOG 0630.

DESIGN, SETTING, AND PARTICIPANTS RTOG has completed 2 multi-institutional, nonrandomized phase 2 clinical trials for patients with localized STS. One hundred forty-three eligible patients from RTOG 0630 (n = 79) and RTOG 9514 (n = 64) were included in this ancillary analysis of pCR and 79 patients from RTOG 0630 were evaluated for long-term outcomes.

INTERVENTION Patients in trial 9514 received CT interdigitated with RT, whereas those in trial 0630 received preoperative RT alone.

MAIN OUTCOMES AND MEASURES Overall and disease-free survival (OS and DFS) rates were estimated by the Kaplan-Meier method. Hazard ratios (HRs) and *P* values were estimated by multivariable Cox model stratified by study, where possible; otherwise, *P* values were calculated by stratified log-rank test. Analysis took place between December 14, 2016, to April 13, 2017.

RESULTS Overall there were 42 (53.2%) men; 68 (86.1%) were white; with a mean (SD) age of 59.6 (14.5) years. For RTOG 0630, at median follow-up of 6.0 years, there was 1 new in-field recurrence and 1 new distant failure since the initial report. From both studies, 123 patients were evaluable for pCR: 14 of 51 (27.5%) in trial 9514 and 14 of 72 (19.4%) in trial 0630 had pCR. Five-year OS was 100% for patients with pCR vs 76.5% (95% CI, 62.3%-90.8%) and 56.4% (95% CI, 43.3%-69.5%) for patients with less than pCR in trials 9514 and 0630, respectively. Overall, pCR was associated with improved OS (*P* = .01) and DFS (HR, 4.91; 95% CI, 1.51-15.93; *P* = .008) relative to less than pCR. Five-year local failure rate was 0% in patients with pCR vs 11.7% (95% CI, 3.6%-25.1%) and 9.1% (95% CI, 3.3%-18.5%) for patients with less than pCR in 9514 and 0630, respectively. Histologic types other than leiomyosarcoma, liposarcoma, and myxofibrosarcoma were associated with worse OS (HR, 2.24; 95% CI, 1.12-4.45).

CONCLUSIONS AND RELEVANCE This ancillary analysis of 2 nonrandomized clinical trials found that pCR was associated with improved survival in patients with STS and should be considered as a prognostic factor of clinical outcomes for future studies.

TRIAL REGISTRATION ClinicalTrials.gov Identifiers: RTOG 0630 (NCT00589121); RTOG 9514 (NCT00002791)

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Multimedia

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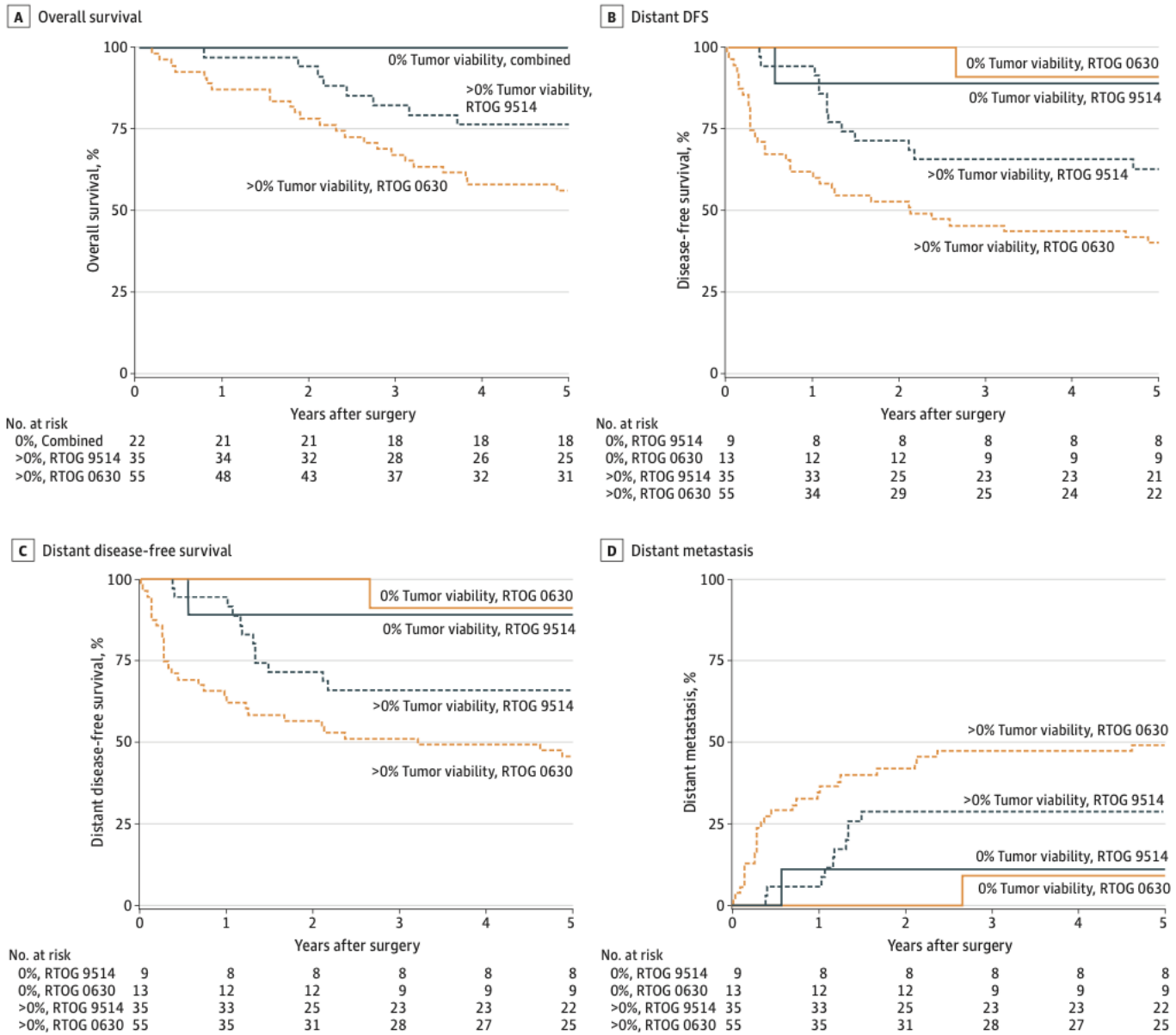
Supplemental content

Figure 2. Participant Clinical Outcomes by Trial and Posttreatment Tumor Viability



Estimated rates of (A) overall survival; B, disease-free survival; C, distant disease-free survival; and D, distant metastasis by posttreatment tumor viability.

- National registry for sarcomas (adults)
- Clinical trials (national and international)
- Research (national and international projects)
- National sarcoma patient advocacy group

REVIEW ARTICLE

Proton Therapy for Sarcomas

Sameer Keole, MD, Jonathan B. Ashman, MD, PhD, and Thomas B. Daniels, MD

Abstract: Sarcomas are a heterogeneous group of tumors that can occur in a wide array of anatomic sites and age ranges with varying histologies. Proton beam therapy, as compared with advanced x-ray radiation therapy techniques, can substantially lower dose to nontarget tissues. This dosimetric advantage can potentially allow for improvement of the therapeutic ratio in the treatment of many of the sarcomas by either increasing the local control, via increased dose to the target, or by decreasing the normal tissue complications, via lowered dose to the avoidance structures. This article reviews the key dosimetric studies and clinical outcomes published to date documenting the potential role proton beam therapy may play in the treatment of sarcomas.

Key Words: Sarcomas, proton beam therapy (PBT), treatment

(*Cancer J* 2014;20: 409–414)

This chapter will attempt to better define the role of proton beam therapy (PBT) in sarcomas. We discuss the major histologies in their anatomic context. In radiotherapy (RT), photon dose is prescribed in the unit of gray (Gy). In PBT, dose is prescribed in the units of cobalt-gray equivalent (CGE) or dose relative biological effectiveness (RBE)–weighted absorbed dose. Dose RBE is the new standard set forth in ICRU 78, but many clinicians and physicists still use the RBE term. For the purposes of this review, all doses, photon and PBT, will be reported in Gy. Photons, also called x-rays, can be delivered using 2-dimensional planning, 3-dimensional (3D) planning, or with intensity-modulated RT (IMRT). Protons are most commonly delivered using 3D planning via double scattering (DS), which is also termed *passive scattering*. More recently, PBT centers are using intensity modulation, and this is most commonly referred to as pencil-beam scanning (PBS).

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ORIGINAL RESEARCH

Cancer Medicine WILEY

Proton radiotherapy for recurrent or metastatic sarcoma with palliative quad shot

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Abstract

Patients with previously treated, recurrent or metastatic sarcomas who have progressed on multiples lines of systemic therapy may have limited options for local control. We evaluated outcomes of palliative proton therapy with the quad shot regimen to unresectable disease for patients with recurrent and/or metastatic sarcoma. From 2014 to 2018, 28 patients with recurrent or metastatic sarcomas were treated to 40 total sites with palliative proton RT with quad shot (14.8 Gy/4 twice daily). Outcomes included toxicity, ability to receive further systemic therapy, and subjective palliative response. Univariate analysis was performed for local progression-free survival (LPFS) and overall survival (OS). Of the 40 total sites, 25 (62.5%) received ≥ 3 cycles with median follow up of 12 months (IQR 4–19). The most common histologies were GIST (9; 22.5%) and leiomyosarcoma (7; 17.5%). A total of 27 (67.5%) sites were located in the abdomen or pelvis. Seventeen (42.5%) treatments involved concurrent systemic therapy and 13 (32.5%) patients received further systemic therapy following proton therapy. Overall subjective palliative response was 70%. Median LPFS was 11 months and 6-month LPFS was 66.1%. On univariate analysis, receipt of four cycles of quad shot (HR 0.06, $p = 0.02$) and receipt of systemic therapy after completion of radiation therapy (HR 0.17, $p = 0.02$) were associated with improved LPFS. Three grade 3 acute toxicities were observed. The proton quad shot regimen serves as a feasible alternative for patients with previously treated, recurrent or metastatic sarcomas where overall treatment options may be limited.

KEYWORDS
metastatic sarcoma, palliative treatment, proton therapy, quad shot regimen, recurrent sarcoma

Skull
Head and neck
Retroperitoneal
Breast
Pelvis
Spine and paraspinal

RMS
Ewing
Chondroma
chondrosarcoma
Osteosarcoma
Radiation induced

The Use of Proton and Carbon Ion Radiation Therapy for Sarcomas

Myrsini Ioakeim-Ioannidou,[*,#] Melanie Rose,[†,#] Yen-Lin Chen,[*] and Shannon M. MacDonald[*]

The unique physical and biological characteristics of proton and carbon ions allow for improved sparing of normal tissues, decreased integral dose to the body, and increased biological effect through high linear energy transfer. These properties are particularly useful for sarcomas given their histology, wide array of locations, and age of diagnosis. This review summarizes the literature and describes the clinical situations in which these heavy particles have advantages for treating sarcomas.

Semin Radiat Oncol 34:207–217

- 3-5 cases of adult sarcomas are referred per year in other European countries (Italy, Germany) for Proton therapy
- average cost of the therapy 30-50.000 euros per patient
- Costs not covered: travel, accommodation, cost of living etc

SAVE THE DATE

7th MASTERCLASS of SARCOMA and RARE CANCERS

December 13-15 2024

American School of Classical Studies

Athens, Greece

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https://eosso.gr/index.php/activities/