
# Sarcoma: Benefit From Brachytherapy in Curative Intention

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## Disclosure

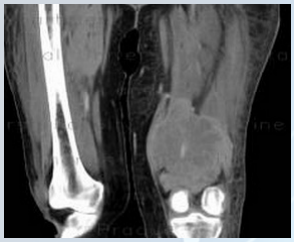
Antonio Cássio Assis Pellizzon, MD, PhD, MSc, does not have any financial relationships or products or devices with any commercial interest related to the content of this activity of any amount during the past 12 months.

## Learning Objectives

- This session will discuss:
  - Tumor staging
  - Surgery indication
  - Brachytherapy techniques
  - Results
  - Complications of treatments

## Incidence

- Rare: for 2013 –
  - 11,400 diagnoses of STS
  - 3,000 bone sarcomas



- Deaths
  - 4,400 (STS) and 1,440 (bone) expected
- Mesodermal origin

NCI
http://www.cancer.gov/

## Overview

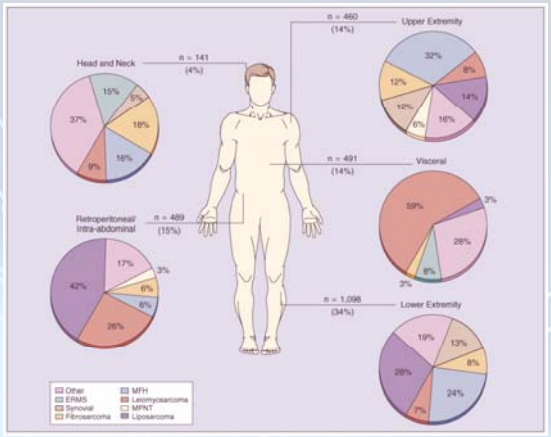
- A variety of radiotherapeutic approaches have been used in the local management of STS
- Randomized trials comparing brachytherapy (BT) and external beam radiation therapy (EBRT) in STS have not been published

## Etiology

- Previous Radiation (increased)
  - Grade of tumors
  - Risk for metastasis
- Chemical exposure
  - Thorotrast, vinyl chloride, arsenic for hepatic angiosarcoma
- Genetic syndromes
  - Neurofibromatosis – nerve sheath tumors
  - Familial gastrointestinal stromal tumor syndrome – KIT mutation
  - Skin hyperpigmentation, urticaria, cutaneous mast cell dx

U Tunn ED
Treatment of bone and soft tissue sarcomas

## Location and Type




Perez and Brady's
Principles and Practice of Radiation Oncology, 6th Ed

## Classification

- Bone
- Soft tissue
  - Visceral – gastrointestinal, genitourinary, and gynecologic organs
  - Nonvisceral – soft tissues (muscle, tendon, adipose, pleura, and connective tissue)

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Treatment of bone and soft tissue sarcomas

## Staging

- **Does not take into account extremity *vs*. visceral**

  **→ Predicts survival and risk of metastasis, but not local recurrence**

- **AJCC/UICC Staging System for STS**
  - T1: <5 cm
    - T1a: Superficial to muscular fascia
    - T1b: Deep to muscular fascia
  - T2: >5 cm
    - T2a: Superficial to muscular fascia
    - T2b: Deep to muscular fascia

N0 X N1: Regional nodal involvement
Grading G1: Well-differentiated
G2: Moderately differentiated
G3: Poorly differentiated
G4: Undifferentiated

AJCC Cancer Staging Manual.
7th ed. New York, NY: Springer, 2010, pp 291-8.

## Staging

| | | | | |
|---|---|---|---|---|
| Stage IA | G1,2 | T1a,b | N0 | M0 |
| Stage IB | G2,2 | T2a,b | N0 | M0 |
| Stage IIA | G3,4 | T1a,b | N0 | M0 |
| Stage IIB | G3,4 | T2a | N0 | M0 |
| Stage III | G3,4 | T2b | N0 | M0 |
| Stage IV | Any G | Any T | N1 | M1 |

AJCC Cancer Staging Manual.
7th ed. New York, NY: Springer, 2010, pp 291-8.

## Relative Risk for Local Recurrence

- High-grade - 4.3
- Deep location - 2.5
- Local recurrence at presentation - 2.0
- Size 5.0–10.0 cm - 1.9
- Microscopically positive margin - 1.8
- Age >50 years - 1.6
- Size >10.0 cm - 1.5

Lewis et al.
J Clin Oncol 15 (2): 646-52, 1997.

## Surgery – Gold Standard

- Limb-sparing vs. amputation → No survival difference
  - Limb sparing + radiation
- Amputation **may still be** indicated for:
  - Neurovascular involvement
  - Bone involvement
  - Function non-preservation

Rosenberg et al
Ann Surg 196 (3): 305-15, 1982

## Resection

- Arbitrary margin – >2 cm
  - Presence of positive margins → increases local recurrence by 10%–15%
- No need for lymph node dissection
  - Only 2%–3% of nodal metastasis

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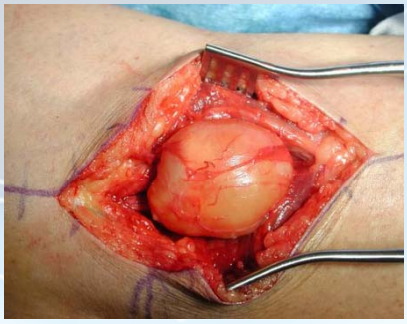
## Adjuvant Treatment Indications

- Will depend on
  - Anatomical location
  - Surgical indication
  - Stage
  - Resectability
  - Margins



## Treatment Options – Stages IA, IB, IIA

- Surgical excision — treatment of choice
  - Margins >2 cm in all directions
- Low metastatic potential
  - RxT or CHT is usually not given as adjuvant

Yang et al.
: Randomized prospective study of the benefit of adjuvant RT in the treatment of soft tissue sarcomas of the extremity. J Clin Oncol 16 (1): 197-203, 1998

## Treatment Options – Stages IA, IB, IIA

**Margins**

**> 2 cm** → may not require radiation (low grade)

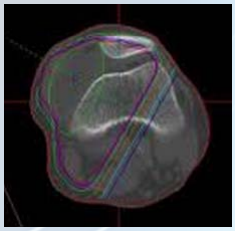
**1-2 cm** – as above (?)

**<1 cm** → Re-resection or adjuvant EBRT and/or BT(?) recommended to prevent LR associated with improved 5-y DFS

Yang et al.
: Randomized prospective study of the benefit of adjuvant RT in the treatment of soft tissue sarcomas of the extremity. J Clin Oncol 16 (1): 197-203, 1998

## Stages IIB, IIC, III

- Pre-operative or post-operative RT
  - In some instances neoadjuvant CHT + RT
- Pre-op – downsize → limb-sparing resections



Temple al.:
Prospective cohort study of neoadjuvant treatment in conservative surgery of soft tissue sarcomas. Ann Surg Oncol 4 (7): 586-90, 1997.
Watson, et al.:
STS of the extremity. Experience with limb-sparing surgery. Med J Aust 160 (7): 412-6, 1994.

## Treatment Recommendations for High-Grade STS and all *Stages II-III*

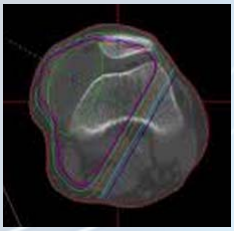
→ High risk of recurrence
→ Potential metastases

- Resectable disease
  - Surgery followed by RT with or without adjuvant CHT
  - Surgery alone
  - Preoperative RT with or without CHT
- Unresectable disease
  - Preoperative or definitive RT with or without CHT with doxorubicin-based regimens

Pollack et al.:
Pre vs. postop RT in the treatment of STS.
IJROBP 42 (3): 563-72, 1998.

## Pre-op or Post-op Radiation?

- Pre-op → increased wound complications (debatable)
  - 35% vs. 17%
  - Risk confined to lower extremity
- Pre-op → may be better for
  - Upper extremity and H&N
  - Equal wound complication risk
  - Benefit of lower RT doses to more vital tissues



Pollack, et al.:
Preoperative vs. postoperative RT in the treatment of STS: a matter of presentation.
IJROBP 42 (3): 563-72, 1998.

## Pre-operative RT

Benefits

- Large retroperitoneal or inguinal tumors may become resectable
- A smaller treatment field is needed
- Potentially less tumor seeding may occur during resection

Negative aspects → increased wound-healing complications

Margins close — (<1 cm) or positive, consider boost with

- BT
- IORT
- EBRT

Pollack, et al.:
Preoperative vs. postoperative RT in the treatment of STS: a matter of presentation.
IJROBP 42 (3): 563-72, 1998.

## Pre-Op vs. Post-Op RT

- Retrospective study
- 517 cases (246 post-op vs 271 pre-op RT)
- No difference in 5- and 10-year survival rates (81% and 78%, respectively)
- 10-year incidence of complications ↑ for post-operative RT (9% vs 5%; *P* = 0.03)

Zagars, et al.
Pre x postop rt for STS: a retrospective comparative evaluation of disease outcome.
IJROBP 56(2):482-8,2003.

## Timing for RXT

- >60–120 days: worse survival
- Retrospective analysis
  - 102 patients
- Short delay (<4 months) vs long delay
  - 5-year – LC favored short delay
  - 88% vs 62% (*P* = 0.048)

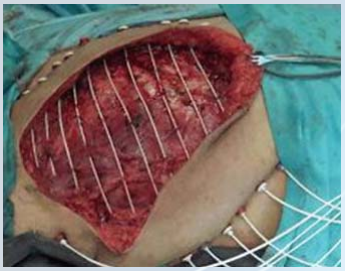
Schwartz et al.
Int J Radiat Oncol Biol Phys 52(5):1352-9,2002.

## Brachytherapy

- Potential radiobiological advantages of brachytherapy include
  - Reductions in normal tissue doses decreasing
    - Probability of growth deformity
    - Dose of EBRT required
    - Rate of 2nd tumor formation

## Techniques

- HDR - Interstitial
- Afterloading catheters
  - Inserted in the tumor bed



  - One or two plans
  - 1.0-1.5 cm distant
  - Preferably transverse to the muscle
  - Catheters can be sutured to maintain equidistance between each other

## Techniques

# Literature Review

**Radiation Oncology**
BioMed Central

Research

Open Access

**High-dose-rate brachytherapy for soft tissue sarcoma in children: a single institution experience**

Gustavo A Viani*[1], Paulo E Novaes[1], Alexandre A Jacinto[1], Celia B Antonelli[2], Antonio Cassio A Pellizzon[1], Elisa Y Saito[1] and João V Salvajoli[1]

18 pediatric patients

**Table 1: Patient and treatment summary**

| Patient/age | Diagnosis | Grade* | Implant site | Margins | CMT | Group* | HDRBT (Gy) | EBRT (Gy) | Local failure | Distant failure | DFS (mo) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| female/9 | RMSE | III | Head neck | Negative | Yes | I | 18 | 41.4 | | | 159 |
| female/16 | Synovial sarcoma | III | extremity | Negative | None | I | 24 | None | | | 19 |
| Female/2 | ASPS | II | Extremity | Negative | Yes | I | 24 | None | | | 21 |
| Female/14 | Synovial sarcoma | II | Extremity Hand | Positive | None | II | 24 | 41.4 | | Lung | 45 |
| Male/5 | Synovial sarcoma | II | Head neck | Negative | Yes | I | 24 | None | | | 79 |
| Female/12 | ASPS | III | Extremity | Negative | None | I | 18 | 30.6 | | | 29 |
| Female/2 | RMSE | II | Pelvic | negative | Yes | I | 24 | None | | | 54 |
| Male/4 | ASPS | II | Extremity | Positive | Yes | II | 24 | None | | | 143 |
| female/1 | ASPS | III | Extremity | Positive | Yes | II | 30 | None | | Lung | 18 |
| Male/2 | fibrosarcoma | II | Pelvic | Negative | Yes | I | 40 | None | | | 83 |
| Female/11 | Synovia sarcomal | III | Extremity | Positive | Yes | II | 24 | 50 | | | 141 |
| Female/9 | RMSE | III | Head Neck | Positive | Yes | III | 18 | 43.2 | | | 65 |
| Female/12 | RMSE | III | Head Neck | positive | Yes | III | 18 | 45 | | | 94 |
| Male/2 | ASPS | II | Pelvic | Negative | Yes | I | 21 | None | | | 12 |
| Male/9 | Synovial sarcoma | II | Extremity | Negative | Yes | I | 30 | None | | | 114 |
| Female/12 | RMS pleomorfic | II | Extremity | Negative | None | I | 21 | None | | | 80 |
| Female/3 | Sarcoma indiferency | III | Extremity | Negative | Yes | I | 21 | 41.4 | | Lung | 38 |
| female/16 | ASPS | III | Extremity | Positive | Yes | III | 24 | 50.0 | yes | NCS | 18 |

*Intergroup Rhabdomyosarcoma Study (IRS) staging used for both rhabdomyosarcomas and nonrhabdomyosarcomas. ASPS= soft tissue sarcoma alveolar, RMSE= Rhabdomyosarcoma embryonary

Male – 5 x Female – 13

Viani et al.
Radiat Oncol.2008, **3**:9 doi:10.1186/1748-717X-3-9

**Table 2: Local control, distant failure, and survival rates according to margin, chemotherapy and treatment modality.**

| | Local control (%) | Distant failure (%) | Overall survival (%) |
|---|---|---|---|
| **Overall** | 94.5 (17/18) | 22 (4/18) | 78 (14/18) |
| **Margins** | | | |
| Negative | 100 (11/11) | 1 (1/11) | 91 (10/11) |
| Positive | 85.7 (6/7) | 42.8(3/7) | 57.1 (3/7) |
| **Neoadjuvant chemotherapy** | | | |
| Yes | 92.8 (13/14) | 21.4(3/14) | 78.5(11/14) |
| No | 100(4/4) | 25(1/4) | 75 (3/4) |
| **Treatment modality** | | | |
| BRT alone | 100 (8/8) | 25 (2/8) | 25 (2/8) |
| BRT+EBRT | 90 (1/10) | 20 (2/10) | 20 (2/10) |

Viani et al.
Radiat Oncol.2008, **3**:9 doi:10.1186/1748-717X-3-9

## HDR for STS in Children: ACCCC Experience

**OS @ 5 years – 84.5%**

**Facts:**

- No local or regional failures in the group treated with HDR alone
- Combined HDR and EBRT
  - 1 local failure (22 months)
  - 3 pulmonary metastatic disease (18, 38, and 48 months after diagnosis)

**Acute Side Effects**

- Skin reactions: 6 patients (33%)
- Wound dehiscence: 4 patients (22%)

**Late Side Effects**

- Extensive fibrosis: 3 patients (16.5%)

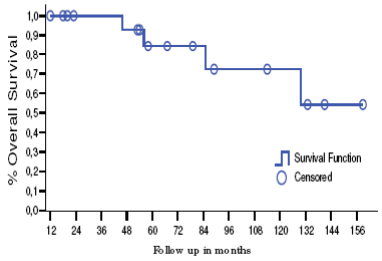



**Figure 1**
**Overall survival for eighteen patients with STS treated with or without BRT.**

Viani et al. Radiation Oncology 2008, **3**:9 doi:10.1186/1748-717X-3-9

## HDR and Limb-Sparing Surgery for STS in Adults: ACCCC Experience

- 21 patients treated from 1993 to 1999
- EBRT:
  - Pre- or post-op 30-50 Gy
- HDR:
  - 18–36 Gy (fx) 3–6 Gy BID

| | | n | % |
|---|---|---|---|
| Gender | male | 16 | 59.2 |
| | female | 11 | 40.8 |
| Clinical Stage | IA | 2 | 7.4 |
| | IB | 11 | 40.8 |
| | IIA | 1 | 3.7 |
| | IIB | 7 | 25.9 |
| | IIIA | 2 | 7.4 |
| | IIIB | 3 | 11.1 |
| | IVA | 1 | 3.7 |
| Anatomic Site | tight | 17 | 60.7 |
| | leg | 4 | 14.3 |
| | arm | 3 | 10.7 |
| | forearm | 3 | 10.7 |

Pellizzon et al. Brachytherapy. 2000;17:43-50

## HDR and Limb-Sparing Surgery for STS in Adults: ACCCC Experience

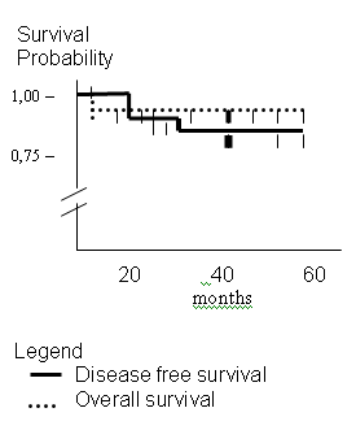
**Results:**

Actuarial @ 5 years

- LC: 85.2%
- DFS: 75%
- OS: 93.7%

**Late Side Effects**

- Extensive fibrosis: 1 (3.5%) (surgical correction)




Pellizzon et al.
Brachytherapy. 2000;17:43-50

## Primary x Recurrent

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – BONE AND SOFT TISSUE SARCOMAS

**Perioperative Hyperfractionated High-Dose Rate Brachytherapy for the Treatment of Soft Tissue Sarcomas: Multicentric Experience**

Jiří Petera, MD, PhD[1], Renata Soumarová[2], Jana Růžičková[3], Renata Neumanová[4], Ladislav Dušek[5], Igor Sirák[1], Zuzana Mačingová[1], Petr Paluska[1], Linda Kašaová[1], Miroslav Hodek[1], and Milan Vošmik[1]

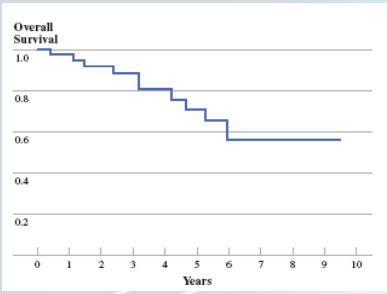
## Primary x Recurrent

- 45 patients
  - 17 primary
  - 28 recurrent
- HDR BT alone
  - 11 (mean dose 40 Gy; 30–54 Gy)
- HDR + EBRT (34 patients)
  - HDR - 34 - (mean 24 Gy; 15–30 Gy)
  - EBRT (40–50 Gy)

Petera et al
Ann Surg Oncol. 2010 Jan;17(1):206-10.

## Primary x Recurrent

- LC – 100% in primary vs 64% recurrent ($P$ = 0.004)
- At 5 years:
  - Overall survival: 70%
  - Local control: 74%
- Prognostic Factors
  - LC → better for extremities x trunk tumors
  - EBRT + BT better than BT alone
  - Doses >65 Gy




Petera et al
Ann Surg Oncol. 2010 Jan;17(1):206-10.

## LDR x HDR

Surjeet Pohar, Rashid Haq, Lizhong Liu, Michael Koniarczyk, Seung Hahn, Timothy Damron, Jesse N. Aronowitz

Adjuvant high-dose-rate and low-dose-rate brachytherapy with external beam radiation in soft tissue sarcoma: A comparison of outcomes

Brachytherapy
Volume 6, Issue 1, Pages 53-57, January 2007

## LDR x HDR

37 patients

Pre- or post-op EBRT

+

LDR or HDR

Patient and treatment characteristics

| | LDR | HDR |
|---|---|---|
| Mean age (years) | 52 | 65 |
| Diabetes, no. (%) | 2 (10) | 1 (6) |
| Upper extremity/lower extremity, no. (%) | 5 (25)/14 (70) | 8 (47)/9 (53) |
| Stages I–II/stages III–IV, no. (%) | 3 (15)/17 (85) | 7 (41)/10 (59) |
| Grades 1–2/grade 3, no. (%) | 7 (35)/13 (65) | 6 (35)/11 (65) |
| Margin positive, no. (%) | 3 (15) | 2 (12) |
| Resection area ($cm^2$) | 166 | 181 |
| Adjuvant chemotherapy, no. (%) | 6 (30) | 4 (24) |
| Known metastases, no. (%) | 2 (10) | 0 (0) |

LDR = low-dose rate; HDR = high-dose rate.

Pohar et al.
Brachytherapy. 2007 Jan-Mar;6(1):53-7.

## LDR x HDR

Radiation details

| | LDR | HDR |
|---|---|---|
| EBRT pre/post, no. (%) | 13 (65)/7 (35) | 3 (18)/14 (82) |
| EBRT mean dose (range) (cGy) | 4995 (44.6–55) | 4826 (45–50.4) |
| BT mean dose (range) (cGy) | 1676 (15–20.5) | 1332 (10.2–18) |
| BT $BED_3$ dose (cGy) | 2531 | 3132 |
| Total $BED_3$ dose (cGy) | 7526 | 7958 |

LDR = low-dose rate; HDR = high-dose rate; EBRT = external beam radiation therapy.

| HDR regimen | N |
|---|---|
| (340–370) × 3 | 5 |
| 400 × 3 | 2 |
| 300 × 4 | 1 |
| (420–450) × 3 | 4 |
| 550 × 3 | 1 |
| 450 × 4 | 3 |

Pohar et al.
Brachytherapy. 2007 Jan-Mar;6(1):53-7.

## LDR x HDR

**LC @ 2 years**

- 90% LDR X 94% HDR

**Complications – Grades 2-4**

- 40% LDR vs. 18% HDR (*P* = NS)

**HDR group – predictive of LC**

- Dose per fraction, total BT dose, and total BED

**CONCLUSION –** HDR may have lower incidence of severe (grade ≥3) acute toxicity than LDR

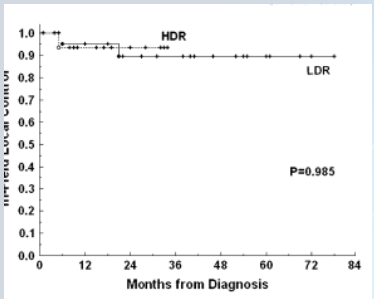


Fig. 2. "In-field" local control in LDR and HDR patients.

Pohar et al.
Brachytherapy. 2007 Jan-Mar;6(1):53-7.

## Published Data HDR

| First Author | Year | FU mo | Modality | *n* | LC | Complications Grade >2 (%) |
|---|---|---|---|---|---|---|
| Koizumi | 1999 | 30 | HDR | 16 | 50 | 6 |
| Itami | 2010 | 50 | HDR | 26 | 78 | 11.5 |
| Chun | 2001 | 31 | HDR + EB | 17 | 100 | NR |
| Martinez-Monge | 2005 | 23 | HDR + EB | 25 | 23 | 28 |
| Aronowitz | 2006 | 34 | HDR + EB | 12 | 83 | NR |
| Petera | 2010 | 38 | HDR | 11 | 55 | 4.4 |
| | | | HDR + EB | 34 | 85 | |
| San Miguel | 2011 | 49 | HDR + EB | 60 | 77.4 | 28.3 |
| Pellizzon | 2000 | 27 | HDR + EB | 27 | 85.2 | 3.5 |
| Emory | 2012 | 11 | HDR | 37 | 92 | NR |
| | | | HDR + EB | 12 | 83 | NR |

Holloway et al.
Brachytherapy. 2013 May-Jun;12(3):179-90

## Nerve Tolerance to HDR in Patients With STS: A Retrospective Study

**BMC Cancer** Open Access

**Nerve tolerance to high-dose-rate brachytherapy in patients with soft tissue sarcoma: a retrospective study**

Tadahiko Kubo*[1], Takashi Sugita[2], Shoji Shimose[1], Toshihiro Matsuo[1], Ken Hirao[2], Hiroaki Kimura[3], Masahiro Kenjo[4] and Mitsuo Ochi[1]

## Nerve Tolerance to HDR in Patients With STS: A Retrospective Study

- 7 patients
  - Involved neurovascular bundle (1995–2000)
- Catheters
  - Placed → tumor bed → directly upon the preserved neurovascular structures

Kubo et al.
BMC Cancer. 2005 Jul 19;5:79.

## Nerve Tolerance to HDR in Patients With STS: A Retrospective Study

| No. | Margin | PTV[a] ($cm^3$) | Brachytherapy (Gy) | EBRT[b] (Gy) | Failure | Complication | Follow-up (months) |
|---|---|---|---|---|---|---|---|
| 1 | Negative | 65 | 50 | - | - | Motor paresis | AWD[c] (77) |
| 2 | Negative | 63 | 50 | (50) | Local | Fracture | AWD (75) |
| 3 | Negative | 52 | 50 | - | - | - | AWD (62) |
| 4 | Negative | 93 | 50 | - | - | - | AWD (43) |
| 5 | Negative | 64 | 30 | 20 | - | Sensory loss | AWD (34) |
| 6 | Negative | 60 | 50 | - | Lung | - | DOD[d] (32) |
| 7 | Positive | 134 | 50 | - | - | - | DOC[e] (13) |

PTV[a] = Planning target volume, EBRT[b] = External beam radiation therapy, AWD[c] = Alive without disease, DOD[d] = Dead of disease, DOC[e] = Dead from other cause

Kubo et al.
BMC Cancer. 2005 Jul 19;5:79.

## Nerve Tolerance to HDR in Patients With STS: A Retrospective Study

**RESULTS:**

- Median follow-up of 4 years
- 5-year actuarial
  - OS: 83.3%
  - DSS: 68.6%
  - LC: 83.3%
- None developed HDR-induced peripheral neuropathy

Kubo et al.
BMC Cancer. 2005 Jul 19;5:79.

## Potential Complications

- Wound complications
- Infections
- Skin reactions
- Seromas
- Catheter failures

Schwartz et al
Clin Orthop Relat Res. 2013 Nov;471(11):3612-7.

## Final Thoughts

- STS needs a relative high dose to achieve local control → BT can be one of the answers
- There is a limited number of reports on the use of PDR for STS
- There is no randomized comparison of HDR and LDR for STS
- Prospective randomized trials using HDR for STS should be encouraged