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Curative potential of radiotherapy (neoadjuvant, adjuvant or definitive radiotherapy as in the case of inoperable Ewings or the use of total lung irradiation) and indications and techniques for palliative radiotherapy

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Secretary of the Belgian Association for Cancer Research (BACR)

Hôpital Erasme ULB iris

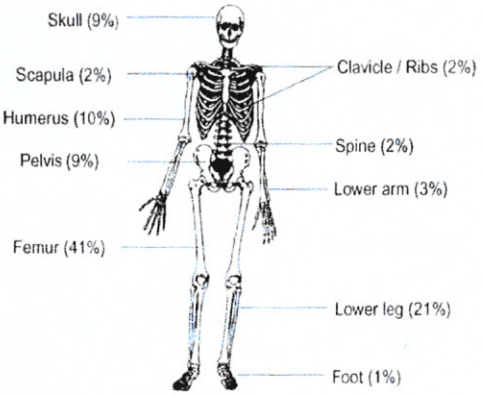
Agenda:

- Bone sarcoma
- Soft tissue sarcoma
  - Conservative surgery requires adjuvant RT
  - Pre-op vs post-op RT
  - 3D RT vs IMRT
  - RT in function of the performed surgery
  - Indications for RT
- Classical palliative RT vs Stereotactic RT for oligo-M+ disease
- Conclusions

Bone sarcoma

Diagnosis	Radiotherapy?
• Osteosarcoma	No (?)
• Chondrosarcoma	No (?)
• Giant cell tumor	No
• Ewing Sarcoma	Yes
• Fibrosarcoma	Yes
• Chordoma	Yes

Bone Sarcoma



Osteosarcoma

- Treatment
  - Chemotherapy and surgery
  - OS 50-85%
- Osteosarcoma = very radioresistant
  - 60 Gy: Limited Tu control (Jenkin,1972)
  - 80 Gy: Living Tu cells in amputation specimen (Lee 1954, Francis 1954)
  - 80-100 Gy: Tu sterilisation (Gaitan, 1981)
- Reason of radio-resistance is unknown
  - Hypoxic Tu
  - Increased capacity to repair sub-lethal damage (Martinez 1985)

Bone sarcoma

Osteosarcoma - Chondrosarcoma

- Indications for radiotherapy
  - Non-resectable lesions
    - Base of skull
    - Vertebrae - Sacrum
  - Refusal of surgery

Role of preoperative CRT?

Role of protons/Carbon Ions?

Bone sarcoma

Ewing Sarcoma

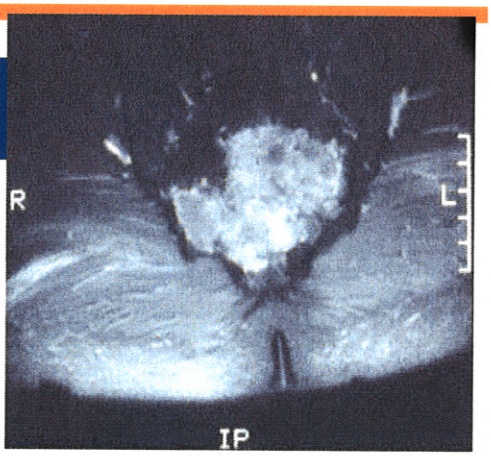
- Treatment
  - Combination of chemotherapy, surgery and RT: MTD!!!!!!!!!!!!!!
  - EURO-EWING protocol (1999 & 2012)
  - Postop RT to start within 6w; avoid CCRT with adria, Actino-D, (Melphalan)
  - OS 60-80%
- Postoperative RT (or 50,4 Gy pre-op when R1 expected)
  - 0 Gy when wide resection
  - 45 Gy when wide resection with <90% necrosis after CT
  - 54 Gy when R1
- Definitive RT after induction chemo
  - When surgery impossible (RT as only local R/)
  - 54 Gy, plus a boost to 59.4 Gy (64 Gy if possible)
- Total lung RT = in case of lung M+: 18Gy/12 fractions after consolidation CT

Bone sarcoma

Fibrosarcoma

- Strongly looks like an osteolytic bone M+
- Age 30-60
- Prognosis strongly depends on the grade
- Treament
  - Radical surgery
  - Considerer adjuvant RT: cf soft tissue sarcoma infra
  - Considerer adjuvant CT

Bone sarcoma



Chordoma

- 1-4% of bone sarcomas
- 'Benign' Tu of the notochord,

  Thus (almost) always on the central axis:
  - Sacrum (50%)
  - Skull base (33%)
- Treatment:
  - In principle radical surgery
  - Non-radical resection is frequent: radiotherapy
  - Radio-sensitivity? Carbon Ion Therapy?

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Soft tissue sarcomas

Indications for radiotherapy

- An old sub-optimal trial of the NCI suggests

  'Limb-saving' surgery + RT = amputation.

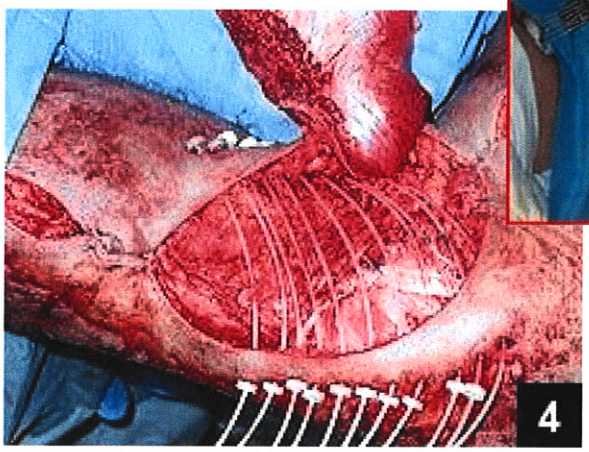
- 2 randomised series of surgery + postop RT vs. Surgery alone:

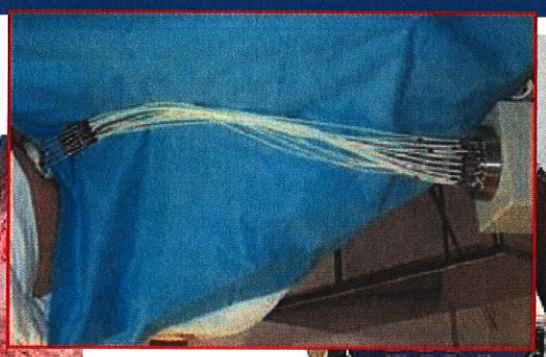
  LC ↑ , OS idem

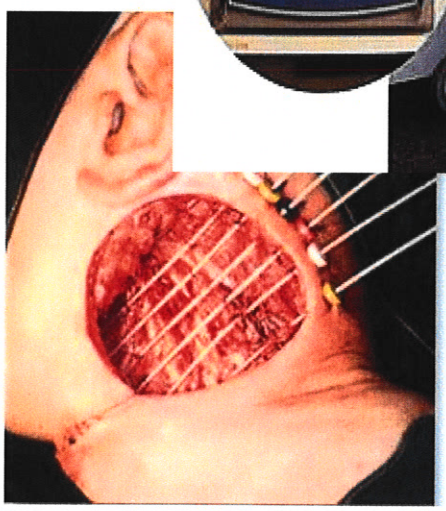
  (Pisters & al, JCO 1996; Yang et al, JCO 1998)

Conservative surgery requires adjuvant RT

Brachytherapy







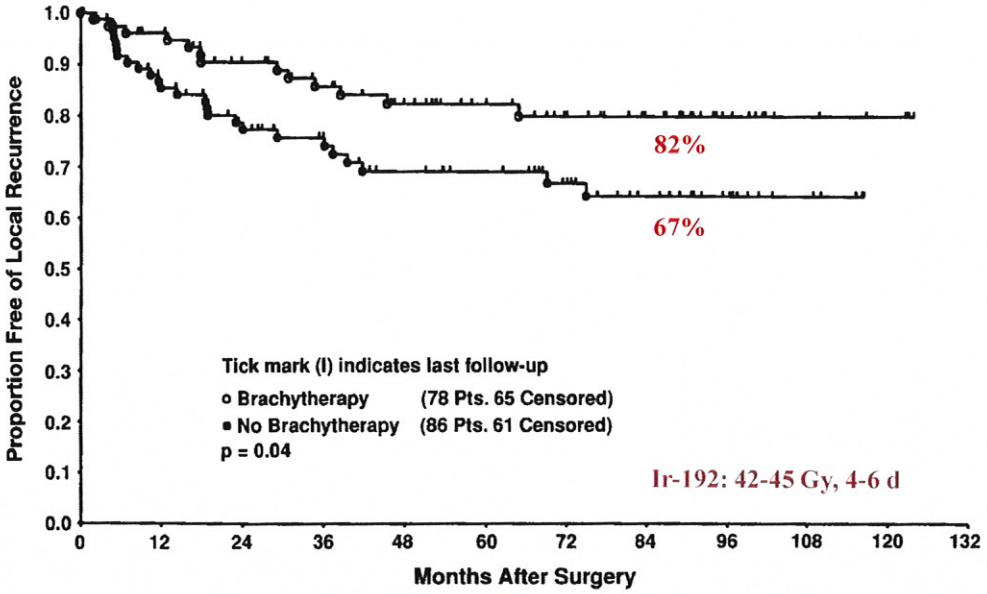
Shorter OTT

Smaller treatment volumes

5Y LC 83% (Alektiar et al)

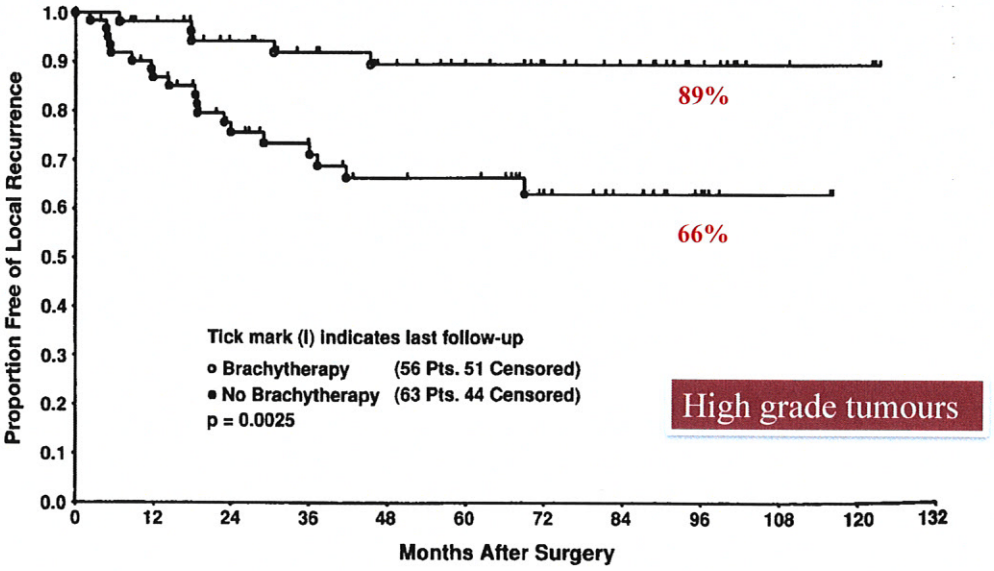
Conservative surgery requires adjuvant RT

Conservative surgery +/- postop BT



Conservative surgery requires adjuvant RT

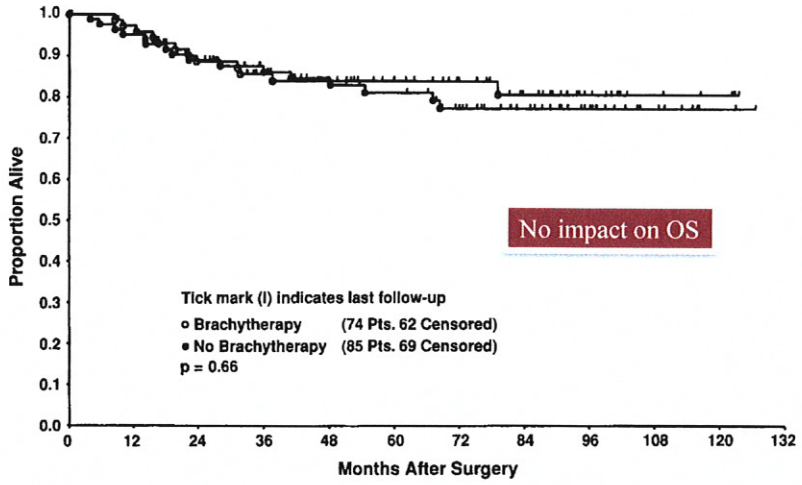
Conservative surgery +/- postop BT



High grade tumours

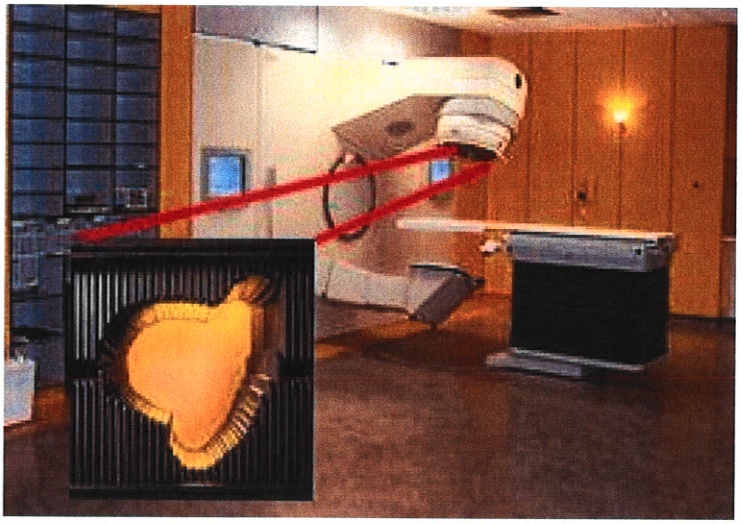
Conservative surgery requires adjuvant RT

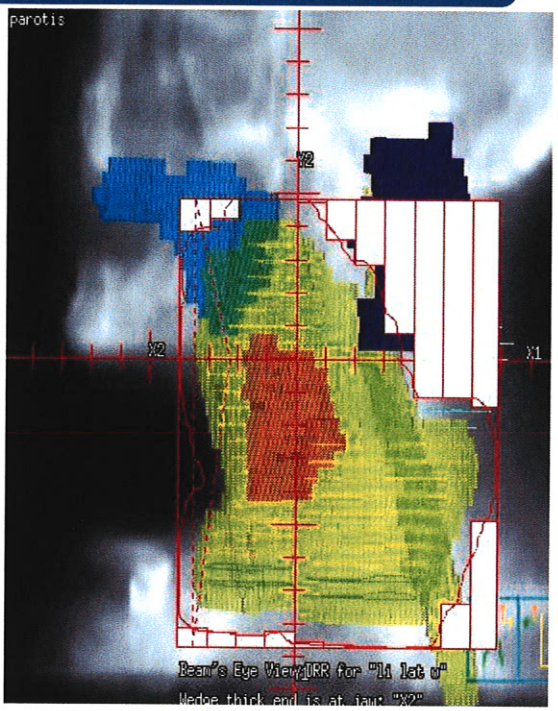
Conservative surgery +/- postop BT



No impact on OS

Conservative surgery requires adjuvant RT

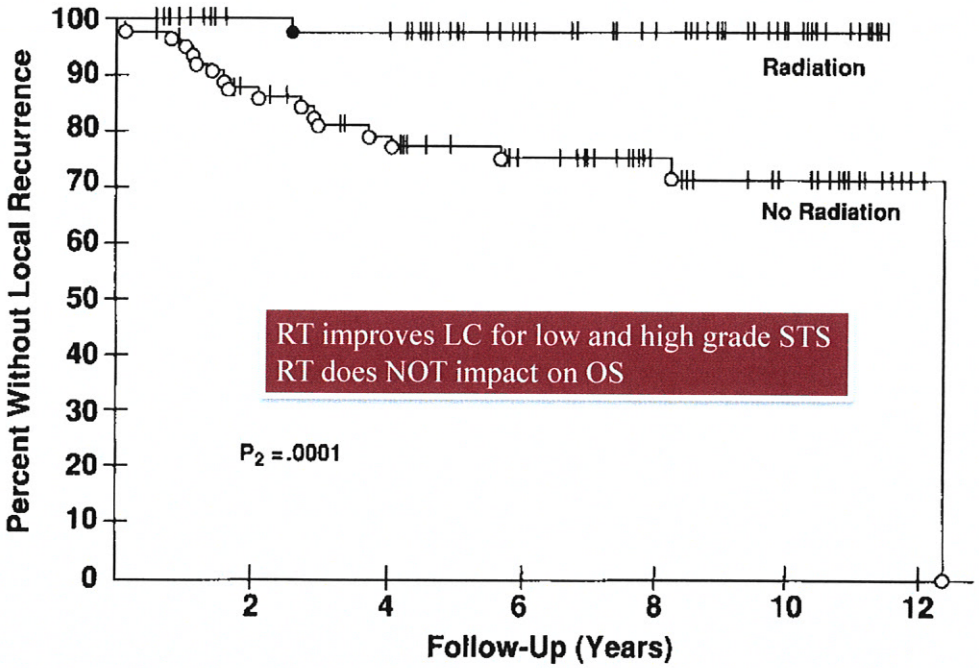




2 - 3 Dimensional EBRT

Conservative surgery requires adjuvant RT

Conservative surgery +/- postop EBRT



Yang et al, National Cancer Institute, JCO 1998

Preop vs postop RT

Preoperative versus Postoperative RT (see Table 3)

Table 3

Advantages and disadvantages of pre- and postoperative radiotherapy

	Advantages	Disadvantages
Preoperative Radiotherapy	• Smaller RT volume • Easier resection • Better oxygenations and vascularization of the area = > larger effect • Reduction of late complications	• Wound complications • Postponing surgery • Fibrosis that could hamper surgery
Postoperative Radiotherapy	• Better staging • Less scar complications	• Large RT Volumes • More late complications (fibrosis, joint stiffness, oedema) • Need for demarcation of the operation field (clips)

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Hoefkens, …., Van Gestel; Radiation Oncology, December 2016

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preop vs postop RT

Author	N	Conclusion
Cheng et al (JSO, 1996)	112	No difference in LC
O' Sullivan et al (Lancet 2002)	190	No difference in CSS •Signif > wound healing problems: 35% vs 17% •Trend for lesser late effects
Zagars et al (IJROBP 2003)	517	No difference in CSS RT sequence not a significant P/ factor on MVA
Kuklo et al (AJO 2005)	117	No difference in LC
Guadagnolo et al synovial sarc. (IJROBP 2007)	150	No difference in LF or OS Pre-op RT: increased risk DF (50% vs. 40%), not significant

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Preop vs postop RT

Pre-op requires less dose (50 vs 60-66 Gy) but might need post-op boost

Local Control

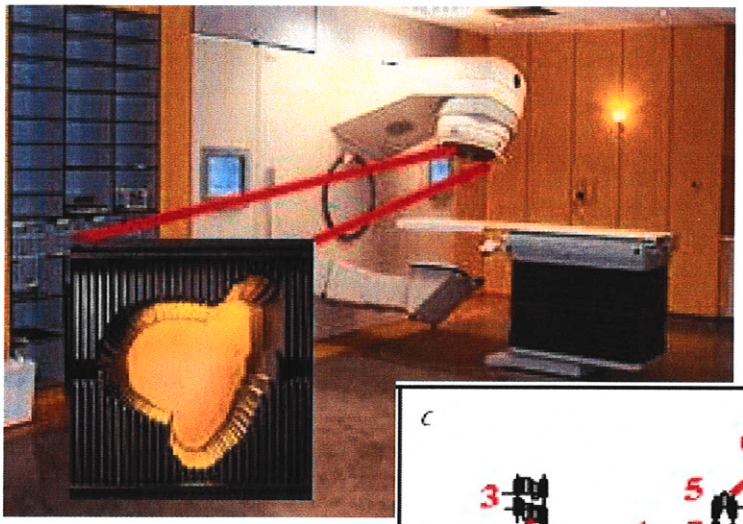
- Pre-op RT: 73-93%
- Post-op RT: 72-92%

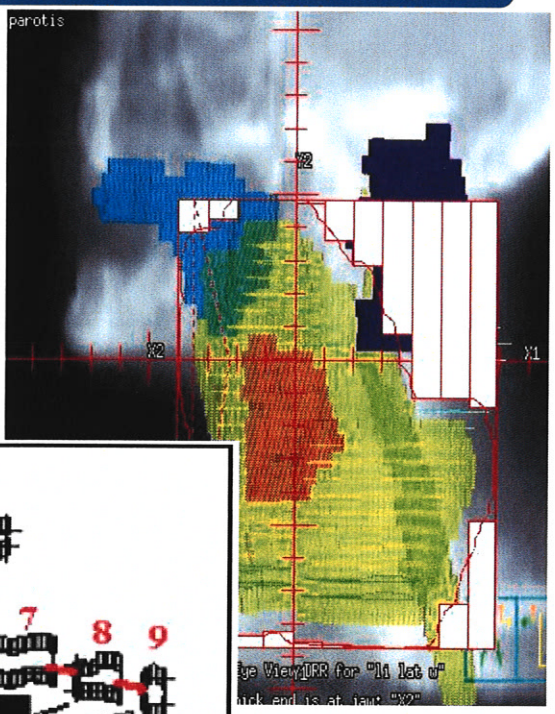
Wound healing problems

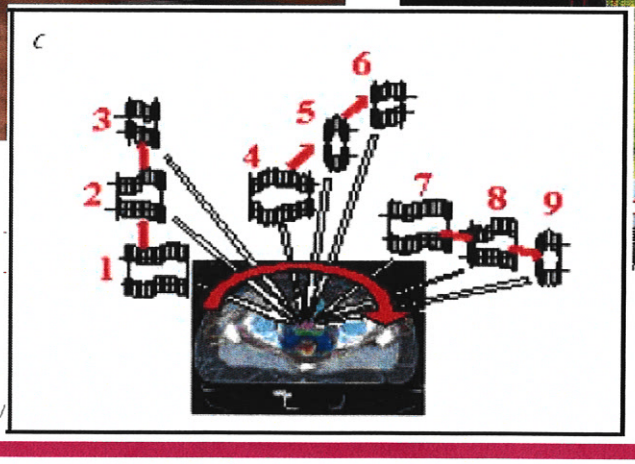
- Pre-op RT: 25% to 46%
- Post-op RT: 6% to 29%

Perez and Brady's Principles and Practice of Radiation Oncology, 2019

3D RT vs IMRT

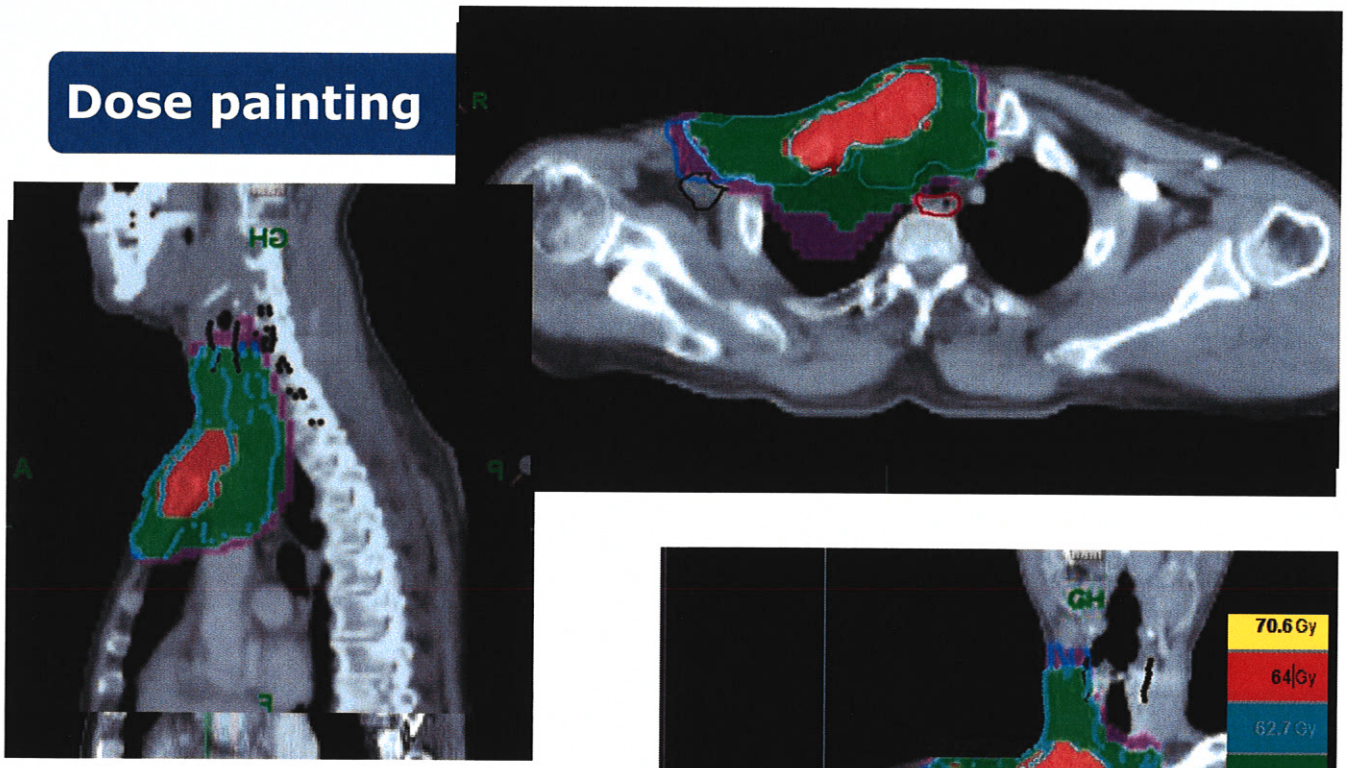


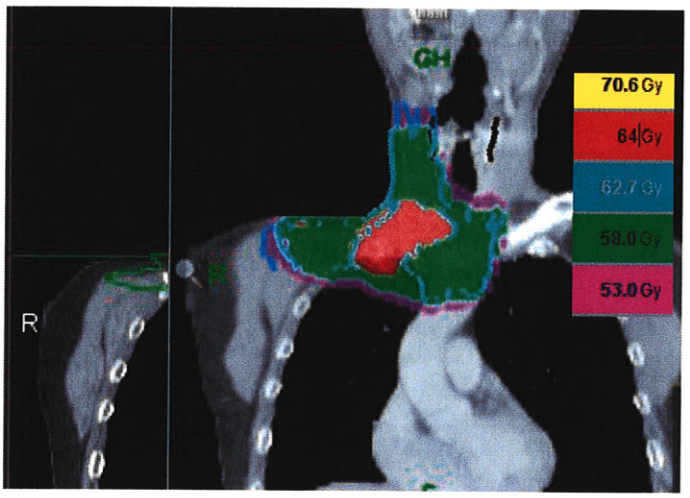




IMRT:

Dose painting





IMRT:

3D RT vs IMRT

	5-yr LR	RT Modality
NCIC RCT, 2004 O'Sullivan	6%, 7%	3D (100%)
BWH/DFCI, 2013 Baldini	10%	3D (84%)
MSKCC, 2014 Folkert	15.1%	3D (100%)
MGH, 2010 Kim	11.5%	3D (88%)
PMH, 2013 O'Sullivan	11.8%	IMRT (flap sparing, 100%)
MSKCC, 2014 Folkert	7.6%	IMRT (100%)
RTOG 0630, 2015 Wang	11.4% (2-yr)	IMRT (75%)

'3D conventional and IMRT: Similarly excellent'

3D RT vs IMRT

Institution	PMH*	MSKCC**	RTOG 0630***	Pre-op Arm NCIC
Treatment Modality	100% IMRT (sparing flap)	100% IMRT (79% post-op)	75% IMRT	100% 3D
≥ Grade 2: Subcutaneous Fibrosis	9.3%	NS	5.3%	31.5%
Joint Stiffness	5.6%	14.5%	3.5%	17.8%
Edema	11.1%	7.9%	5.3%	15.1%

'Use of IMRT may be the main reason for reduced toxicity'

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* *B O'Sullivan, Cancer 2013*
** *Folkert, JCO 2014*
*** *Wang, JCO 2015*

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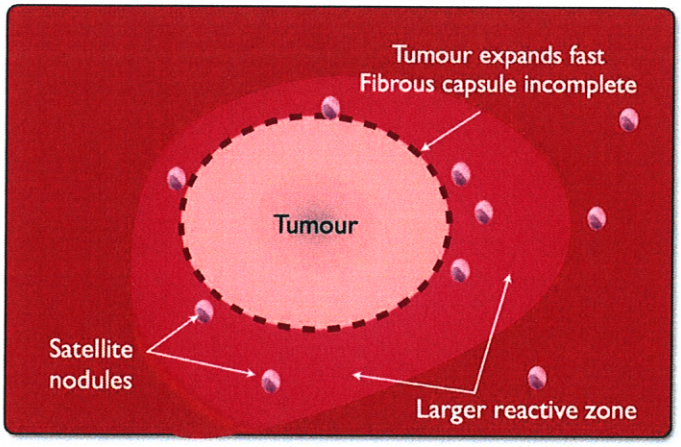
Soft Tissue Sarcoma: RT in function of surgery

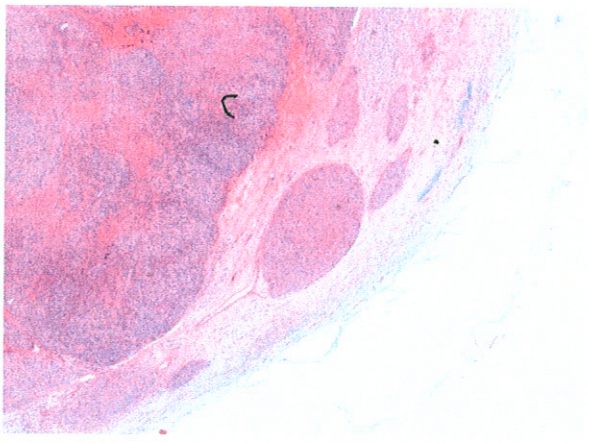
RT in function of the performed surgery

- Surgery (+ pathology) = corner stone
- **RT can not correct for bad surgery**
- Multidisciplinary discussion as soon as possible, even before invasive diagnostics

→Referral to specialised centres!!!

RT in function of the performed surgery

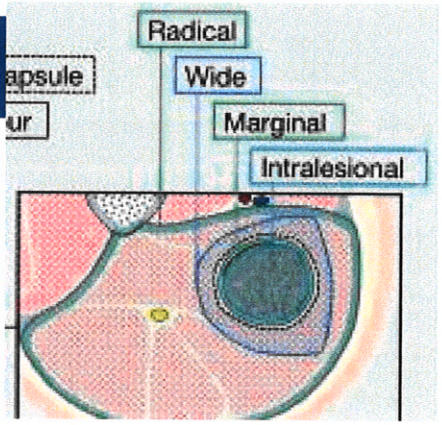




Satellite Tu cells can be found up to 4cm from GTV

(White et al, IJROBP 2005)

RT in function of the surgery



- Intra-lesional (R2)
  (through pseudo-capsule)
- Marginal resection (R1)
  (Intracapsular or <1-2 cm around tumor)
- Wide resection
  (margins >1-2cm in nl tissue)
- (Radical resection)
  (compartment)

Local recur. after surgery

100%

Consider a **2nd operation**

60-90%

Consider a **2nd operation**

25-35%

RT to be discussed

5-20%

NO RT if tumor is confined to compartment

Indications for RT

In combination with wide resection,

- Adjuvant RT is recommended:
  - High-grade (G2-3) STS
  - Deep STS
  - >5 cm STS
  - Recurrent STS
- Adjuvant RT is optional:
  - Low grade, deep, <5 cm STS
- Adjuvant RT is not recommended for:
  - Low grade, superficial, <5 cm STS

ESMO

CLINICAL PRACTICE GUIDELINES

Soft tissue and visceral sarcomas: ESMO–EURACAN Clinical Practice Guidelines for diagnosis, treatment and follow-up†

Indications for RT

J Surg Oncol. 2014 Jan 24. doi: 10.1002/jso.23569. [Epub ahead of print]

Compliance with National Comprehensive Cancer Network guidelines in the use of radiation therapy for extremity and superficial trunk soft tissue sarcoma in the United States.

Bagaria SP, Ashman JB, Daugherty LC, Gray RJ, Wasif N.

Of 5,075 patients, 50% received RT. Although routine RT is not recommended for Stage I patients, 25% still underwent RT. Even though routine RT is recommended for Stage II and III tumors, only 60% underwent RT.

CONCLUSIONS:

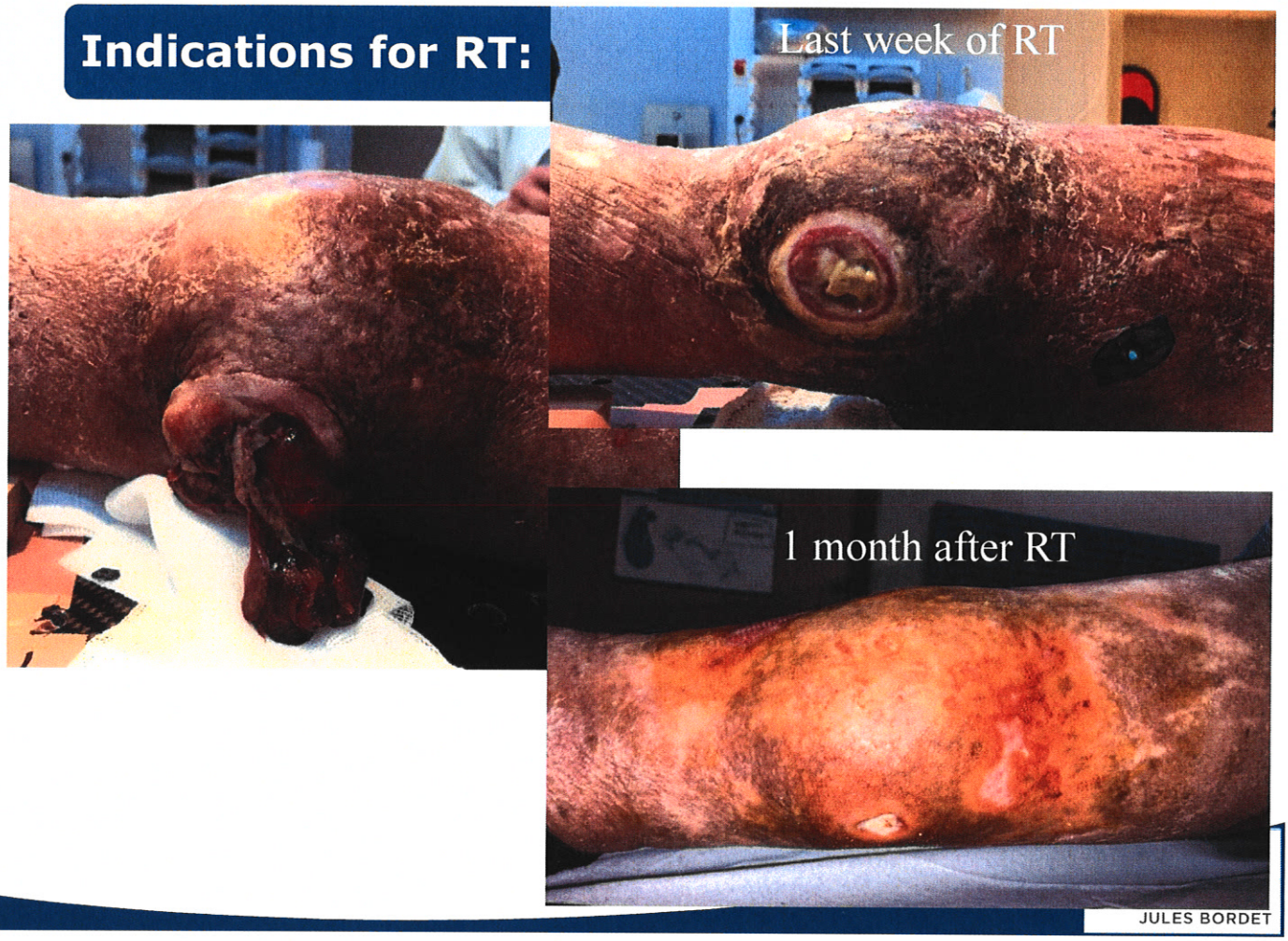
Underuse of RT is seen for a significant proportion of patients undergoing treatment for STS in the United States. More effort needs to be directed towards compliance with appropriate treatment recommendations, perhaps by regionalizing sarcoma care or remote multidisciplinary tumor boards. J. Surg. Oncol. © 2014 Wiley Periodicals, Inc.

Indications for RT: Radical radiotherapy

Mr PV, 82 years old presents with a high grade myxofibrosarcoma of the left calf

- He refuses amputation

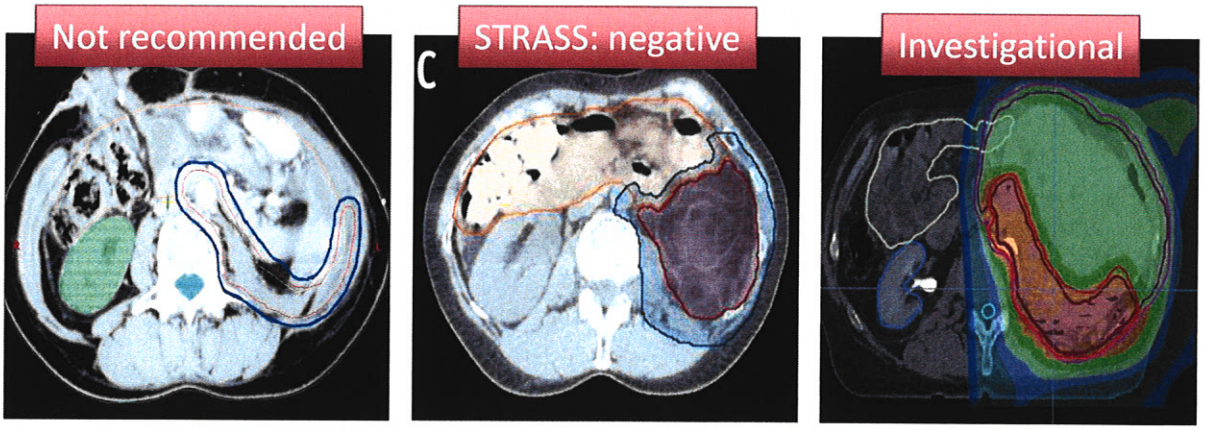
Indications for RT:



Indications for RT: RetroPeritoneal STS

Before STRASS!

- Only small studies, better LC, no evidence on OS, highly debated



POSTOPERATIVE RT
- TV poorly identifiable
- OARs within the PTV
- Higher dose (54-60 Gy)
- Acute/late toxicities ↑

PREOPERATIVE RT
- TV well identifiable
- OARs outside PTV
- Lower dose (50 Gy)
- Acute/late toxicities

HADRONTHERAPY + BOOST
- Excellent OARs sparing
- Boost to high risk regions

Courtesy X Geets

Indications for RT: RetroPeritoneal STS

Journal of Clinical Oncology®
An American Society of Clinical Oncology Journal

STRASS (EORTC 62092): A phase III randomized study of preoperative radiotherapy plus surgery versus surgery alone for patients with retroperitoneal sarcoma.

Sylvie Bonvalot, Al
Pierre Meeus, ...

significance level. **Results:** 266 patients from Europe, USA and Canada were randomized between January 2012 and April 2017; 198 patients (74.5 %) had liposarcoma (LPS). Eighteen patients were designated ineligible. Overall rate of re-operation for any complication was 10.1%: 13 (10.9%) and 12 (9.4%) patients in RT/S versus S groups. 19 pts (14%) progressed during RT, 4 of whom did not undergo surgery. 3-year ARFS was 60.4% (95% Confidence interval (CI) 51.4-68.2%) and 58.7% (49.5- 66.7%) (HR = 1.01, 95%CI 0.71-1.44, p=0.954) in RT/S versus S groups. In the sensitivity analysis, 3-year ARFS was 66.0% (57.1-73.5%) and 58.7% (49.5-66.7%) in RT/S versus S groups (HR = 0.84, 95% CI 0.58-1.21, p=0.340). In the LPS subgroup, 3-year ARFS (sensitivity analysis) was 71.6% (61.3-79.6%) and 60.4% (49.8-69.5%) in RT/S versus S groups (HR = 0.64, 95%CI 0.40-1.01, p =0.049).
Conclusion: STRASS failed to demonstrate a benefit of pre-operative RT for RPS. In the exploratory analysis, preoperative RT may benefit the LPS subgroup. Funding

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Classical palliative RT

Control/prevention of symptoms due to a tumor

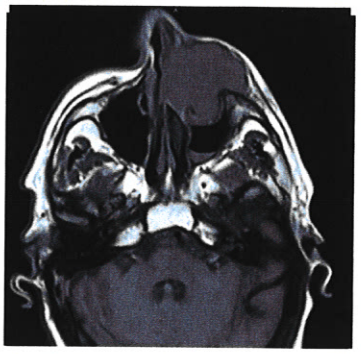
- Pain = most often

BUT ALSO:

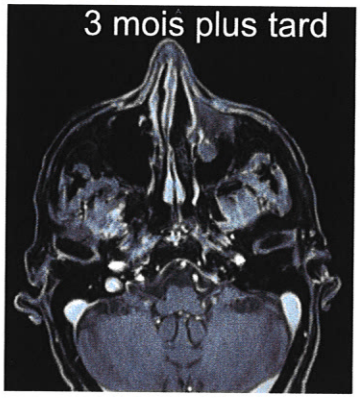
- Neurological troubles,
- Bleeding,
- Obstruction (pulmonary, intestinal, …),
- Hygienically or psychological problems,
- …

1-5 fractions , can be repeated!

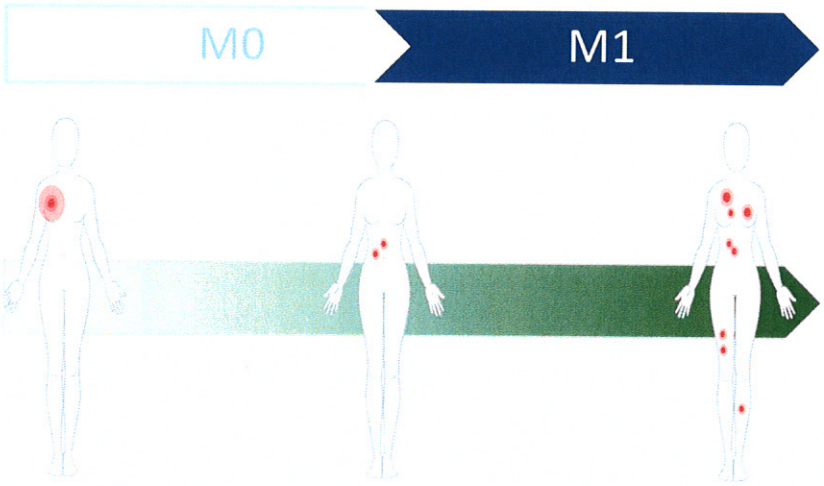
Symptom Control quite fast + often persistent



35 Gy/ 15 fr



Oligo-metastatic disease



Oligometastases:
Role of local therapy?

- Surgery
- Ablation
- Radiotherapy

Oligo-metastatic disease

Not so new:

- Hellman and Weichselbaum first proposed the concept of oligometastases in 1995
- Resection of lung M+ of sarcoma
- Resection/ablation of liver M+ of GI
- Surgery/GammaKnife for brain M+
- Bojko et al. SBRT prospective on oligomets in breastCa in 2004

SBRT for oligo-metastatic disease

SABR-COMET trial (Palma; Lancet 2019, JCO 2020)

Randomized phase II screening design: SOC +/- SBRT

(± pall. RT in SOC alone)

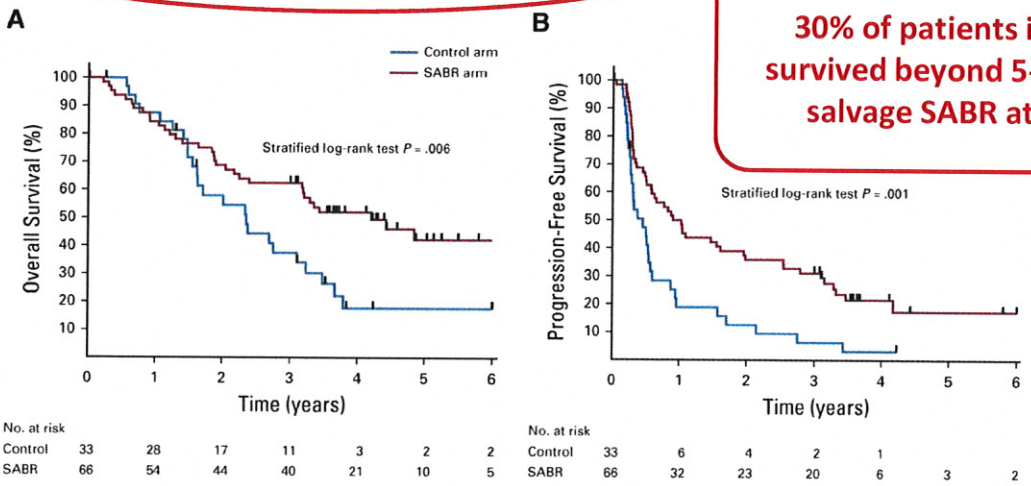
- 99 patients randomized (n=92:1-3 metastases);
- FU: median follow-up 51 months

SBRT for oligo-metastatic disease

SABR-COMET trial (Palma; Lancet 2019, JCO 2020)

- LC: 46% vs 63%, p=0.039 (adrenal, 100%; bone, 72%; lung, 51%; liver, 50%; P = .04)
- 4y PFS: 3,2% vs. 21,6%, p=0.001
- 5y OS: 18% vs. 42%, p=0.006

30% of patients in Arm 2 who survived beyond 5-years received salvage SABR at some point



Ongoing randomized trials for genuine oligometastases

- Various primaries:
  - SABR-COMET-3 (phase III, 1-3 mets)
  - SABR-COMET-10 (phase III, 4-10 mets)
  - CORE (phase III, prostate, breast, non-small-cell lung cancer)
  - OligoRare (phase III, excluding prostate, breast, NSCLC and colorectal)
- Prostate:
  - PEACE V: STORM (phase II, oligo-recurrent prostate cancer, SBRT vs. profylactic RT)
  - PCS IX (phase II/III, castration-resistent oligometastatic recurrence)
  - STAMPEDE
- NSCLC:
  - NRG-LU002 (phase II/III, after induction therapy)
  - SARON (phase III, after induction therapy)
  - SINDAS (phase III, TKI +/- SBRT)
- Breast:
  - NRG-BR002 (phase II/III, new OMD)
  - STEREO-SEIN (phase III, before start of systemic therapy)

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Conclusions: Bone sarcoma

When to considerer RT?

- Non-radical surgery
- Radio-sensitive Tu in combination with surg +/- chemo
  - Ewing Sarcoma
  - Fibrosarcoma
- Carbon Ions (protons): Chordoma/Chondrosarcoma; Osteosarc??

www.bonetumor.org

Conclusions: Soft tissue sarcoma

- Few randomised trials
- Conservative Surgery (often) needs RT: LC: 72-93%, OS idem
- RT indicated when margins <1cm or >G1
- Pre-op = post-op: post-op less wound healing problems
- IMRT > 2D/3D : for toxicity, not for outcome
- Toxicity very acceptable, so **do not underuse RT!!!**
- Quid retroperitoneal sarcoma? Strass: Indication for LPS?

Conclusions: Palliative RT

- Classical RT
  - Few fractions, excellent tolerance
  - Symptom Control quite fast and often persistent
- Stereotactic RT for oligo-M+ disease
  - Ablative RT
  - Phase II study: 5y OS: 18% vs. 42%
  - Phase III studies ongoing

Radiation-Oncology for sarcomas

I thank you for your attention

dirk.vangestel@bordet.be

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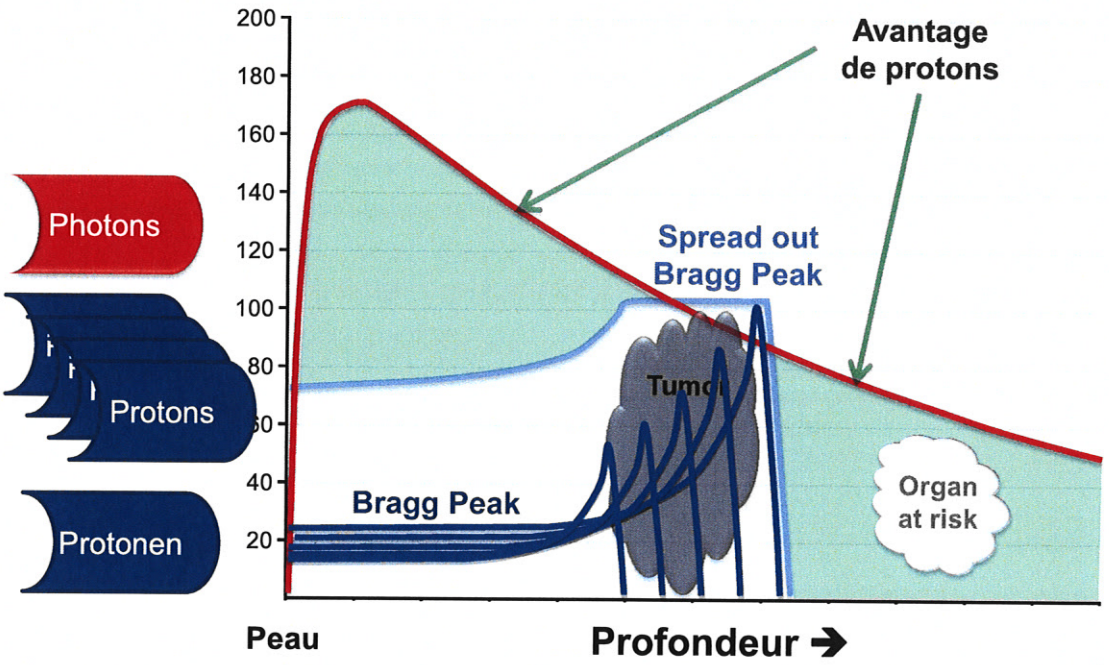
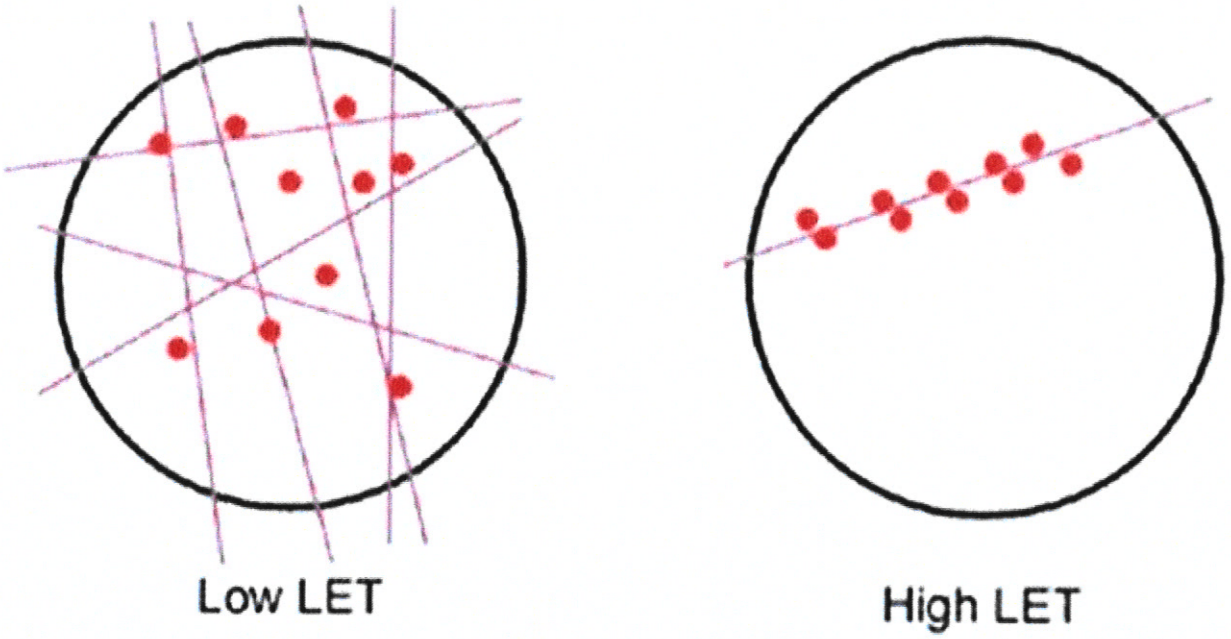
Protons versus Photons



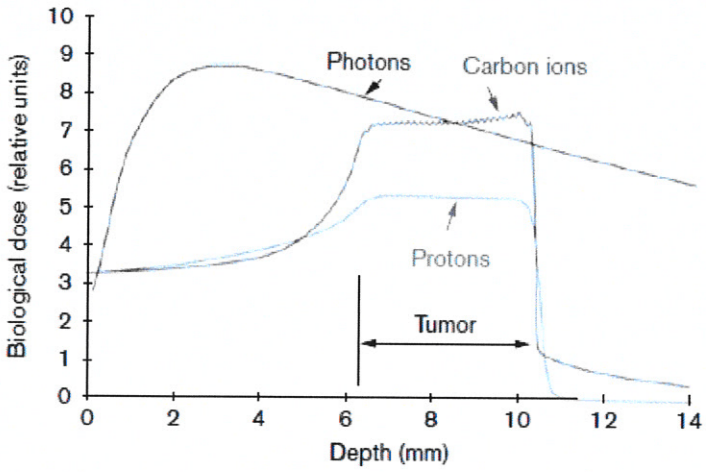
Courtesy H Langendijk, UMC Groningen

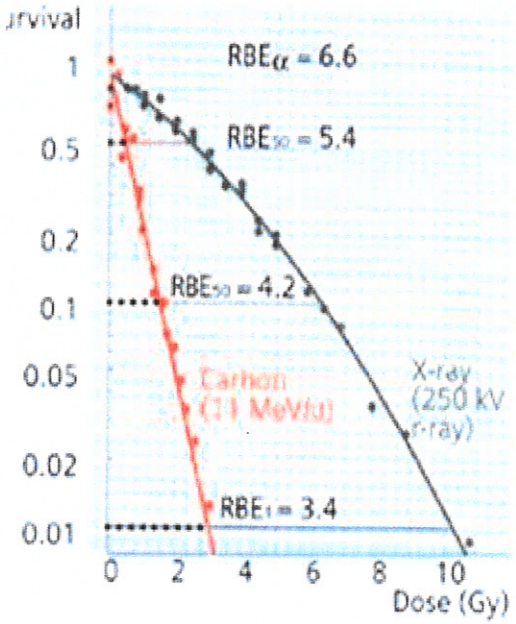
Particle Therapy: Protons vs Carbon Ions

Energy: heavy ions (Carbon ions, …)



Particle Therapy: Protons vs Carbon Ions





Less oxygen dependent!

Thariat et al, 2011

Particle Therapy: Protons vs Carbon Ions

Indications for Proton Therapy in adults:

1) Ocular melanoma, where brachytherapy is not possible
2) Paraspinal or sacral, skull base chordoma
3) Paraspinal or sacral , skull base chondrosarcoma/sarcoma
4) Meningioma, for which no other medical treatment is possible
5) Cerebral arterio-venous malformations (AVM), for which no other treatment
6) Medulloblastoma

CAVE! NO level 1 evidence

Particle Therapy: Protons vs Carbon Ions

Indications for Carbon Ion Therapy in adults:

1) malignant mucosal melanoma

2) non-resectable or insufficiently resected adenoid cystic carcinoma

3) non-resectable or insufficiently resected salivary gland carcinoma

4) Paraspinal or sacral, skull base chordoma

5) Paraspinal or sacral, skull base chondrosarcoma/sarcoma

CAVE! NO level 1 evidence