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A Phase I / II Pilot Study of Proton Radiotherapy and Hyperthermia in Primary or Recurrent Unresectable Adult Soft Tissue Sarcoma (HYPROSAR)

(ClinicalTrials.gov NCT01904565)

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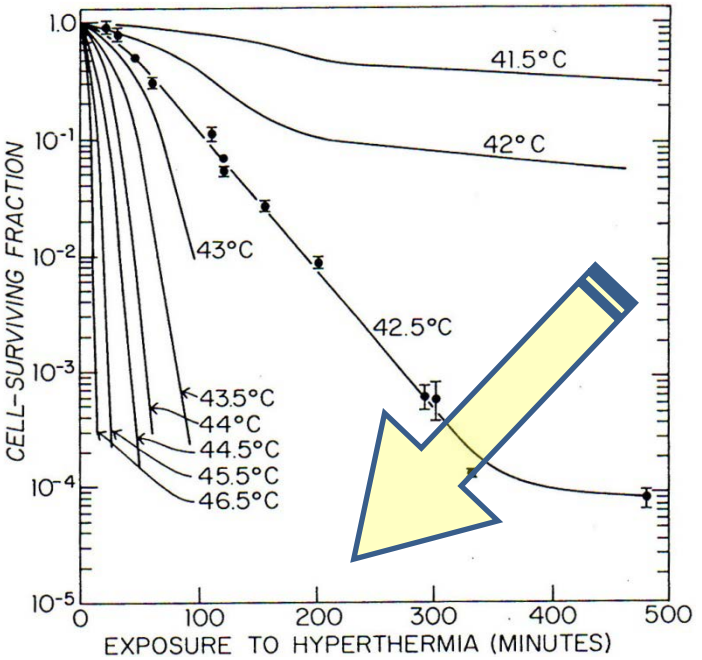
Phase I / II trial: “HYPROSAR”

- **The Rationale:**
  - Hyperthermia
  - Proton
  - Hyperthermia and Protons
- **Trial design and work flow**

Hyperthermia

Cellular Basis of Hyperthermia:

- Neoplastic cells intrinsically more heat sensitive
- Hypoxic and nutritionally deficient cells are heat sensitive
- Cells at low pH are heat sensitive
- Radioresistant “S” phase cells are heat sensitive
- Heat inhibits repair of radiation induced DNA SSB
- Thermal synergism with a number of chemotherpeutic drugs



Temperature dependent changes in shape of Cell survival curve

(Dewey WC, Radiology,123,463-77,1977)

Thermal synergism

Hyperthermia and Radiation

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- Well oxygenated
- Normal pH
- Sufficient nutrients
- Cell proliferation

- Hypoxic
- Low pH
- Insufficient nutrients
- No proliferation

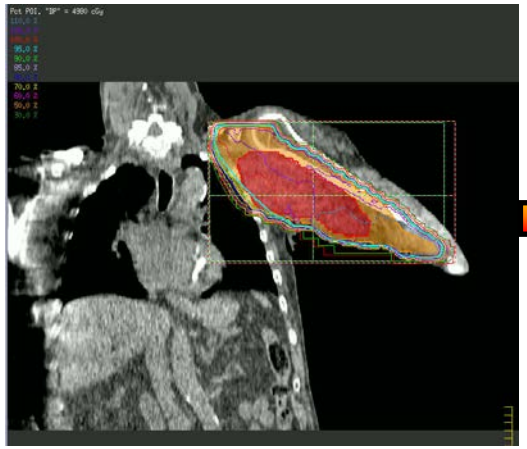
Heat resistant
Radiosensitive

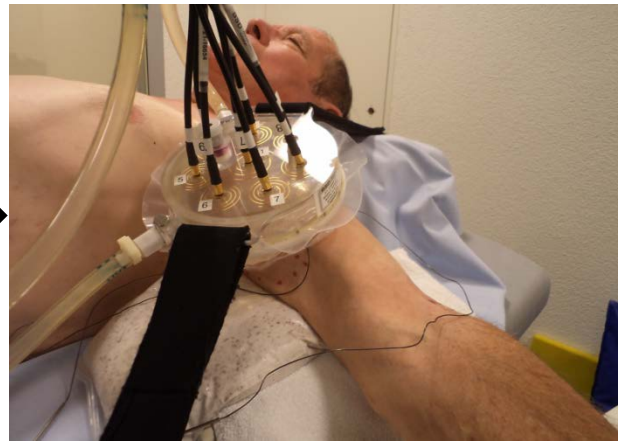
Heat sensitive
Radioresistant

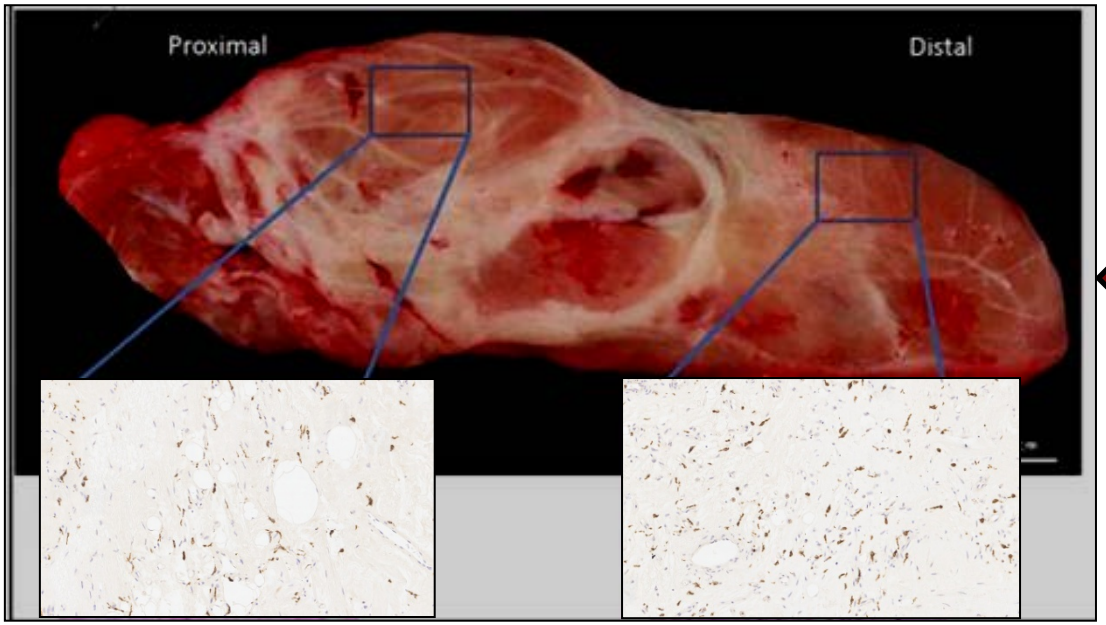
Hyperthermia
and
Radiotherapy
are Complementary to each other

A case illustration:

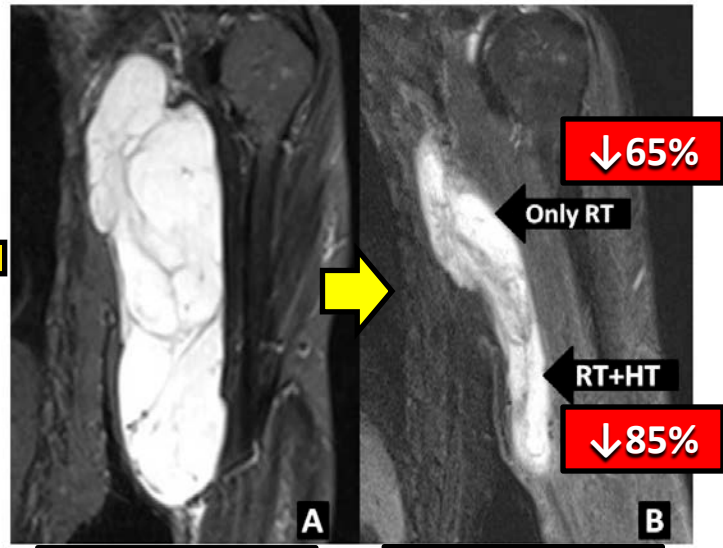
RT alone (Proximal part); RT+HT (Distal part)







CD 68+ (Macrophages) (↑23%)

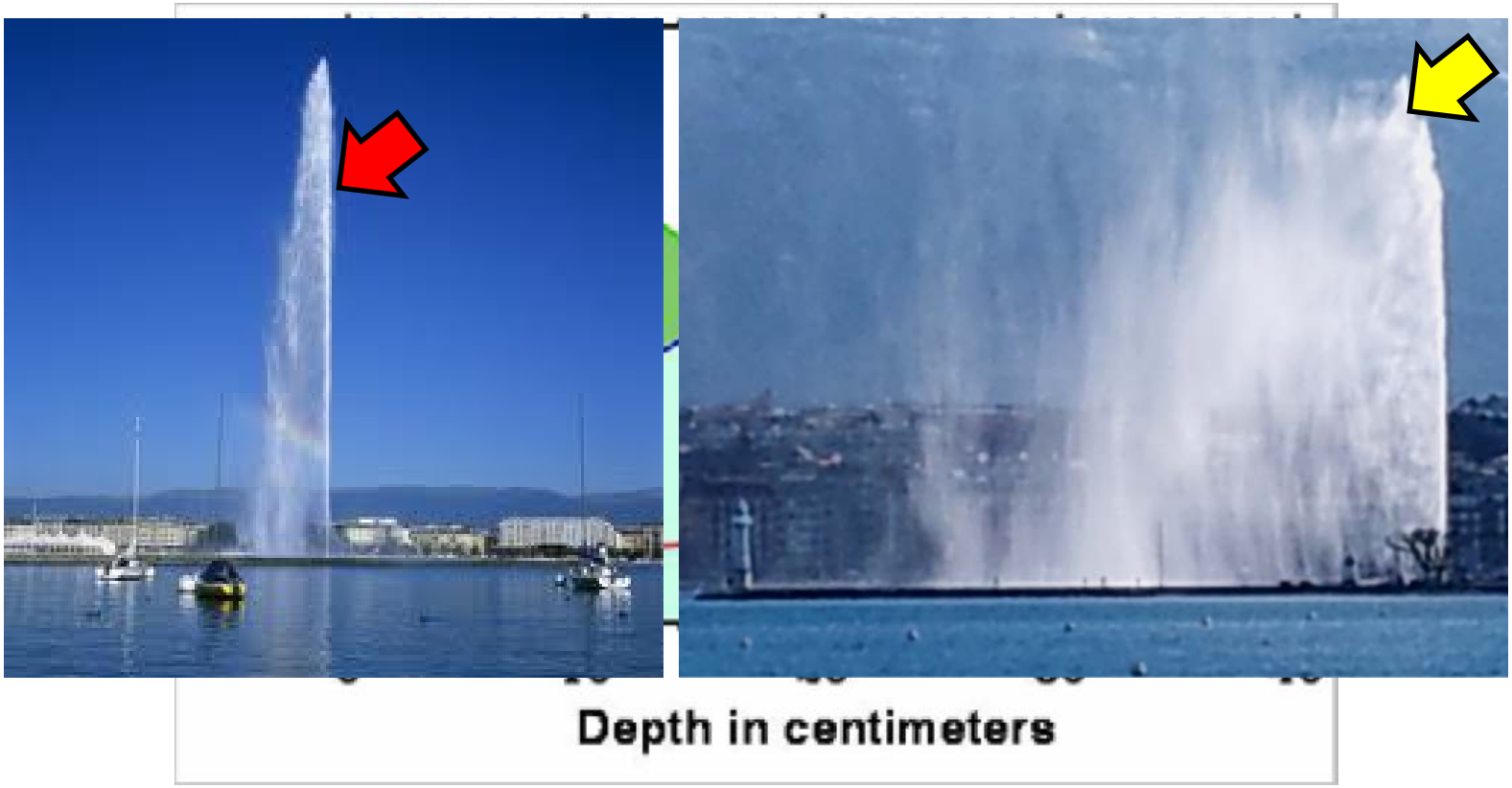


Pre RT

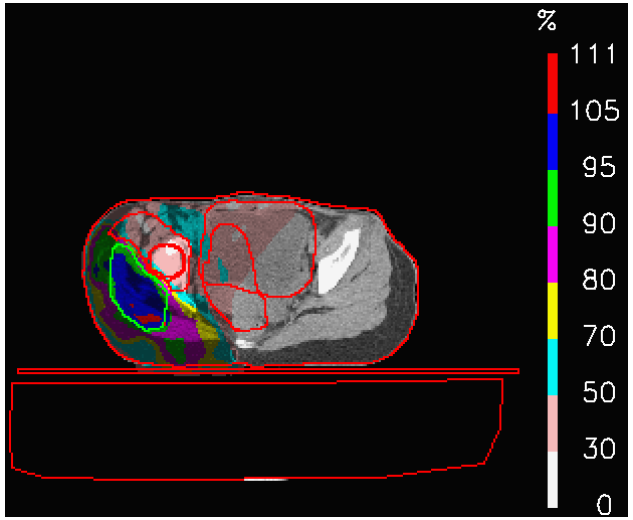
Post RT

Proton beam therapy

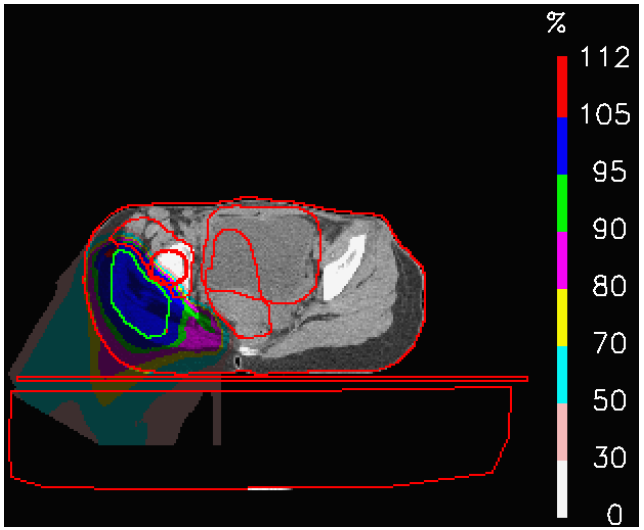
Protons:
Physical dose distribution



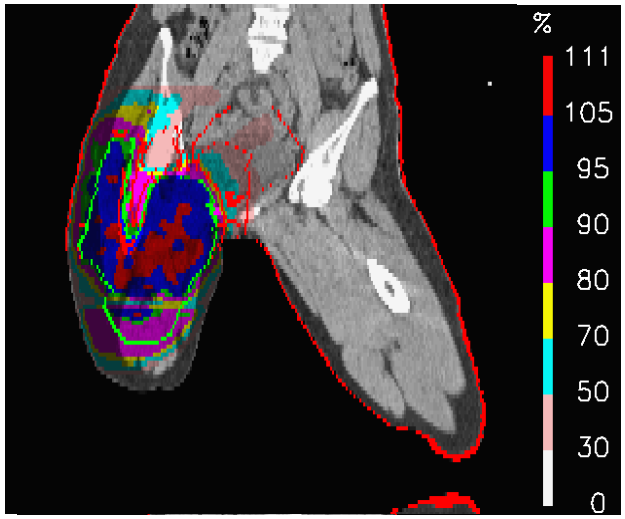
Photon vs. Proton : Dose Profile Comparison



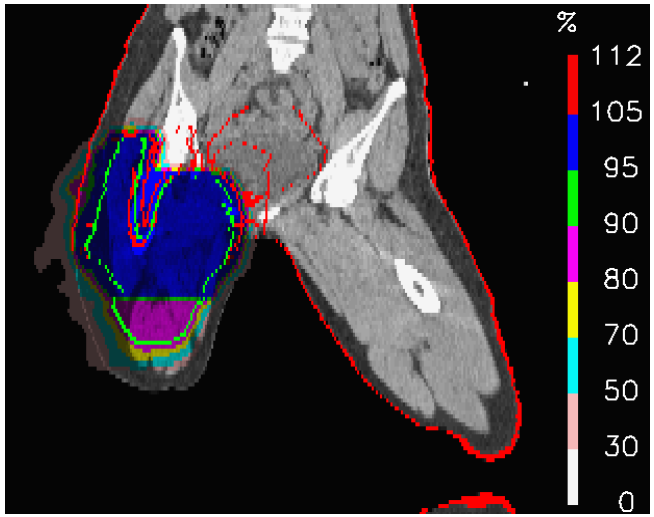
Transaxial



Better tumour coverage, less normal tissue dose with Proton

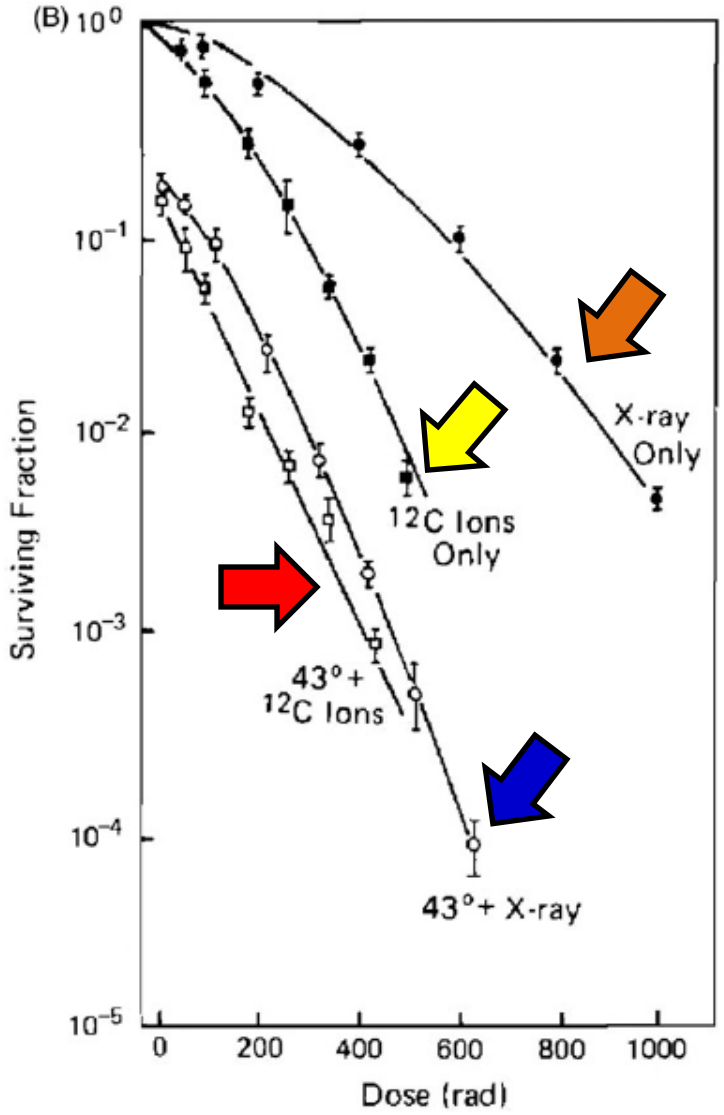


Coronal



Hyperthermia and Proton beam therapy

Hyperthermia and Particle Radiation:
Radiobiological Implictions



Absence of significant Heat radiosensitization with Carbon ions compared to X rays

Does it indicate "High LET" properties of Hyperthermia?

"Hyperthermia – A poor man's High LET radiation"

(Ilakis G et al, Int J Hyperthermia 2008; 24:17-29)

Protons and Hyperthermia:
Physical dose & Radiobiological advantage?

Could Physical Advantages of Protons

coupled with

High LET properties of Hyperthermia

Could it mimic "Carbon Ion Therapy"?

Phase I / II trial:

Primary and Secondary Objectives

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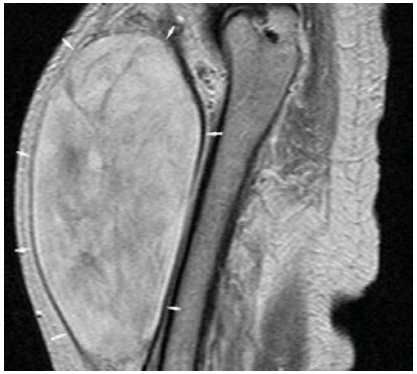
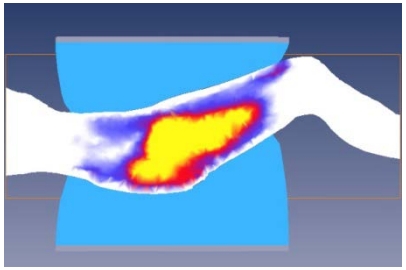
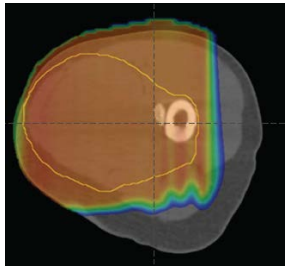
Primary Objectives

Safety and Efficacy of Hyperthermia (HT) + Proton beam RT







1. Acute morbidity
2. Wound complication
3. Local tumour response

Secondary Objectives

Survival outcomes:

- Local disease control at 2 years
- Local disease free survival at 2 yrs

Phase I / II trial: "HYPROSAR"

Major Eligibility Criteria for Recruitment

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Inclusion Criteria

- Age ≥ 18 years
- ECOG : 0 and 1
- **Primary Unresectable or Recurrent** STS of extremities, trunk, retroperitoneum
- **T2 and G2 or G3 with M0** (Stages IIB & III, AJCC 2010)
- No prior radiotherapy to the site of proposed treatment

Exclusion Criteria

- RMS, Extraosseous Ewing's, PNET, Desmoids, Dermatofibrosarcoma protuberans, GIST, Kaposi's sarcoma or angiosarcoma of scalp/face/neck
- **Intra-abdominal STS**
- **N+ or M1 stages**
- Metal markers, Clustered markers, Pacemaker

Phase I / II trial: "HYPROSAR"

Schema

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Review by the Joint Sarcoma Tumour Board
(Radiologists, Pathologist,
Surgical, Radiation & Medical Oncologist)

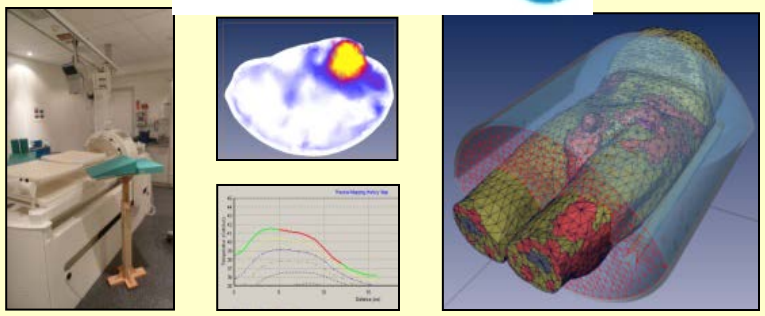
Primary Inoperable STS
or **patient refusal** or
medically unfit for surgery

Recurrent Inoperable STS
or **patient refusal or**
medically unfit for re-surgery

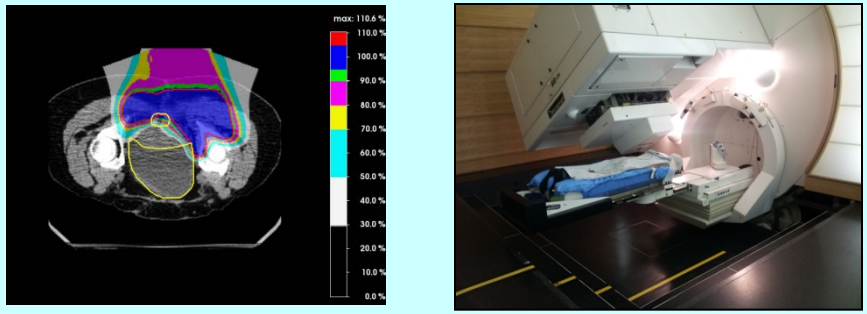
Criteria for Inoperability on case by case basis based on
Local tumour infiltration to vital structures and neurovascular bundle

Phase I / II trial: HYPROSAR

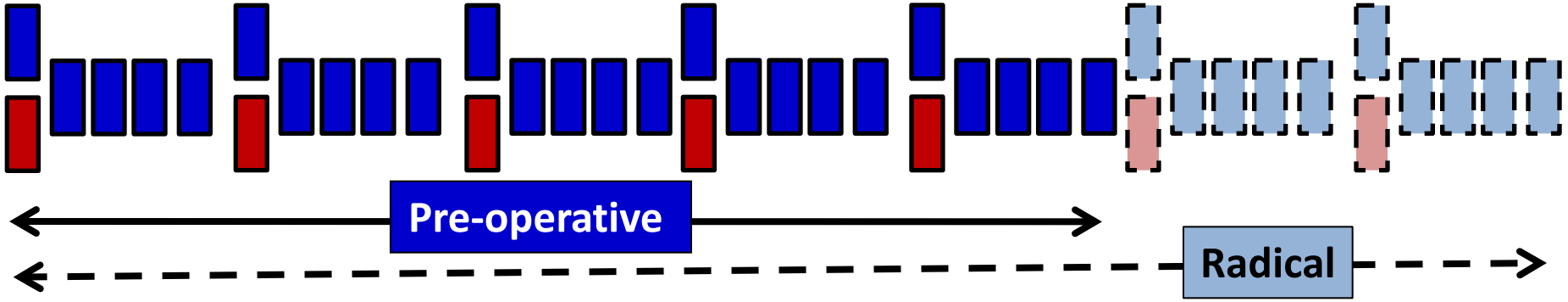
Treatment Protocol



Hyperthermia: 41.5-42.5°C x 60 mins, Superficial or Deep Hyperthermia at KSA after RT

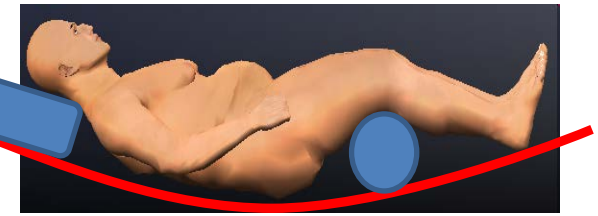


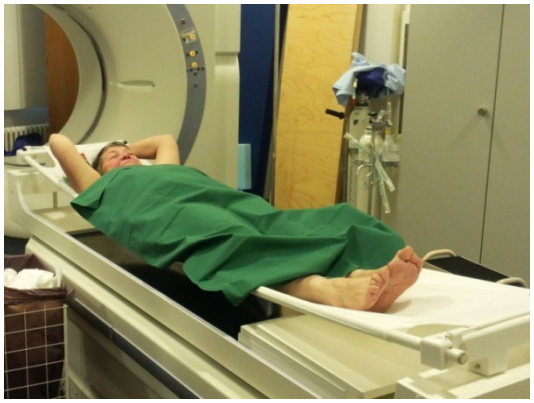
IMPT, 5 days a week,
Pre op: 55 – 60 GyE (RBE);
Radical: 72 – 76 GyE (RBE)[1.8 -2.0 Gy/fr.]

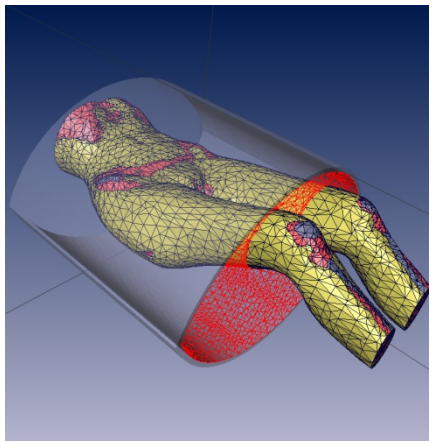


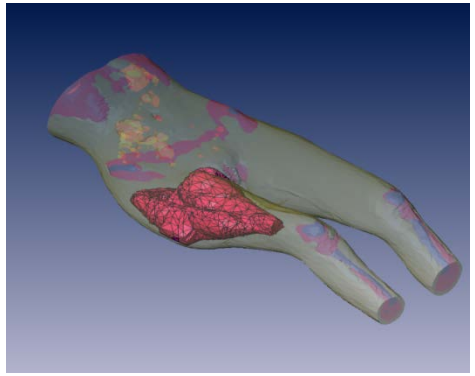
(On the days of both HT treatment at KSA and Proton therapy at PSI
Time interval between HT and RT : 90 mins to 150 mins; RT to precede HT)

Hyperthermia Planning

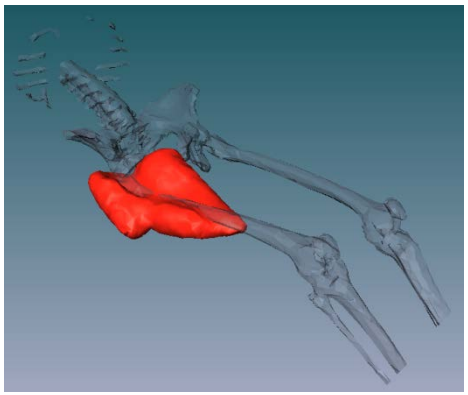




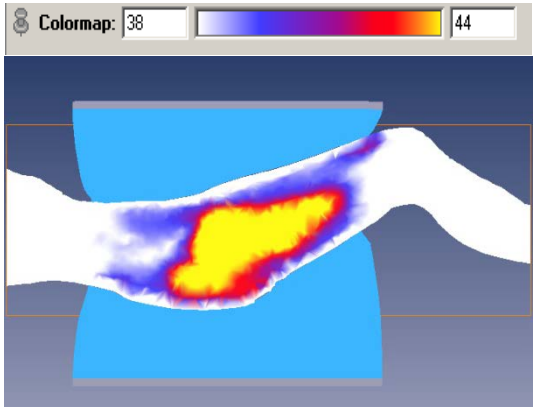




Segmentation and creation of a grid model for tissues



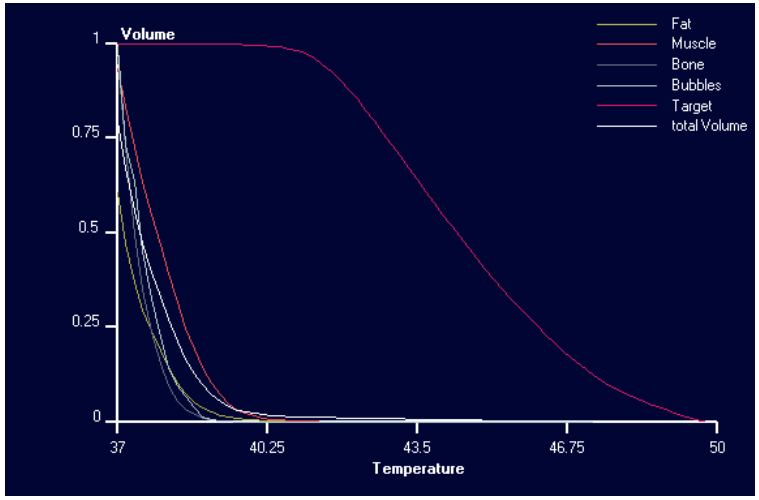
Isosurface Temp > 43°C

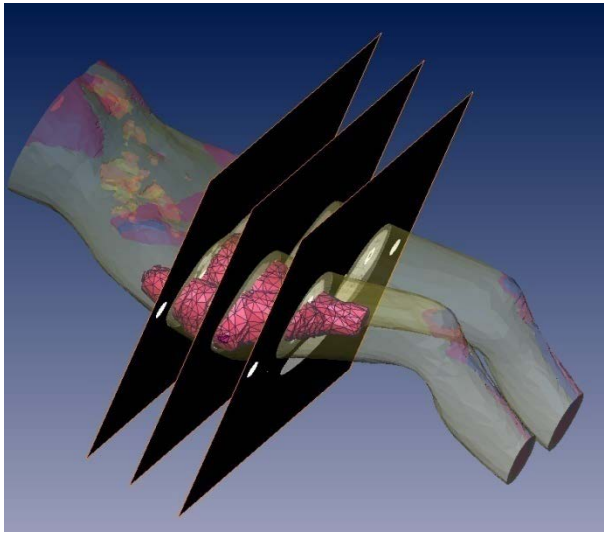


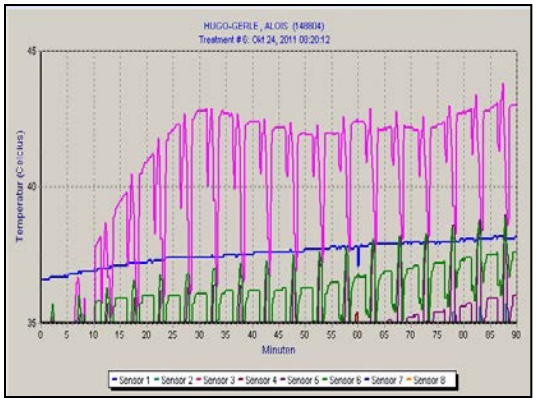
Temperature fieldcut

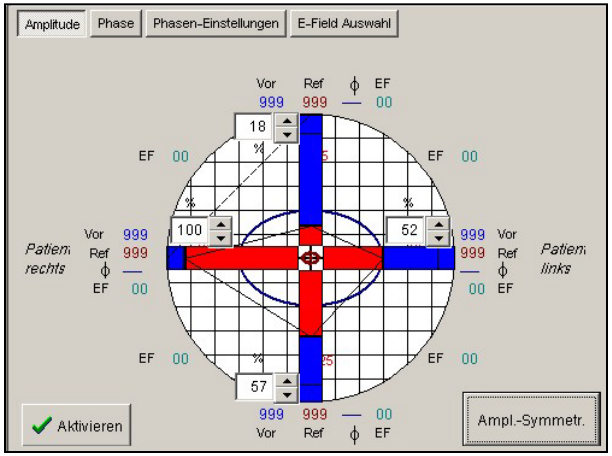
Hyperthermia Planning & Delivery

Evaluate Thermal DVH









Concurrent temperature monitoring

Amplitude & Phase Steering

Phase I / II trial: "HYPROSAR"

Post treatment Management

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Review by Sarcoma Board

Good response (↓>30%) :
Continue with **Preop RT** and consider for Surgery (attempt R0 resection)

Still considered inoperable:
Continue RT to **Radical Dose**,
Patient on follow-up, **review at 3 months**

If **good response**
Consider for surgery

If still considerable **inoperable**

To evaluate resected specimen for pathological response & molecular studies

Adjuvant Chemotherapy, Follow up and close monitoring for response and toxicities

Sample size considerations

Sample size consideration

Phase I / II : Proton + Hyperthermia

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Phase 2 Study of Preoperative Image-Guided Intensity-Modulated Radiation Therapy to Reduce Wound and Combined Modality Morbidities in Lower Extremity Soft Tissue Sarcoma

Brian O'Sullivan, MD[1,2]; Anthony M. Griffin, MSc[3]; Colleen I. Dickie, MSc[1]; Michael B. Sharpe, PhD[1,2]; Peter W. M. Chung, MD[1,2]; Charles N. Catton, MD[1,2]; Peter C. Ferguson, MD[2,3]; Jay S. Wunder, MD[2,3]; Benjamin M. Deheshi, MD[2,3]; Lawrence M. White, MD[2,4]; Rita A. Kandel, MD[2,5]; David A. Jaffray, PhD[1,2]; and Robert S. Bell, MD[2,3]

were deep to fascia. **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 dimin-

(Wound Complications with Image Guided IMRT : 30.5%)

Improvement from 30% (p0) to 10% (p1); α = 0.05, Power = 0.80
Total sample size: 26 (+2)

(Cancer, 2013; 119: 1878-84)

Proton Beam Thermo- radiotherapy : A Novel Approach

Radiotherapy & Oncology
European Society of Radiotherapy and Oncology

Editorial

The heat is (still) on – The past and future of hyperthermic radiation oncology

Jens Overgaard *

Department of Experimental Clinical Oncology, Aarhus University Hospital, Aarhus C, Denmark

November 2013

Thus, the heat is still on – and we need to give full credit to the most powerful way of sensitizing ionizing radiation and thus once again focus on this not fully explored opportunity of combining radiotherapy with hyperthermia, but it must be done with an open mind and a cool head.

Gantry 2 at PAUL SCHERRER INSTITUT PSI

Phase I / II trial: "HYPROSAR"

Time line

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Trial opens: **Jan 2014**

↓

Attempts for recruiting
1-2 patients / month

↓

Recruitment finishes:
Dec 2015

↓

Minimum patient FU:
30 months by July 2018

↓

Data compilation, analysis,
publication of results by **Dec 2018**

↓

Trial ends : Dec 2018

HYPROSAR

HYPROSAR Trial Group

Kantonsspital Aarau

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ICTR-PHE 2014

Thank you

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