

Four case reports on complex high risk sarcoma cases treated with modulated electro-hyperthermia

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www.oncotherm.com/sites/oncotherm/files/2021-02/Minnaar_Highrisksarcoma.pdf

Abstract

Introduction: Radiative hyperthermia (HT) for the treatment of sarcomas has been applied in combination with chemotherapy, showing improved local control and survival ^[1,2]. Only two small studies have assessed HT plus radiotherapy (RT) ^[3,4] and few have assessed mEHT for the management of sarcomas.

Objectives: To determine if there is sufficient motivation for the addition of mEHT, as a more affordable and practical HT solution, in the management of sarcomas, in the absence of any further options.

Material and methods: We present four interesting and complex cases of local recurrences in a previously irradiated region treated with modulated electro-hyperthermia (mEHT) locally, combined with chemotherapy or RT, at our facility.

Results

Patient 1: 42yr old female with a synovial sarcoma of the heart valve treated with a heart transplant and chronic immunosuppressant medication; mediastinum and pulmonary nodules developed 5yrs later. Treatment: 30x2Gy fractions + mEHT to the mediastinum. Inactive pacemaker present, outside the treatment field. Patient is stable at 18months post treatment and is enjoying an excellent quality of life.

Patient 2: 68yr old male with a local recurrence of a myxoid liposarcoma in the right thigh (30cm) 1yr after excision and RT. Treatment mEHT twice weekly for 19mnths (12 of which chemotherapy was administered 3wkly). Tumour shrunk significantly and remained stable until the patient died of septicaemia from a wound infection on his foot.

Patient 3: 52yr old woman with an RAS 5yrs after treatment for a SCC of the left maxilla sinus. Prescribed RT+mEHT. Treatment was tolerated well but the tumour did not respond.

Patient 4: Male patient with a sarcoma in the right shoulder, treated initially with surgery, followed by several local recurrences treated with either surgery, external beam radiation, or brachytherapy, over five years. Prescribed external beam radiation combined with mEH

Conclusions: mEHT could be considered when no further options are available as a safe adjunct to treatments. There is motivation for the design of a trial investigating RT+mEHT for the management of high-risk sarcomas, especially in cases in which patients have been previously irradiated.

^[1] Issels RD et al, Lancet Oncol [Internet]. 2010;11(6):561–70

^[2] Issels RD et al, JAMA Oncology. 2018;4(4):483-492

^[3] Leopold A et al, Int J Radiat Oncol Biol Phys. 1989;16(1):107–15

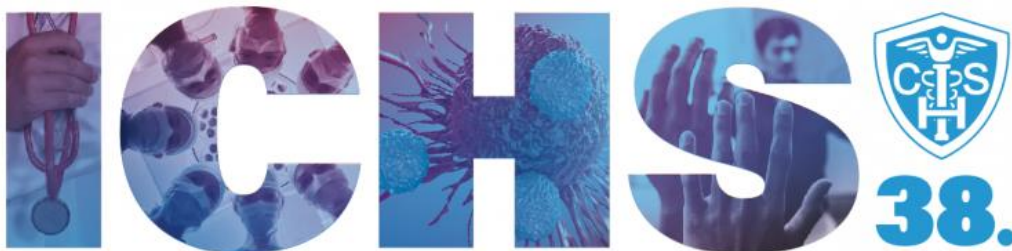
^[4] de Jong MAA et al, Cancer. 2012;118(1):180-187

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Sarcomas

- Sarcomas are rare (<1% of all cancers) and heterogenous tumours
- More than 100 unique sarcoma subtypes
- Metastatic and refractory tumors have poor outcomes
- Management involves a multidisciplinary approach
 - Surgery
 - Radiation
 - Chemotherapy
 - Rehabilitation
- Management guidelines have been developed in high-income countries, but their applicability in low-income countries, where resources may be limited, remains a challenge.

DOI: 10.1200/EDBK_200589 American Society of Clinical Oncology Educational Book 38 (May 23, 2018) 916-924.

Sarcomas and Hyperthermia

ESMO guidelines mention Hyperthermia (HT) for the management of high risk soft tissue sarcomas.

HT combined with radiotherapy or chemotherapy indicated for:

- Irresectable, locally advanced deep high-risk soft tissue sarcomas (>5 cm) grade 2 or 3,
- Limb-preserving surgery – isolated limb perfusion/regional;
- Metastatic or recurrent tumours that have been previously exposed to treatment and require re-treatment.

Including Liposarcoma, leiomyosarcoma, synovial sarcoma

Based on a Phase III clinical trial with a 10 year follow

Casali P, Bbecassis N, Bauer S, et al. Soft tissue and visceral sarcomas: ESMO – EURACAN Clinical Practice Guidelines for diagnosis, treatment Clinical Practice Guidelines. ESMO Clinical Practice Guidelines. 2018;29

Sarcomas and Hyperthermia

- Randomised controlled multicentre Phase III, multicentre
- 329 participants with grade 2 or 3 STS >5cm (deep)
- Neoadjuvant chemotherapy: EIA x 8 cycles 3 wks apart
- 16 HT (administered on day 1 and 4 of each cycle)

Outcome	HT+ChT	ChT	p
Progression free at 2yr	30%	19%	p=0.035
Median PFS	120mnths	75mnths	p=0.003
Median DFS	18mnths	32mnths	p=0.011
5yr Survival	63%	51%	p=0.04
10yr Survival	53%	43%	
Median time to local progression	67.3mnths	29.2mnths	p=0.002
Median survival	15.4yrs	6.2yrs	p=0.04

[1] Issels RD et al, *Lancet Oncol*. 2010.11(6):561–70.
[2] Issels RD et al, *JAMA Oncology*. 2018;4(4):483-492.

Sarcomas and Hyperthermia

Only two small studies have assessed HT plus radiotherapy (RT) for the management of sarcomas:

1. Phase II study investigating neoadjuvant RT+HT (n=17):
Showed Significantly higher histopathological regression when HT applied 2/wk vs 1/wk [1]
2. Retrospective study of RAS of the thorax (n=16):
Treated with RT (AMC/BVI protocol*) +HT
7 CR; 2 PR and a median survival of 15.5 months [2]

*AMC protocol: 8x4Gy (twice per week) + HT once a week
BVI protocol: 12x3Gy (4 per week) + HT twice a week

[1] Leopold A *et al*, *Int J Radiat Oncol Biol Phys*. 1989;16(1):107–15
[2] de Jong MAA *et al*, *Cancer*. 2012;118(1):180-187

Sarcomas and Hyperthermia

Triple modality Study

- CRT+HT (8MHz RF capacitive) was administered to 60 STS patients in Japan and compared to retrospectively to the bone and soft tissue tumour registry
- OS was not significant between groups (HR=1.26, p=0.532);
- LC was significantly improved with HT (HR=4.82, p=0.037).
- Higher 5 year LC rate with HT and amputation was averted despite wider resection margins in the retrospective group.

Aiba *et al*, (2018) *Cancer Original Research*. doi: 10.1002/cam4.1366

Modulated Electro-Hyperthermia (mEHT)

- Capacitive heating technology
- Transmits amplitude modulated radiofrequency (RF) waves 13.56MHz, between two electrodes.
- Small electrode is covered by a water bolus in an adjustable arm,
- Large electrode is in the bed and is covered by a water mattress.
- Amplitude modulation is the main difference between mEHT and other capacitive devices
- Modulation is a key component of the enhanced efficiency of mEHT, allowing for a lower power output and increased safety

Minnaar et al (2020) Int J HT, VOL. 37, NO. 1, 263–272

mEHT and Sarcomas

Case Study:

Case report on Synovial Sarcoma, published in 2013 [1]:

- 48-year-old female with synovial sarcoma in the right thigh
- Treated surgically in 2004
- Lung metastasis diagnosed in 2011
- Treated with RT (10x3Gy) - Partial regression
- mEHT administered as a monotherapy: (39 treatments over 6 months) – Partial response

[1] Jeung et al, Conference Papers in Science, vol. 2013, Article ID 392480, 12 pages, 2013.

mEHT and Sarcomas

Report on 13 Cases:

Patients between 18 to 73 years old, 6 male and 7 female, primary and recurrent. Histologic type:

- 2 rhabdomyosarcomas,
- 2 synovial sarcomas,
- 3 leiomyosarcomas,
- 1 malignant peripheral nerve sheath tumor,
- 1 spindle cell sarcoma
- 1 malignant fibrous histiocytoma,
- 2 chondrosarcomas,
- 1 osteosarcoma.

Treatments involved RT+mEHT post-op or primary treatment
mEHT applied twice a week, for a median of 18 treatments (2-108)
1 case received ChT as well

All patients showed stable disease or partial regression

Jeung et al (2015) Case Reports in Clinical Medicine, 4, 157-168

Objectives

To determine if there is sufficient motivation for the addition of mEHT (an affordable option), as a unique therapeutic approach, in the management of sarcomas, in the absence of any further options.

Materials and Methods

We present four interesting and complex cases of local recurrences treated with mEHT locally, combined with chemotherapy or RT, at our facility.

All patients provided consent for the use of their data for this report

Patient 1

42yr old female

2014:

- Diagnosed with a synovial sarcoma of the heart valve
- Heart transplant, pace maker inserted; prescribed chronic immunosuppressant medication (Satican).
- 6 months later the pacemaker was deactivated as heart was functioning normally.

2015 recurrence:

- Multiple pulmonary nodules
- Treated with radio-ablation

2018:

- CT scan revealed progressive disease and multiple pulmonary nodules: Right upper, middle and lower lobe (largest 9.6mm); Left upper, and lower lobe (largest 19.2mm); and Subcarinal and Mediastinal lymphadenopathy.
- Histopathology confirmed monophasic synovial sarcoma
- Gene sequencing showed no relevant mutations
- PDL-1 negative, MLH-1; MSH-2; MSH-6 positive

Patient 1

Treatment:

- Not eligible for chemotherapy.
- Prescribed EBRT to the mediastinum: 33x2Gy fractions
- mEHT:
 - 20cm electrode used, modulation on from 3rd session
 - Progressed from 45W to 90W over 5 sessions.
 - Inactive pacemaker was outside the treatment field.

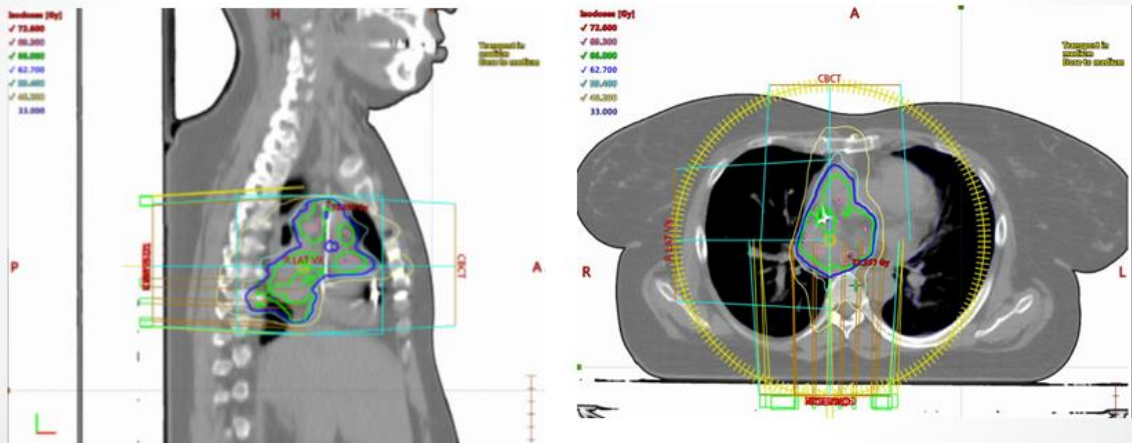
Follow up scan revealed stable disease.

Patient is still stable at 18months post treatment and is enjoying an excellent quality of life.

Patient 1

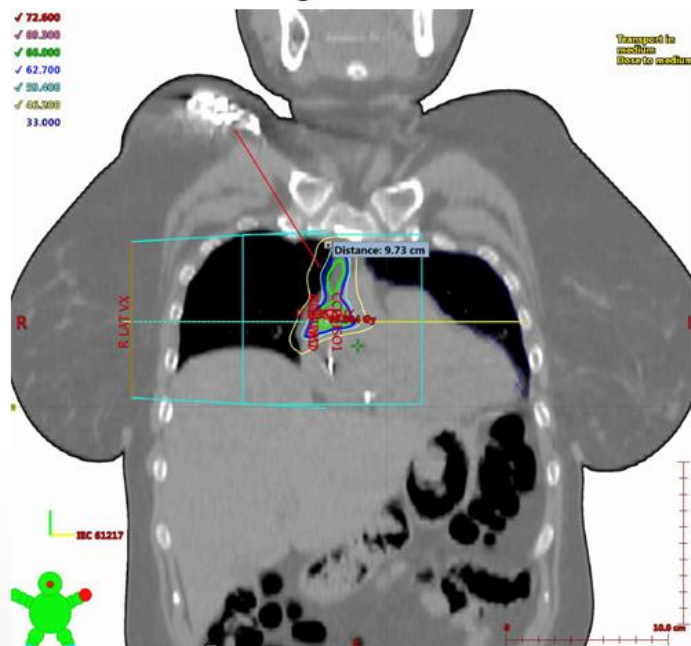
Axial Plan

Coronal Plan



Patient 1

Sagittal Plan



Patient 2

68yr old male

2015

- Diagnosed with Myxoid Sarcoma in the right thigh
- 21x15x10cm
- Surgically excised
- Treated with EBRT (2Gy x 33 treatments) in early 2016
- Followed by another surgically

2018

Inoperable local residual myxoid liposarcoma in the right thigh (30cmx25cm)

Tumour extended from the pelvis, into the anterior thigh and right scrotum, with bladder and rectal compression and displacement, and bilateral hydronephrosis (not eligible for chemotherapy or further RT).

Patient 2

Treatment.

mEHT twice weekly for 3 months (150W for one hour using the 30cm electrode)

CT scan revealed stable disease and improved renal function which allowed for the addition of Caelyx (6 cycles administered 3 weekly) combined with mEHT twice weekly

November 2019 CT showed:

- Resolution of bilateral hydronephrosis,
- Significant decrease in the pelvic portion of the tumour,
- Resolved bowel and bladder obstruction.
- Patient reported normal bowel and urinary function.

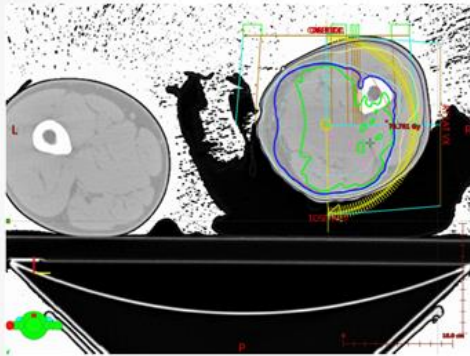
A further 6 cycles of chemotherapy + mEHT were prescribed

CT in May 2020 revealed stable disease, with the tumour remaining predominantly in the anterior portion of the right thigh.

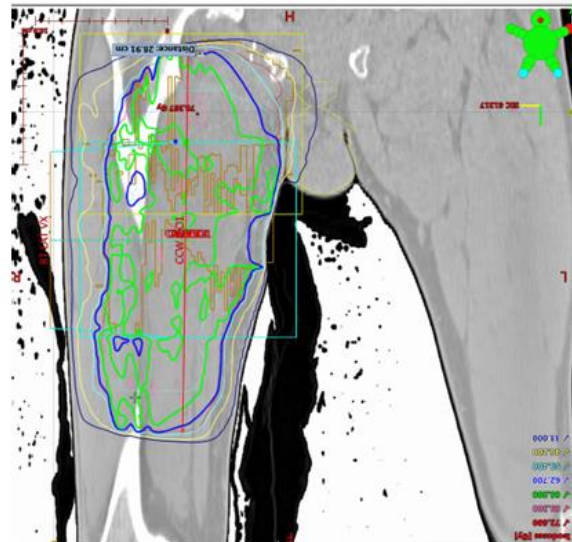
Disease remained stable until the patient died of septicaemia at 19 months from a wound infection on his foot.

Patient 2

Sagittal Plan



Coronal Plan



Patient 3

52yr old woman

2013

SCC of the left maxilla (T4a No Mo)

Left maxillectomy in September 2013

Completed adjuvant EBRT in January 2014

2018

Presented with an enhancing necrotic mass in left maxillary sinus.

Histopathology confirmed a pleomorphic soft tissue sarcoma

In a previously irradiated region

No possibility of surgical resection

Not eligible for chemotherapy

Treatment

IMRT: 2Gy x 25 (large field), then 2Gy x 5 (gross tumor volume boost)

mEHT weekly up to 100W

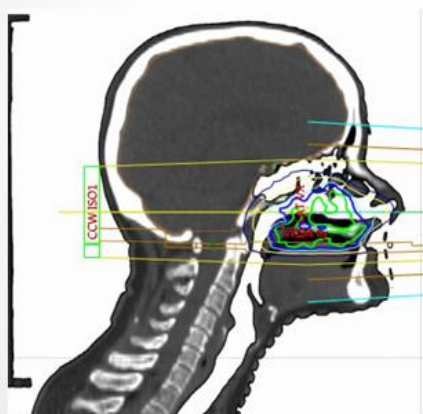
Patient 3

Outcome

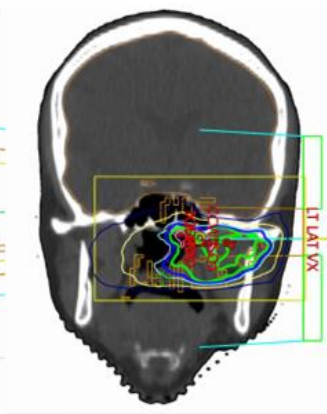
- Radiation Associated Sarcomas are notoriously difficult to manage.
- Post-treatment CT showed progressive disease.
- mEHT did not result in any additional RT related toxicity
- No AEs resulted from mEHT

Patient 3

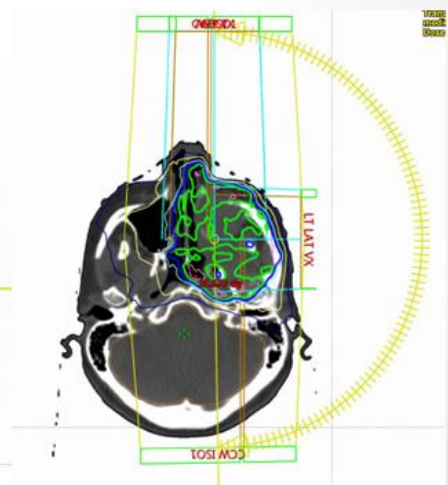
Sagittal Plan



Coronal Plan



Axial Plan



Patient 4

57 year old male

2013

Diagnosed with dermatofibrosarcoma of the right clavicle
Treated with EBRT

2015

Local recurrence,
Surgically resected and treated with brachytherapy

2017; 2018; and 2019:

Local recurrence treated with surgical resection and brachytherapy

2020

Local recurrence: 1.6x11x14mm, at the remaining stump of the clavicle

Patient 4

Treatment:

Resection

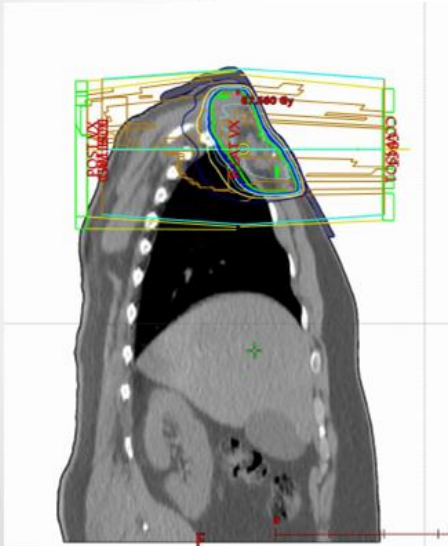
Followed by EBRT (2Gy x 32)

mEHT twice weekly at 100W using a 20cm electrode

Patient has completed treatment, with changes in pigmentation being the only adverse event noted.

Patient 4

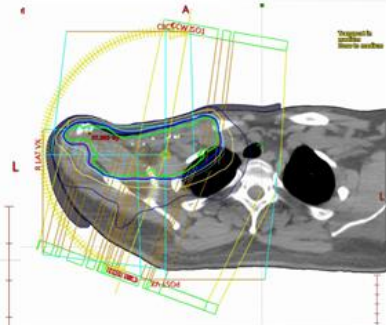
Sagittal Plan



Coronal Plan



Axial Plan



Discussion

These four cases represent interesting situations in which predicted **outcomes were poor** and further **treatment options were limited**.

- No adverse events were reported when administering mEHT to a patient with a **deactivated pacemaker outside the treatment field**.
- No adverse events have been reported after administering mEHT to the mediastinum with a portion of a **transplanted heart** in the treatment field
- mEHT plus RT in a **previously irradiated region** was **not associate with additional toxicity** in the head region and the shoulder region
- **Chronic management** of a residual, previously irradiated sarcoma in the thigh afforded the patient an additional 19 months of **improved quality of life**

Conclusion

The addition of mEHT to improve the chance of a positive outcome in these cases was safe, practical and affordable in comparison to other treatments

mEHT could be considered when no further options are available as a safe adjunct to treatments, both chemotherapy and radiotherapy, for complex, inoperable sarcoma cases.

There is motivation for the design of a trial investigating RT+mEHT for the management of high risk sarcomas, especially in cases in which patients have been previously irradiated.

Acknowledgements

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