HITRI plus
Heavy Ion Therapy Research Integration

Heavy ion irradiation for malignant mucosal melanoma

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This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 101008548

Mucosal Melanoma

Rare tumour, approx. 0.8 to 3.7% of all melanoma cases

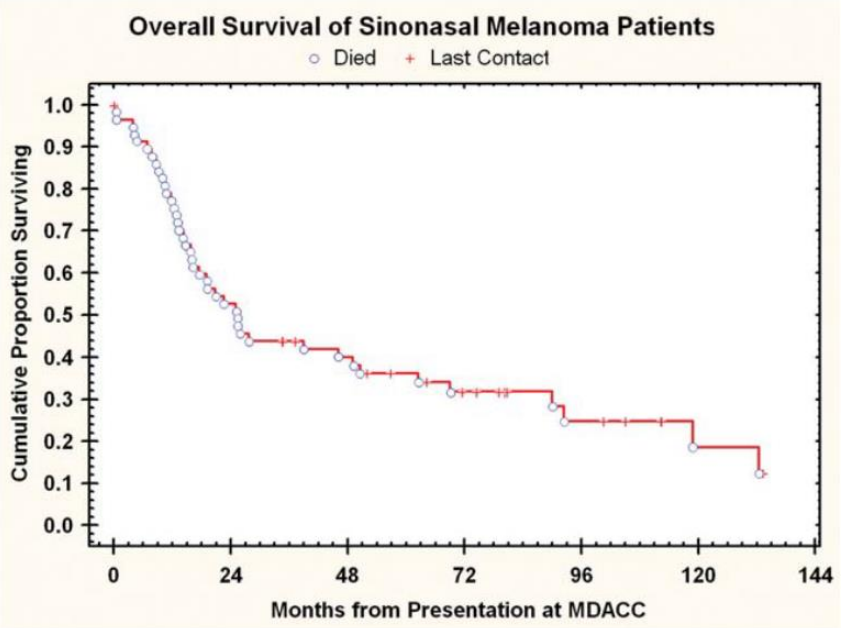
Can originate from any location of mucosa in the body,
the 3 most common sites are ENT (bis approx. 50%), anus (25%) and vulva (20%).

In contrast to cutaneous melanoma:

- Stable incidence (1.5/mio M, 2.8/mio W)
- Median age 70, majority of cases between 50 and 80 yo.
- BRAF mutation detectable in only 10% of cases

Prognosis worse than melanoma of the skin

- 5Y-OS in majority of conventionally treated series between 20-40%.



Moreno 2010

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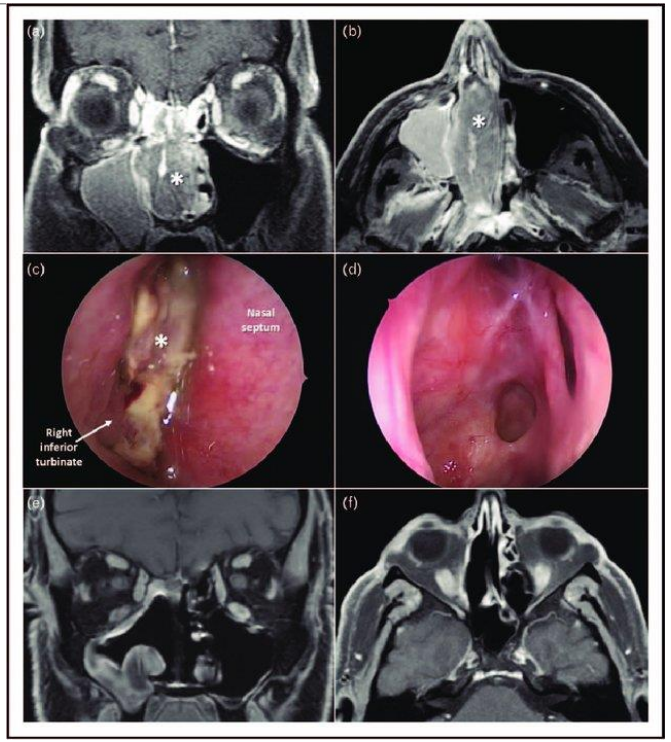
Mucosal Melanoma

Therapy of choice: Wide resection with acceptable morbidity, with best possible attempt to achieve microscopically free margins, similar to skin melanoma.

- Tumour-free resection margins achievable in 75%-80% of cases
- In several series, dependence between margin status and prognosis could not be shown: Moreno 2010 and Bachar 2008 have seen insignificant trend, significant influence only in publication of Penel 2006 (20 cases, RR = 21, p = 0.013).
- Lymph node status prognostically ambiguous: contradictory results concerning both END and SNB, therefore not recommended without clinical LK involvement (Postow 2012, Tomicic 2003).



Crippen 2017

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Mucosal Melanoma

Adjuvant therapy?

Postoperative radiation improves outcomes in some series (Local control: advantage in studies by Moreno, Pandey 1998, Pfister 2012 and others), but NO influence on overall survival.

In clinical practice only indicated for R1/R2 margins

Few data on adjuvant systemic therapies

- Lian et al. 2013: RCT 3 groups postoperatively: W&W, high-dose interferon alpha, temozolamide+cisplatin
- Advantage of OS with HDI & chemotherapy: 21.2 vs 40.4 vs 48.7 months
- ... but advantage of relapse-free survival only with chemo: 5.4, 9.4, and 20.8 M (p = 0.001)

No data on immunotherapy in MMM similar to KEYNOTE-054 in cutaneous melanoma.

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Mucosal Melanoma

Problem: Inoperable but not metastatic cases

In the main nasal cavities (80%) and paranasal sinuses (20%), which often grow extensively, inoperability is not an uncommon situation.

Lower number of BRAF-mutated cases - use of BRAF/MEK inhibitors rarely indicated, durable response not expected with this therapy

KIT mutations more frequent (up to 25%): Individualised application

Checkpoint immunotherapy: good option, but again not as good as in skin melanoma

- Yentz 2019: Analysis of MMM subgroups of patients from KEYNOTE 001, 002 and 006.
- Other characteristics: Lower TMB (2 mut/MB vs. 13 mut/MB in skin melanoma).
- This corresponds to effect of PD-L1 immunotherapy: ORR 23% vs 40%, but equal in PD-L1 positive patients subgroups (both approx. 55%).

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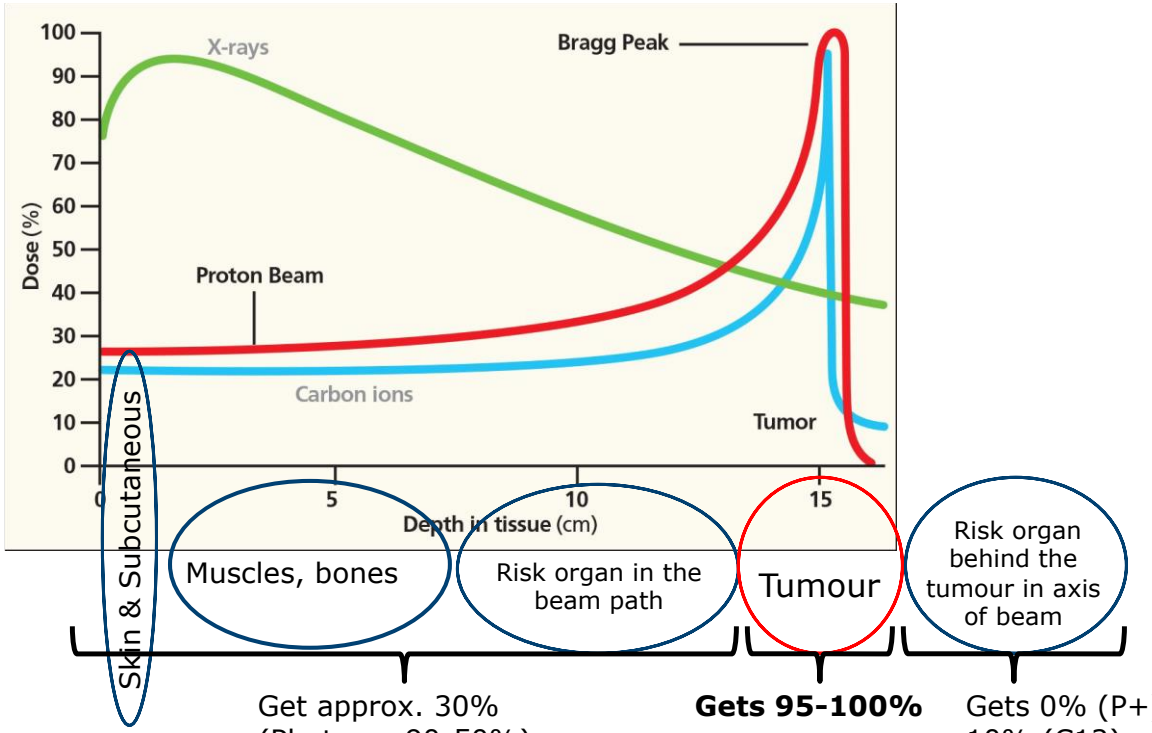
Heavy ion therapy: Introduction



- From 100% relative dose of each individual beam:

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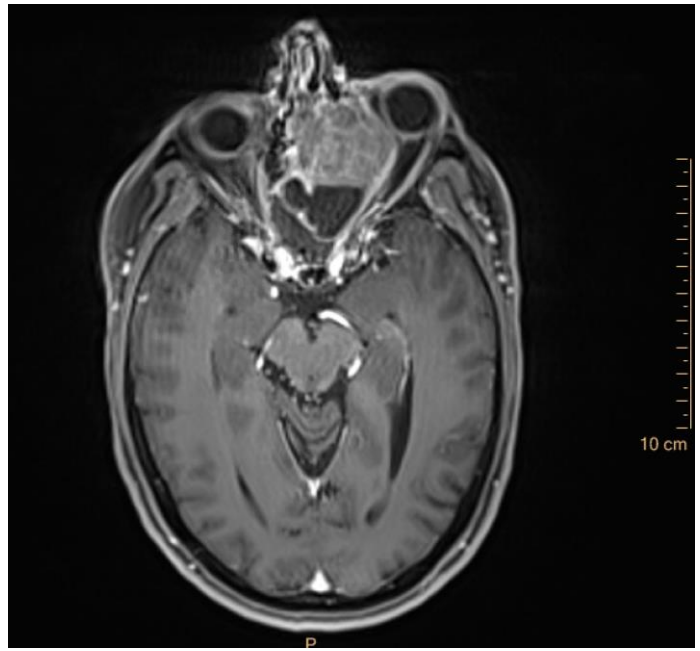
Heavy ion therapy: Introduction

In several locally advanced head & neck tumours, definitive (chemo)radiotherapy up to approx. 70-74 Gy has been introduced as an equivalent alternative to surgery, which offers no significant chance of a tumour-free margin.

In the area of the orbit, nasal cavity, paranasal sinuses and base of the skull, many organs at risk (OARs) with lower tolerance than the prescription dose:

- Brainstem: D_{max} < 63 Gy
- Optic nerves & chiasm: $D_{2\%}$ < 60 Gy
- Temporal lobe: D_{2cc} < 70-72 Gy
- Inner ears: D_{mean} < 45 Gy

Modern photon techniques allow sparing of single OARs, but at higher doses simultaneous sparing of several OARs, in particular on the affected side is often impossible without under-dosing the tumour!



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Heavy ion therapy: Introduction

On the contrary, particle therapy can basically spare multiple organs at risk densely packed in tight space as long as they located within sufficient distance to the target volume

Dose falloff: up to 5 Gy/mm for proton beams and up to 7.5 Gy/mm for C12 beams

Clinical indications for use:

- Absolute: Similar to lower dose to OARs but escalated, compared to maximum achievable by photon radiation with acceptable toxicity, dose to the tumour. Only the escalated dose results in satisfactory local disease control.
- Relative: No indication for dose escalation (good results and/or no advantage shown in dose escalation trials) therefore prescription dose same as for VMAT, but lower dose to organs at risk when it corresponds to lower toxicity

Major differences in the approach of healthcare systems to financing particle therapy between absolute and relative indications

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Heavy ion therapy: Introduction

EBM justification for sinonasal tumours:

Meta-analysis (hardly available for particle therapy!): Patel et al, Lancet Oncol, 2014

- Primary tumours and recurrences in the area of the nasal cavity and paranasal sinuses
- 43 cohorts of 41 non-comparative studies
- Median follow-up:
  - Photons 40 months
  - Particle 38 months
- Advantage of particle therapy versus IMRT in 5Y DFS and locoregional control at longest FU

	Cohorts (n)	Patients (n)	Event rate (95% CI)	I^2	Relative risk (95% CI)	p
Overall survival*						
PBT	8	191	0·63 (0·53–0·76)	59·3%	1·02 (0·77–1·35)	0·89
IMRT	8	348	0·62 (0·50–0·77)	86·9%	..	..
5-year overall survival						
PBT	5	124	0·66 (0·52–0·85)	69·7%	1·39 (0·99–1·94)	0·057
IMRT	4	212	0·48 (0·38–0·60)	45·1%	..	..
Disease-free survival*						
PBT	2	56	0·49 (0·21–1·16)	83·6%	0·98 (0·40–2·42)	0·97
IMRT	3	187	0·50 (0·38–0·67)	69·3%	..	..
5-year disease-free survival						
PBT	1	36	0·72 (0·59–0·89)	..	1·44 (1·01–2·05)	0·045
IMRT	3	187	0·50 (0·38–0·67)	69·3%	..	..
Locoregional control*						
PBT	7	147	0·81 (0·71–0·92)	55·2%	1·26 (1·05–1·51)	0·011
IMRT	4	258	0·64 (0·57–0·72)	33·7%	..	..
5-year locoregional control						
PBT	2	36	0·43 (0·09–2·10)	89·5%	0·73 (0·15–3·58)	0·70
IMRT	2	166	0·59 (0·52–0·67)	0·0%	..	..

I^2 ≥50% suggests high heterogeneity across studies. IMRT=intensity-modulated radiation therapy. PBT=proton beam therapy. *At longest duration of complete follow-up.

Table 4: Comparison of primary outcomes for proton beam therapy cohorts and intensity-modulated radiation therapy cohorts

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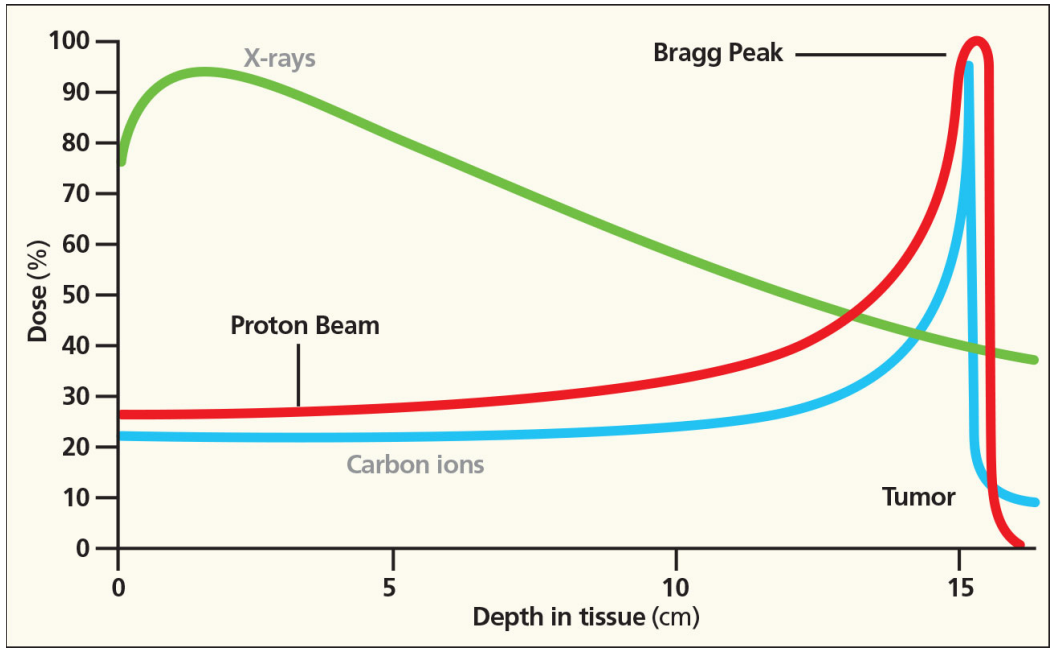
Heavy ion therapy: Introduction

Both protons and carbon ions have a dosimetric advantage over photons, so where is the difference between the two?



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Heavy ion therapy: Introduction

LET (Linear Energy Transfer)

Corresponds to the amount of energy deposited by radiation in the medium per distance reached, unit of measurement: kV/µm

Protons, like photons, belong to the low-LET radiation types, in contrast to carbon ions, which, like neutrons and ions, have a high LET

Differences in effect of high-LET compared with low-LET radiation at cellular level:

- More DNA damage in direct mechanism
- More secondary electron radiation on the particle track
- Less dependence on hypoxia
  (low OER: 1.1-1.6 vs 2.5-3.0 for XRT)

Radiation Type	LET (keV/µm)	RBE
Linac X-rays (6–15 MeV)	0.3	~0.8
Beta particle (1 MeV)	0.3	0.9
Cobalt-60 γ-rays	0.2	0.8–0.9
250 kVp X-rays (standard)	2	1.0
150 MeV protons (therapy energies)	0.5	~1.1
Neutrons	0.5–100	1–2
Alpha particles	50–200	5–10
Carbon ions (in spread out Bragg peak)	40–90	2–5

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Heavy ion therapy: Introduction

Research of high-LET radiation already in the 70s, in the course better systematised

Randomised study by RTOG/MRC: XRT versus fast neutrons in salivary gland tumours (majority non-SCC): XRT 70 Gy/7 wks or 55 Gy/4 wks vs. neutrons 16.5-22 Gy, 3x/w. for 4 wks.

Dramatic difference in number of patients with CR: 85% vs 33% to the advantage of fNBT, as well as in 2y locoregional control (67% vs 17%).

Significant toxicity of fast neutron beams (the OARs were located within high LET of neutron beams) did not allow for their more widespread use.

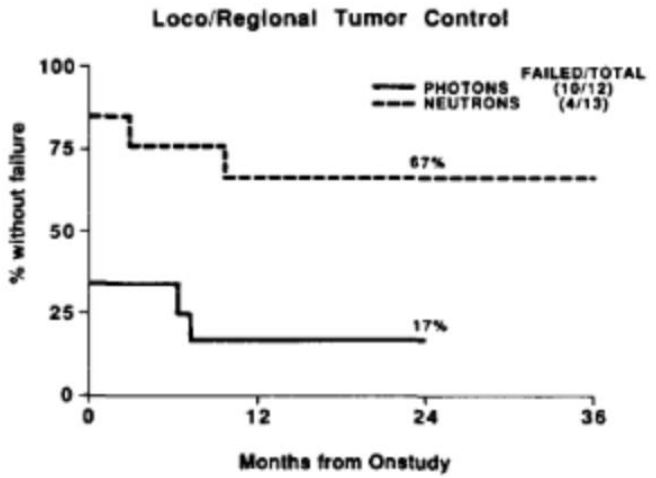

Table 8. Comparison of the RTOG-MRC study results with historical results

	Number of patients	Loco/regional tumor control %
Low LET		
Low LET historical experience	254	24
RTOG/MRC photon controls	12	17
Neutron		
Historical neutron experience	289	67
RTOG/MRC neutron results	13	67

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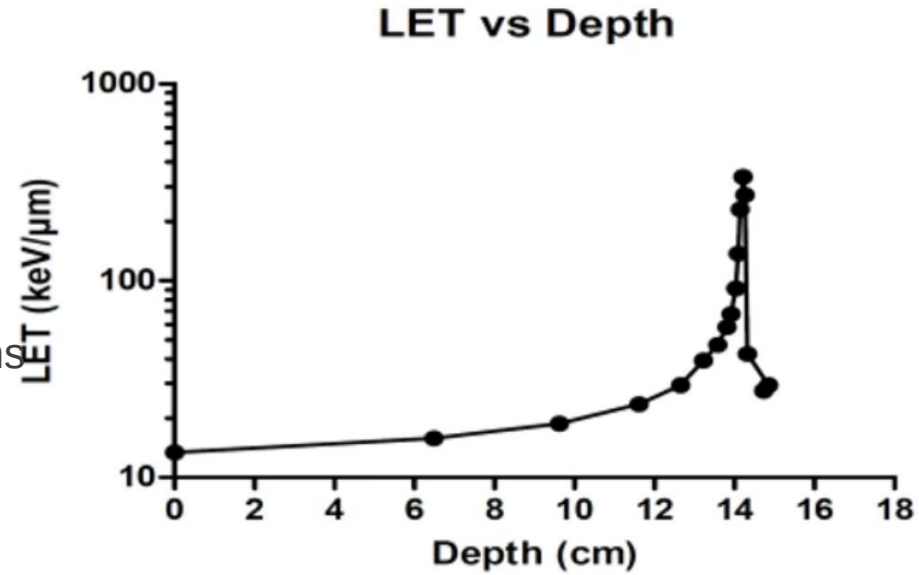
Heavy ion therapy: Introduction

Several types of ions have been researched since the 1960s and of these, carbon ions (CIRT, C^{12+}) have been identified as the most optimal. They collect several optimal individual properties from other particles:

- Dose-depth curve comparable to protons (both have plateau, Bragg peak sharper and thus dose fall-off steeper but low exit dose present).
- High LET as for neutrons - expected better effect on radiation-resistant tumours than protons
- Lower toxicity than for neutrons, as not only relative dose in plateau is lower, but also LET; thus C^{12+} are really the best possible combination of properties of protons and neutrons
- Molecular weight low enough to allow for cost-effective devices accelerating them to therapeutic energies



Buglewicz et al. 2019

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Mucosal melanoma: Clinical case

60-yo woman presented in 01/2020 with right-sided exopthalmus

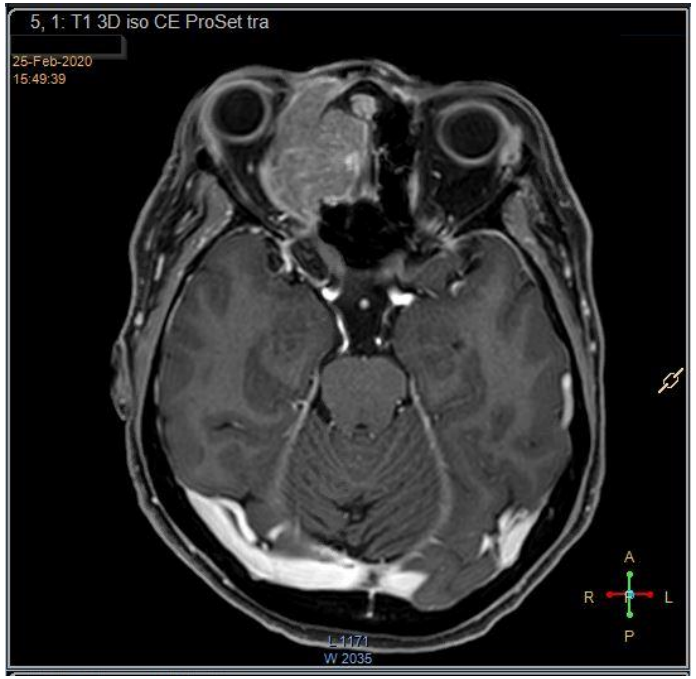
MRI head & neck: tumour mass in right ethmoid cells, destruction of lamina papyracea, infiltration of right orbit and anterior fossa cT4b cN0 M0.

Biopsy 10.01.2020: Malignant mucosal melanoma

Ophthalmological examination: no visual deficit on both sides, no double vision, no optic nerve atrophy on affected side in OCT.

Physical: Discrete asymmetry in eye setting, nasal congested, otherwise unremarkable

Staging: No evidence of distant metastases



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Mucosal melanoma: Clinical case

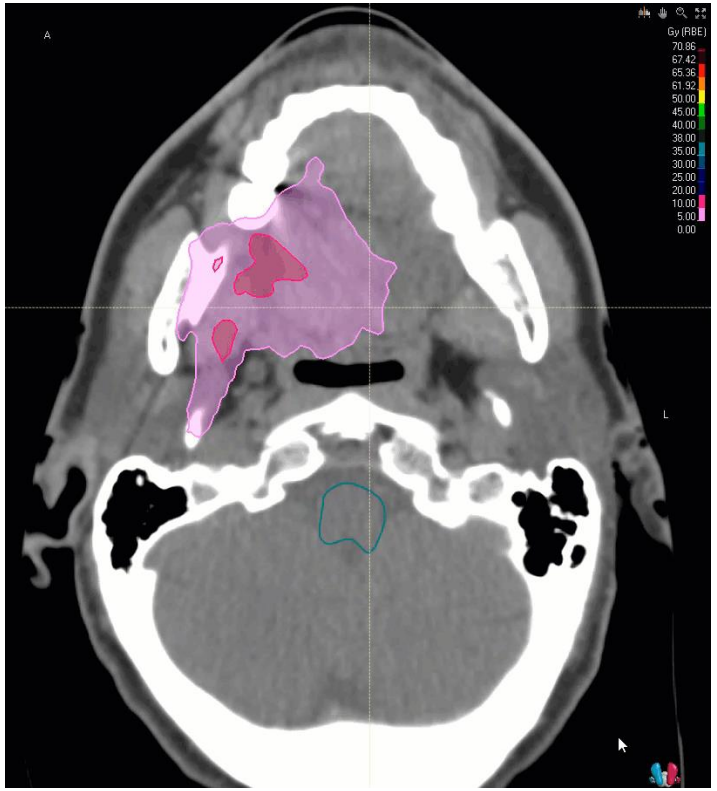
Definitive CIRT, 68.8Gy RBE /16 Fx, 4x/W

Concomitant pembrolizumab on individual basis to reduce the risk of metachronic distant metastasis

In planning, the tumour could be completely covered with curative dose, but the patient had to accept increased risk of visual loss on the affected right side (15-20%)

Control MRI in week 2 already showed partial tumour response, which allowed replanning - risk of vision loss reduced to 5%.

Acute side effects: Expected CTCAE grade 2 mucositis, CTCAE grade 1 conjunctivitis and dermatitis



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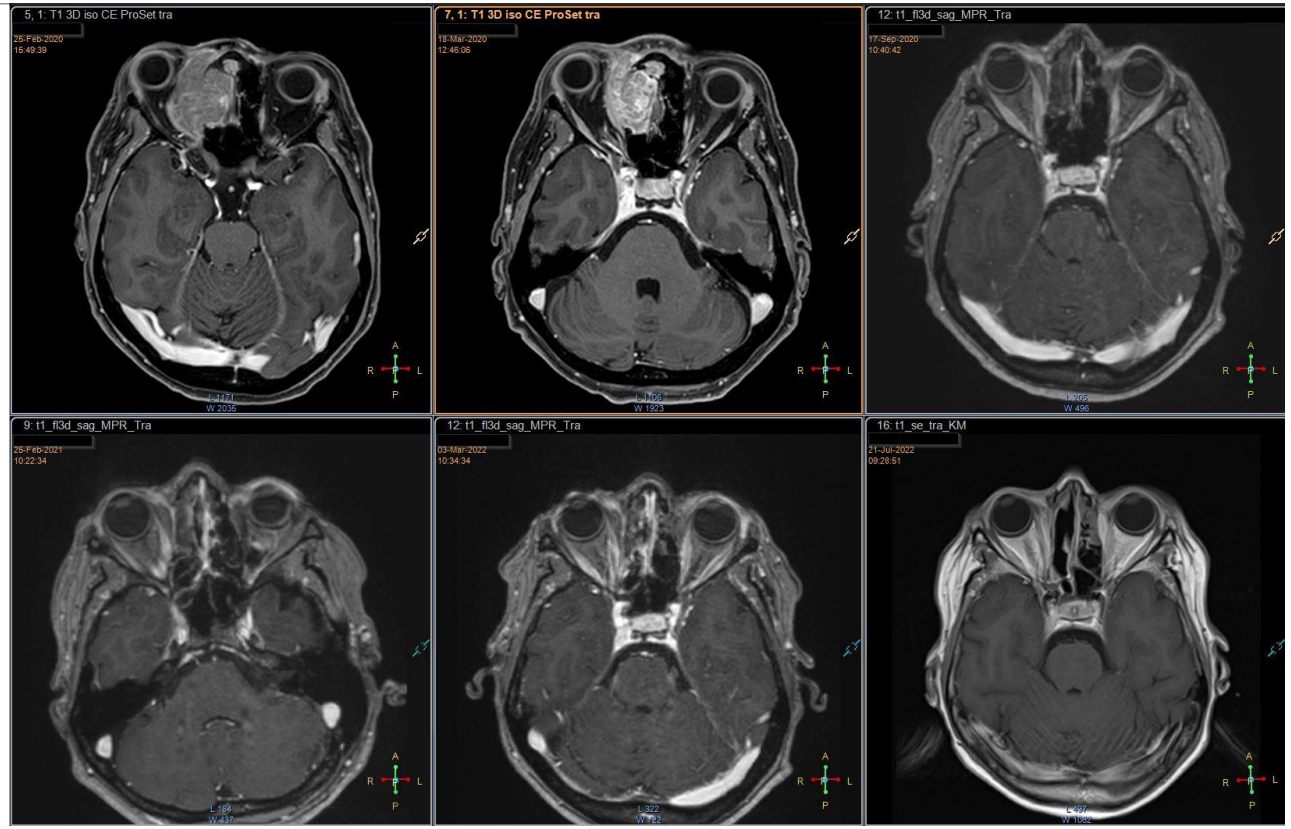
Mucosal melanoma: Clinical case

Immunotherapy was continued

After 6 months, solitary lung metastasis was found and completely resected; pembrolizumab terminated after resection of lung metastasis

No evidence of distant metastases until present (36M FU post treatment)

Late side effects: Overproduction of tears, mild nasal congestion that needs sea salt rinsing



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Heavy ion therapy in mucosal melanoma: EBM

How good is heavy ion therapy in locally advanced mucosal melanoma?

Are there differences in efficacy between proton and carbon ion radiation?

- Several tumours typically considered "radioresistant" do not show a clear superiority of CIRT against low-LET escalated dose (i.e. adenoid cystic carcinoma, comparable local control PBT vs CIRT: Takagi et al. 2014, 5Y LC 76% vs 78%)

Systemic therapy: evidence and perspectives?

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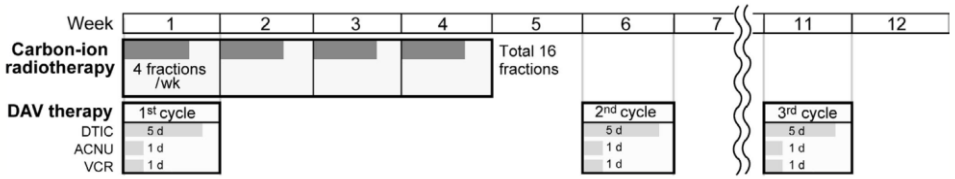
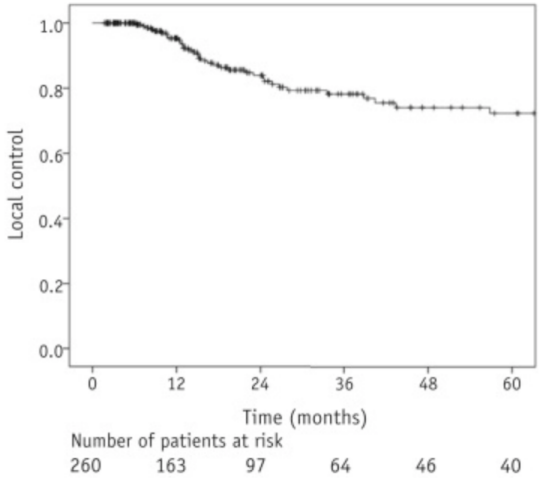
Heavy ion therapy in mucosal melanoma: EBM

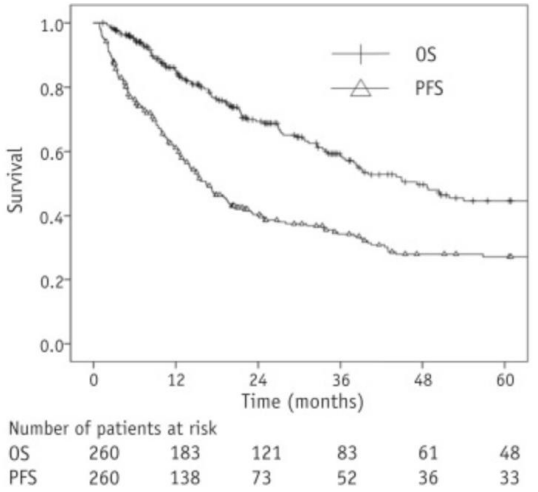
Koto 2017: CIRT in ENT mucosal melanoma

- 260 patients, T3-T4 inoperable, irradiated with ^{12}C ions
- Dose: 57.6 Gy RBE / 16 Fx over 4 weeks
- Chemotherapy in 60% of patients (DTIC)



- Majority of progression cases were distant metastases (40%), therefore PFS 2Y/5Y correspondingly worse: 40.4% and 27.2%.
- OS: improvement in patients who received chemotherapy: 2Y 75.8% vs 62.2% (p = 0.024)
- Late toxicity ≥ G3: 13%





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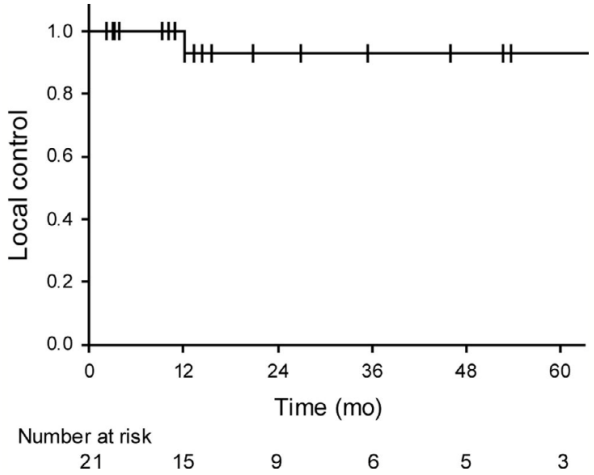
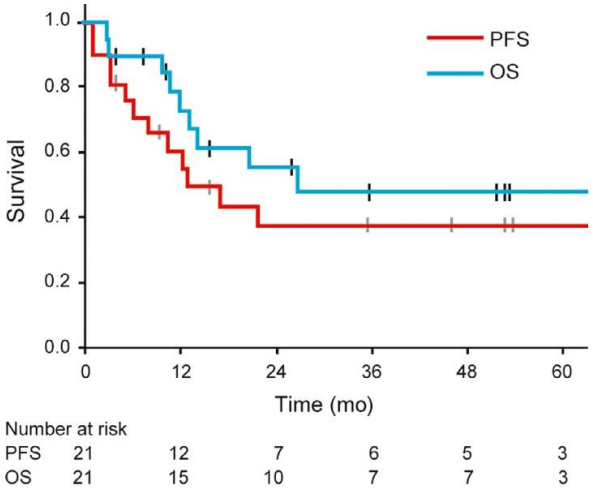
Heavy ion therapy in mucosal melanoma: EBM

Takayasu 2017: 21 patients with sinonasal MMM

- Even more advanced: all patients T4a-T4b
- In all patients concomitant + adjuvant DAV chemo
- More dose: in some patients already 64 Gy RBE/16 Fx
- Excellent LC: Only 1 progress everywhere (!), current 3Y LC = 92.3%.
- Distant metastases always a problem: 3Y OS 49%, PFS 37%.
- Authors say CIRT in MMM shows excellent local control, but benefit from addition of chemotherapy less than expected





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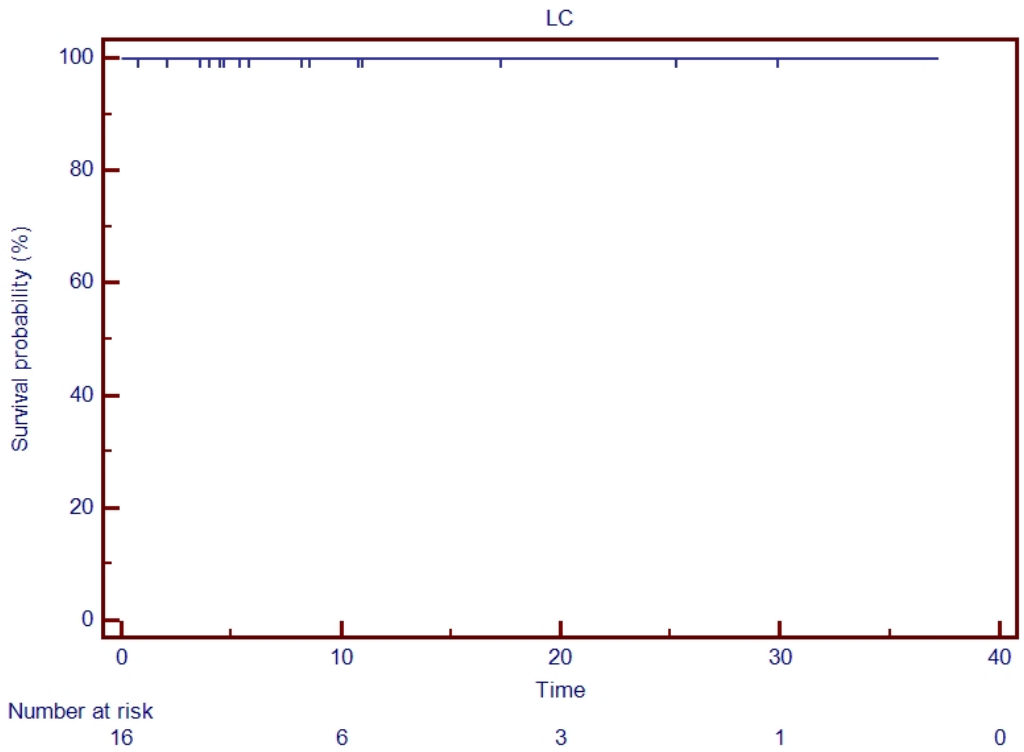
Heavy ion therapy in mucosal melanoma: EBM

Preliminary MedAustron data on sinonasal MMM

- 16 patients, mean age 72 (56-90), M:F 1:1
- 15 nasal cavity/ 1 oral cavity
- All tumours primarily inoperable or with inoperable macroscopic residual disease
- All tumours T4 locally advanced, 1 case N+
- Mean GTV 40.2 ml (1.8-150.9 ml)
- Prescription dose 68.8 Gy RBE /16 Fx, 4x/W



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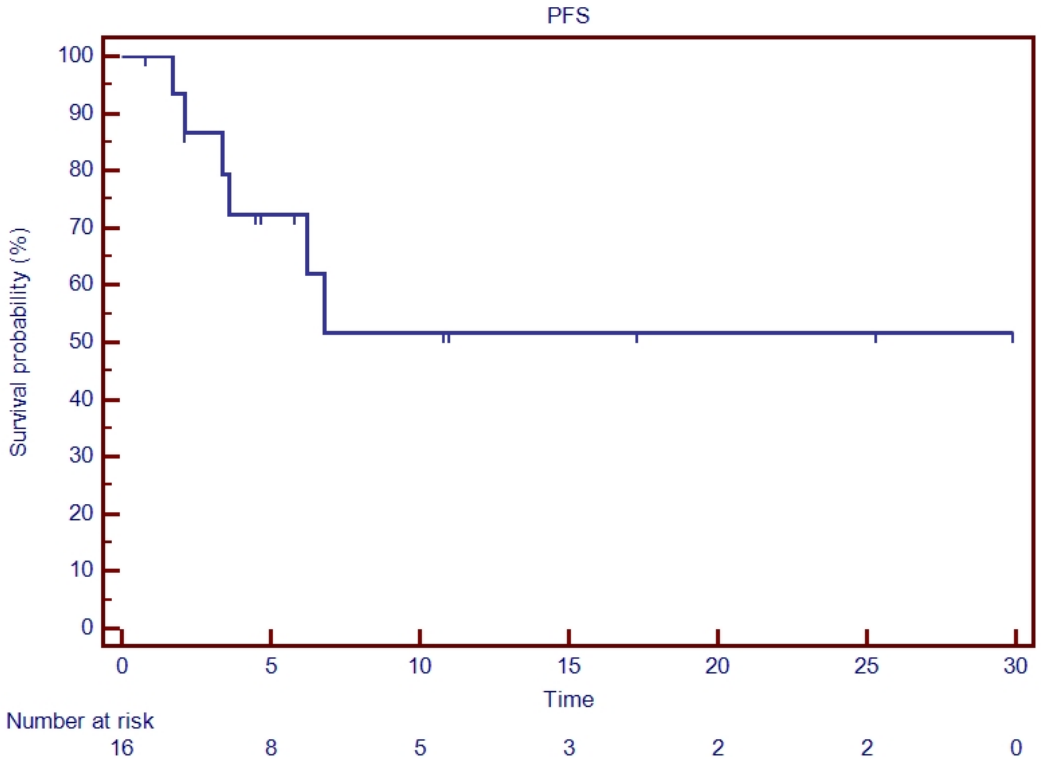
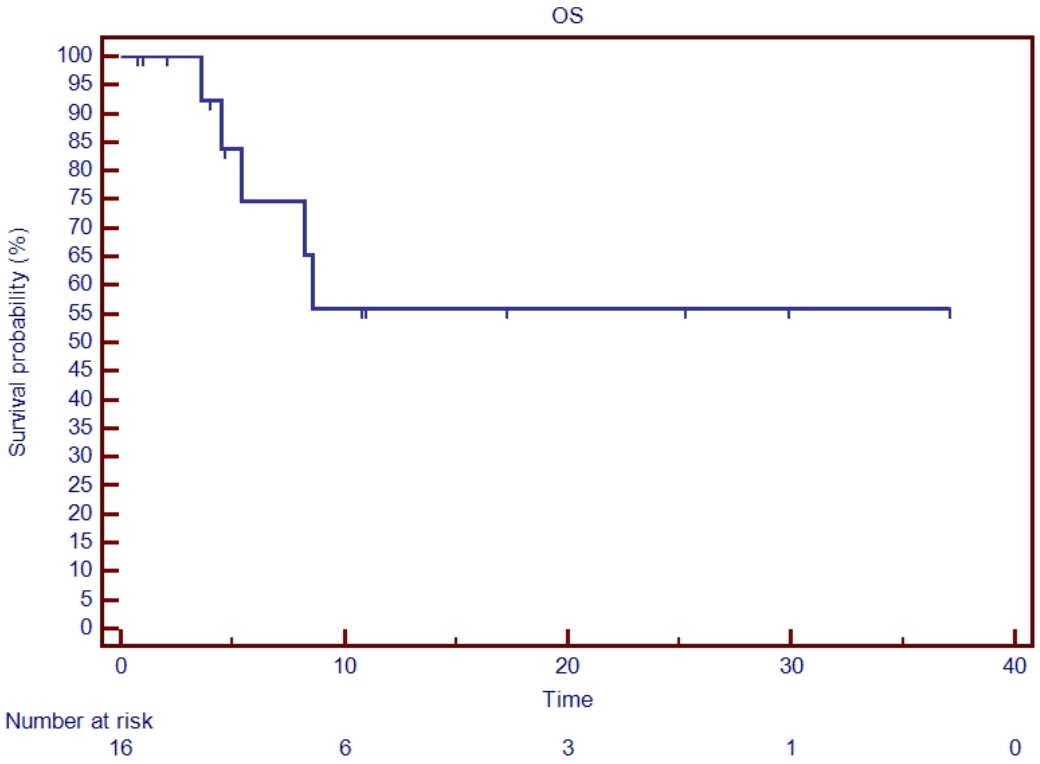
Heavy ion therapy in mucosal melanoma: EBM





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Heavy ion therapy in mucosal melanoma: EBM

Why do we see benefit from heavy ions?

- Much data that melanoma is highly radiation resistant and requires high single dose: Moreno 2010 saw benefit of radiation only if TD was above 54 Gy
- Wada 2003: ED ≥ 3 Gy prognostically better in univariate analysis, but...

> younger patients, p = 0.046) was the only significant factor. Radiotherapy for gross residual lesions after surgery did not seem to impact the significant gain of local control and survival. We observed two fatal late complications of mucosal ulcer and bleeding in the high dose per fractionated radiotherapy group.

- Comparison of data from CIRT versus other techniques indirectly (unfortunately) shows that melanoma benefits not only from particle therapy-based dose escalation but specifically from high-LET radiation versus low-LET

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Heavy ion therapy in mucosal melanoma: EBM

Morimoto 2014: Mixed PBT & CIRT patient group from J-CROS study, analysis included ENT cases and non-PEC histology only.

- N = 339 patients (!), majority of tumours in nasal cavities and sinuses
- Histological types: Melanoma (42%), ACC (24.5%), olfactory NB (18.5%) and other (18.3%).
- Important: Melanoma patients in this study were treated with PBT only

Histology	5Y LC	5Y PFS	5Y OS
All	71.2%	36.8%	61.2%
Melanoma	64.2%		40.2%
ACC	71.5%		72.9%
Olfaktorius NB	79%		86.2%
Other	60%		74.7%

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Heavy ion therapy in mucosal melanoma: EBM

Improving distal outcomes: Immune therapy?

CAVE: While there is potential in immune therapy for mucosal melanoma, it has to be acknowledged that in standard approaches (immune therapy in not locally curable or metastatic disease) results so far inferior to expectations driven by data of cutaneous melanoma

- Lower ORR due to less frequent PD-L1 expression and lower TMB
- So far no data on checkpoint inhibitors in adjuvant and neoadjuvant setting
- CTLA-4 addition to anti-PD-L1 tested and no benefit

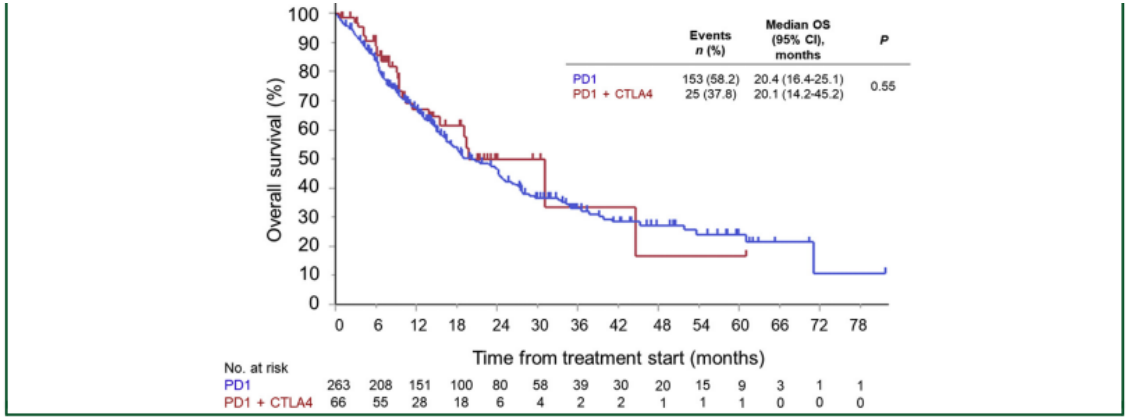

Figure 1. Kaplan–Meier survival estimates for the all-patient cohort treated with anti-PD-1 antibody monotherapy or anti-PD-1 plus anti-CTLA-4 combination therapy.
(A) Progression-free survival. (B) Overall survival.
CI, confidence interval; OS, overall survival; PD1, anti-programmed cell death protein 1 antibody monotherapy; PD1 + CTLA4, anti-programmed cell death protein 1 plus anti-cytotoxic T lymphocyte-associated antigen-4 combination therapy; PFS, progression-free survival.

Nakamura 2021

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Heavy ion therapy in mucosal melanoma: Combined therapy?

Improving distal outcomes: better use of abscopal effect with concomitant therapy?

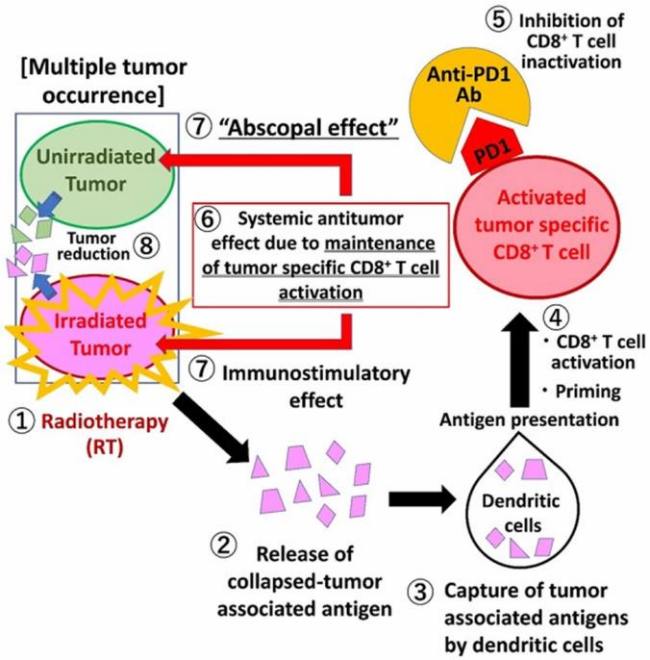

Table 3. Type and site of response in patients with abscopal responses. Details of the site and dose of locoregional RT, and type of abscopal response observed in distant lesions

Patient, #	RT site (type)	RT dose, Gy/fractions	Response	Site of abscopal response (distant target lesions)
1.	Brain (WBRT)	30/10	PR	Liver metastases
2.	Brain (WBRT)	30/10	PR	Pelvic relapse
3.	Chest wall (cutaneous relapse) + right axilla	50/25	PR	Liver and cutaneous metastases
4.	Right inguinal lymph node	20/5	PR	Gastric, cutaneous, lung, lymphnodal and retroperitoneal abdominal metastases
5.	Brain (WBRT)	30/10	PR	Liver, bilateral axillary and right ovaric metastases
6.	Brain (WBRT)	30/10	PR	Lung, cutaneous, lymphnodal and abdominal metastases
7.	Right chest wall (cutaneous relapse)	30/10	SD	Lymphnodal, cutaneous and chest wall metastases
8.	Vertebral metastasis	30/10	SD	Lung metastases
9.	Brain (SRT)	24/1	PR	Cutaneous metastases
10.	Brain (SRT)	20/1	PR	Liver metastases
11.	Brain (SRT)	24/1	PR	Lung metastases

In 52.3%!

Open in a separate window

The responses reported in the table are the systemic responses; however, all 11 patients with an abscopal response also had a local response to RT. **Abbreviations:** PR, partial response; RT, radiotherapy; SD, stable disease; SRT, stereotactic radiotherapy; WBRT, whole-brain radiotherapy.

JADE Health, Grimaldi 2014

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Heavy ion therapy in mucosal melanoma: Combined therapy?

Combining checkpoint inhibitors with CIRT: WHY NOT?

All requirements for optimal candidate of mucosal melanoma fulfilled...:

- Tumour type with immunogenic potential
- Abscopal effect with anti-PD1 antibody already reported in *vitro*
- Known good results of PD-L1 therapy (KEYNOTE RCTs)
- Good local control, but insufficient effect of conventional system therapy to prevent metastasis in CIRT
- High single dose/radiation type with increased LET
- With immune-specific side effect profile in current limited experience, no significant increase in toxicity in concomitant treatment with anti-PD1 and CIRT.
- No study yet available ☺

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Conclusions

Mucosal melanoma differs biologically and prognostically from cutaneous melanoma

Complete surgical resection is the treatment of choice, but often not possible

Is a radiation-resistant disease that requires particle therapy

For cases with macroscopic tumour present, advantage of heavy ions over protons

Distant metastasis remain a problem that has not yet been adequately addressed with conventional system therapy, gain from immune therapy when waited until distant metastases lower than in cutaneous melanoma

Combination with immunotherapy in concomitant setting a safe and promising option

HITRI
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Thank you for your attention
Questions are welcome

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