

Proton therapy in advanced hematologic malignancies with extremely unfavourable prognosis: a single-centre experience

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Introduction

Hematological malignancies (HM) are generally considered systemic diseases. Radiotherapy (RT) is used as a local treatment modality and is therefore thought to have limited potential in advanced HM. However, there is increasing evidence that RT can induce a systemic effect through tumor antigen presentation via its disintegration. Off-target response - the „abscopal effect“ attributed to stimulation of the immune system has been repeatedly observed. Initiation of a systemic response presupposes the patient's immunocompetence. Serious lymphopenia decreasing condition of immunity is often associated with RT. Proton therapy (PT) is a modern RT technique that offers the advantage of delivering a lower dose of radiation to surrounding tissues. Recent publications show that PT is less lymphodepleting compared to modern photon techniques such as IMRT and VMAT, mainly due to the lower dose to lymphocyte-rich organs such as the heart, spleen, great vessels and bone marrow. The toxicity profile of PT even in advanced HM is very favourable and its use may contribute to an unexpectedly better outcome in some patients with a poor prognosis.

Methods

Patients with highly unfavourable HM, mostly with refractory or relapsed HM (leukemias, lymphomas) indicated for PT are presented. Pencil beam scanning (PBS) PT was used in all patients.

CASE 1. 29-years old male M.O.

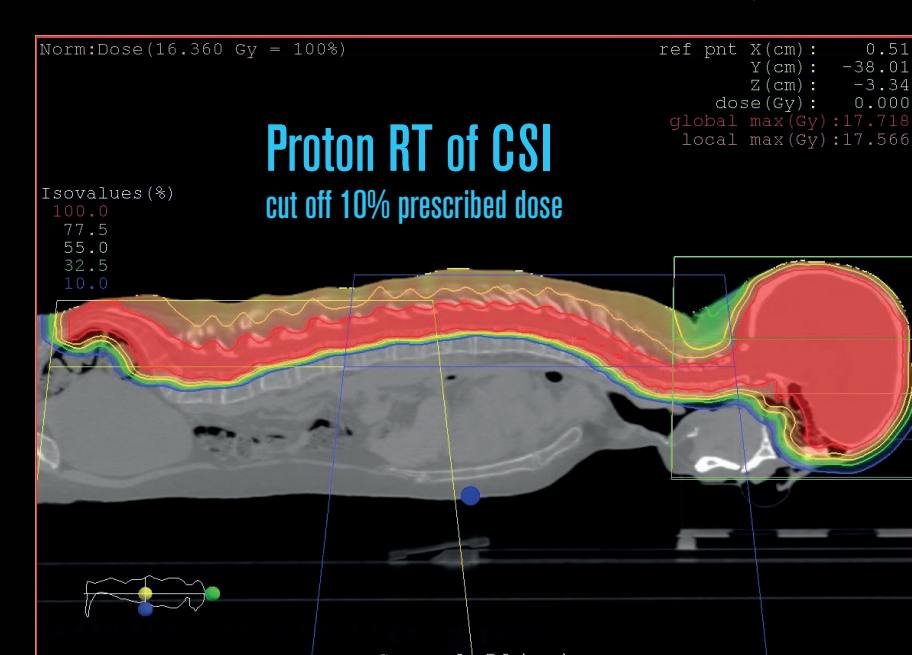
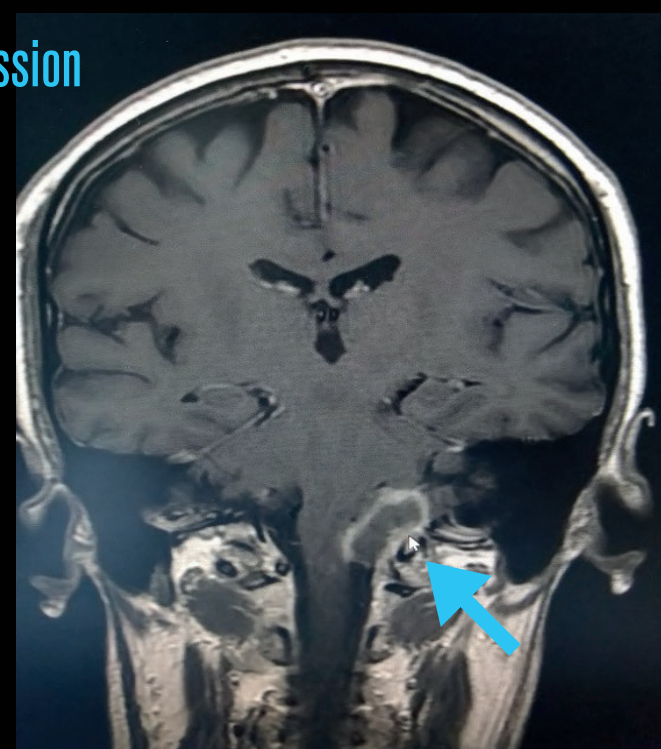
• dg. T-NHL, peripheral T-cell (PTCL) 11/2019, IVB, PIT 3 multifocal CNS, lungs, kidneys, infradiaphragmatic nodal involvement

• 1s line systemic treatment MATRIX

CNS progression during 2nd cycle of 1st line of chemo: serious neurologic deficit Wallenberg's sy of medulla oblong. L.sin. ECOG/WHO score=3-4

Acute indication for proton RT of CNS (craniospinal 18CGE/9fr +boost for all CNS lesion to 36CGE/18fr), 12/2019-1/2020.

MRI in progression



For primary chemoresistant disease follows indication for HD BEAM+ASCT

8/2023 complete remission, very good QoL, mild residual instability and minimal impairment of fine motorics, slight decline in chess game efficiency (former chess champion)

CASE 3. 66-years old female E.F.

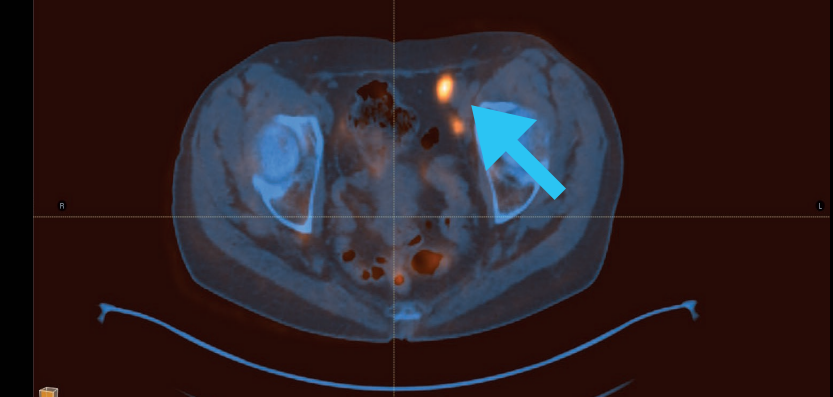
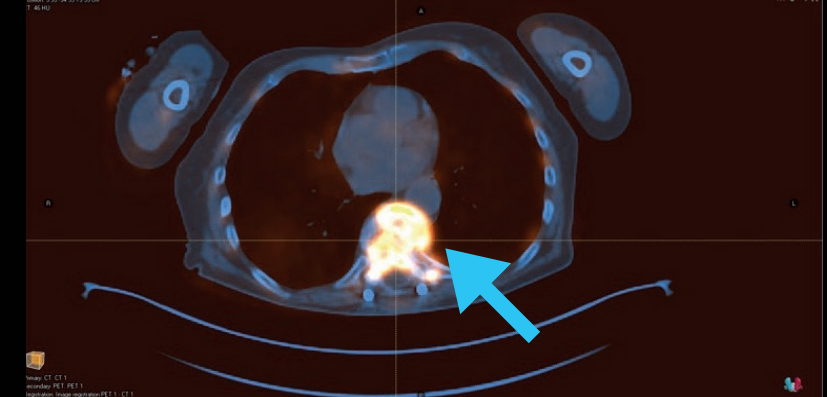
• dg. B-NHL, diffuse large B-cell (DLBCL) 5/2021, centroblastic, GC-like without double expression, IVA, IPI 5, CNS IPI 5 (supra-and infradiaphragmatic nodal, osteolytic lesions with patol fracture of T10 -paraplegia, neurosurgical stabilisation)

• 6xR-CHOP+4x MTX i.t. 5/2021-9/2021+2xR 11/2021

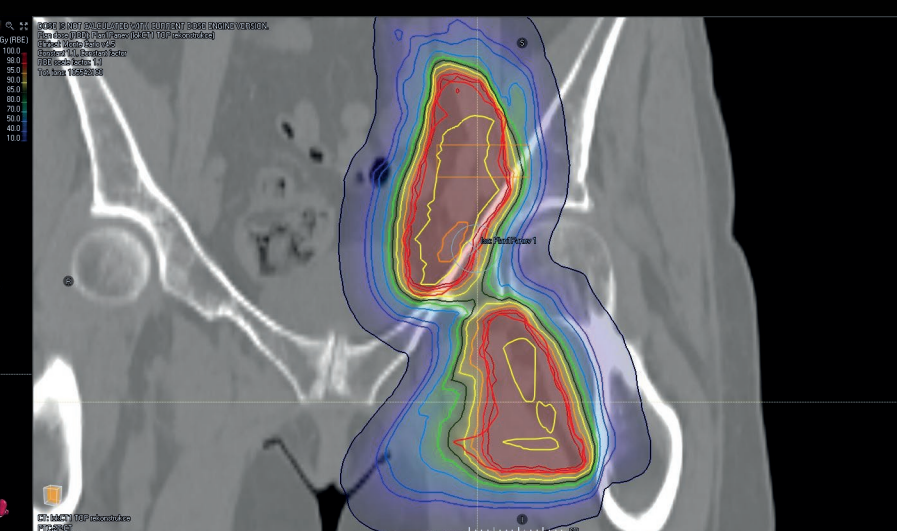
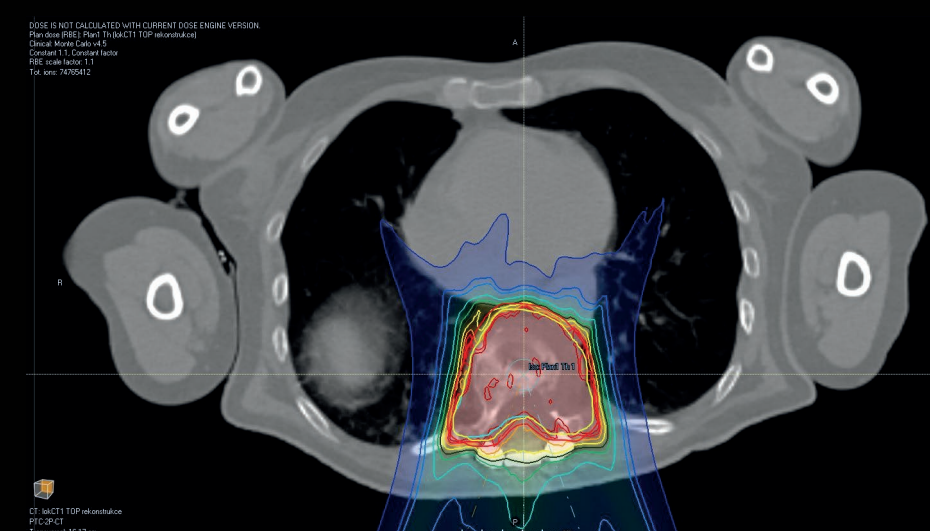
Primary refractory symptomatic extremely painful lesion in T10, progression inguinal and pelvis nodes L.sin. 1/2022

Progression in T10

Progression in pelvis



Indication for proton RT of all areas of progression (40 CGE/20fr) 2-3/2022 as a bridge for CAR-T 4/2022



8/2023 complete remission, very good QoL, no neurologic impairment

CASE 4. 29-years old male O.V.

• dg. acute promyelocytic leukemia (AML-M3 FAB) 1/2015

• CNS relapse 5/2017, treatment incomplete due to patient refusal

• 9/2019 massive CNS infiltration involving brain, nerve roots of the lumbar spine and medullary relaps, PS=3, serious neuropathic pain-palliative systemic HAM+MTX i.t.

• pt refused more intensive approach

Multifocal recurrent relapse including CNS with limited treatment opts

Indication for palliative proton RT (craniospinal 24CGE/12fr+boost for brain lesions to 30CGE/15fr) 10-11/2019 No other treatment

2/2020 complete remission, very good QoL, neuropathic pain relief
Exitus letalis 13.6.2021 - 20 months after PT with a sign of bone marrow relapse

CASE 2. 42-years old female J.Z.

• dg. B-NHL, primary mediastinal (PMBL) 2/2021, CD30+, IVA, IPI 3 (LD, st.IV, 2 E-lesions) bulky mediastinum with L chest wall infiltration

• 1s line 6xR-CHOP+2xR 2-6/2021, RR: DS=5

• 2nd line salvage CHT incl.HD+ASCT (24.8.2021)

Primary refractory-metabolic active infiltration after second line of systemic treatment including ASCT

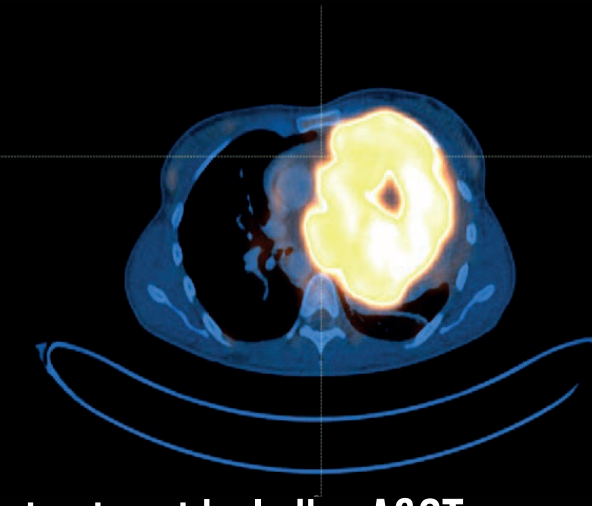
Indication for mediastinal proton RT in DIBH (RT IS 30CGE/15 fr+boost for PET+areas to 44CGE/22fr) 10-11/2021

8/2023 complete remission, very good QoL, no late toxicity

Other 6 similar pts were treated-all in complete remission, no late toxicity

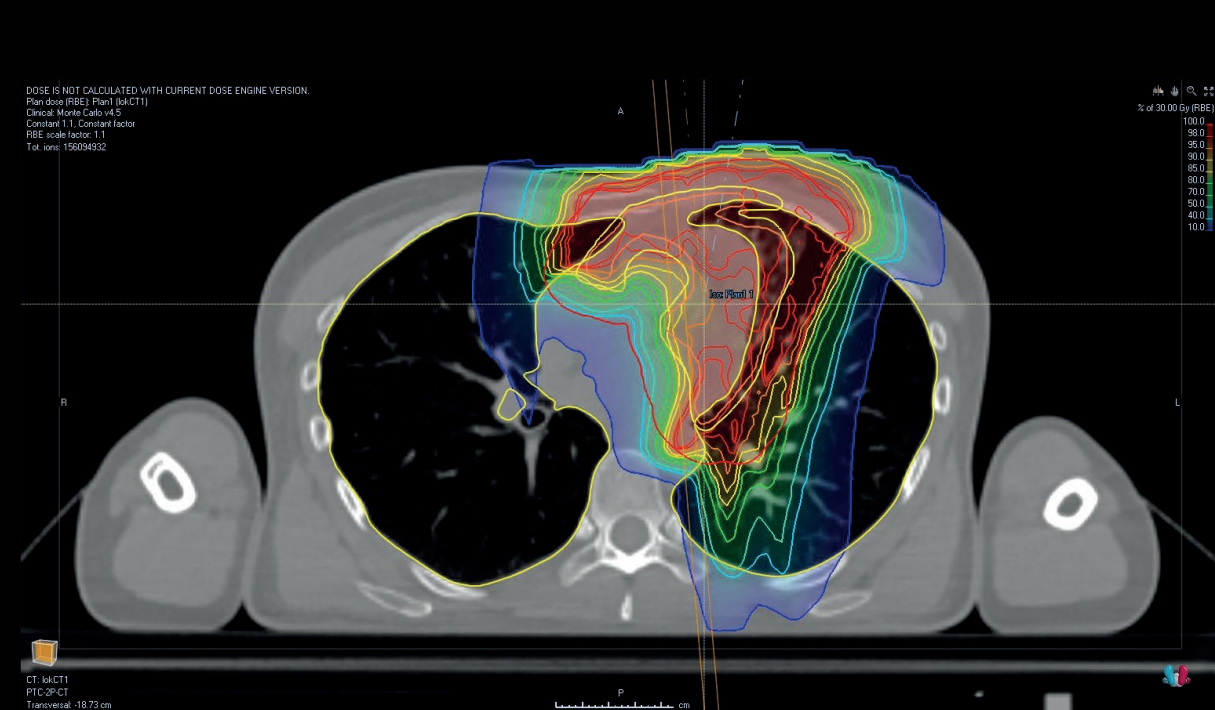
Initial PET/CT

Pre-RT PET/CT



Proton RT in DIBH

cut off 10% prescribed dose



Results

We present several patients with a poor prognosis of HM. PT was used either as a separate treatment method or as part of a combination therapy. PT was very well tolerated, even by highly pretreated patients with target volumes in high-risk areas. In our experience, the inclusion of PT in the treatment regimens has often been associated with unexpectedly good treatment outcomes.

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Conclusion

- PT is a safe and effective RT technique even in patients with advanced HM (lymphomas, leukemia) and could offer another line of effective salvage therapy in some patients.
- The inclusion of PT in the treatment regimen for advanced HM could correlate with better treatment outcomes - perhaps a higher chance of inducing an abscopal effect through the use of a less lymphodepleting RT technique.
- Maintaining maximal immunocompetence in patients with HM becomes much more important with the constantly growing indications for immunotherapy.
- Positive feedback from hemato-oncologists regarding the use of PT even in patients with an extremely unfavourable course of HM leads to a renaissance in the use of RT in hematooncologic diseases in the Czech Republic.