PENCIL BEAM SCANNING PROTON THERAPY FOR LYMPHOMAS: CLINICAL EXPERIENCE

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PURPOSE: Proton therapy using pencil beam scanning (PBS) in the treatment of lymphomas allows achieving an excellent coverage of the target volumes while maximizing protection of the surrounding organs at risk such as the heart, breast, lungs, spinal cord and blood stem cells. Reported clinical outcomes of PBS in lymphomas are limited, mostly due to the novelty of the PBS and difficulties that limit the administration of PBS for lymphoma patients, particularly for mediastinal and upper abdominal target volumes (moving targets). We are presenting our clinical experience with PBS in Hodgkin and non-Hodgkin lymphomas with mediastinal or non-mediastinal targets.

MATERIALS AND METHODS: One hundred mediastinal Hodgkin lymphoma pts (follow-up median 24 months, range 0.3-70 months) and 32 mediastinal non-Hodgkin lymphoma pts (follow-up median 20 months, range 1-68 months) were treated via PBS from April 2013 to February 2019**.** Most of them were irradiated under the deep inspiration breath hold (DIBH) condition. Twenty-two patients were treated under free breathing conditions with 4D-CT supported with the use of repainting to suppress interplay effect at the beginning of the center operation. All recent patients were treated in DIBH using a Dyn´R spirometer. Repainting was used to suppress the influence of heart movement in selected patients. Furthermore, 16 pts with non- mediastinal lymphomas were treated in different locations (subhepatic, pelvic, axillar, craniospinal axis and others).

Hodgkin lymphoma pts with mediastinal target	
Males/females [pts.]	36/64
Age at time of RT median [years]	33.0 (13.3-79.2)
Stage: early+intermediate/advanced	75/25
RT volume [pts.]	
Involved field	12
Residual disease	25
Involved site	63
Follow-up median [months]	23.9(0,3-70.0)
RT on PET neg/PET positive disease/unknown	71/20/9
RT in DIBH/free breathing [pts.]	83/17
Median dose [CGE]	30 (19.8-40.0)
Achieved local control/uncertain LC/early after RT [pts.]	93/4/3
Complete remission/progression/uncertain+early after RT	91/2/7
Progress in target /distant region (n = 93)	0/2

Non-Hodgkin lymphoma pts with mediastinal target	
Males/females [pts.]	15/17
Age at time of RT median [years]	38.6 (20.5-74.8)
Stage: I+II/III+IV	14/18
RT volume [pts.]	
Residual disease	10
Initial bulk	22
Follow-up median [months]	20(1.0-68.0)
RT on PET neg/PET positive disease [pts.]	10/22
RT in DIBH/free breathing [pts.]	27/5
Median dose [CGE]	36.4 (24.0-50.0)
Achieved local control/early after RT/unknown [pts.]	26/4/2°
Complete remission/early after RT/death from NHL/death from other causes	24/4°/2/2†
Progress in target/ distant region/unknown (pts.)	0/1/1

° Early after RT 2 pts died without possibility of LC evaluation 1 on fast early progression , 1 on reactivation of CMV infection

† 2 patients died of non-lymphoma causes: 1 CMV infection reactivation, 1 in CR death from multiorgan failure with possible impact of postradiation pneumonitis 7 months after RT

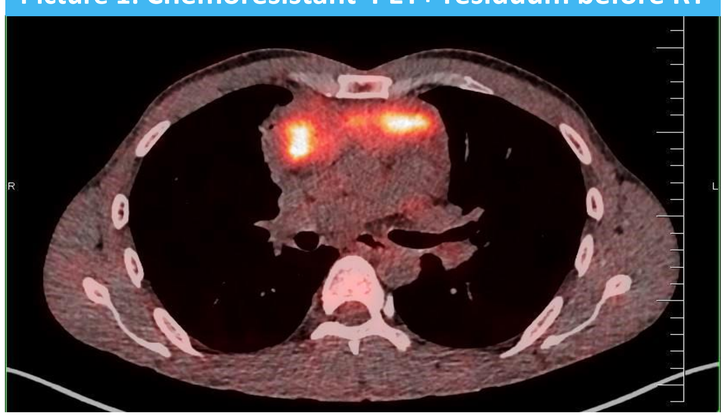
Lymphoma pts with non-mediastinal target	
Males/females [pts.]	8/8
Age at time of RT median [years]	50 (37,9-62)
HL/NHL	8/8
RT volume [pts.]	
Supradiaphragmatic	9
CNS	2
Infradiaphragmatic	5
Follow-up median [months]	17.5(4,2-45.3)
RT on PET neg/PET positive disease [pts.]	8/8
Median dose [CGE]	34.0 (24.0-44.0)
Achieved local control/unknown (pts)	15/1°
Complete remision/death on lymphoma (pts)	12/4
Progress in target /distant region (pts)	0/4

° Early after RT 1 pt ied without possibility of LC evaluation

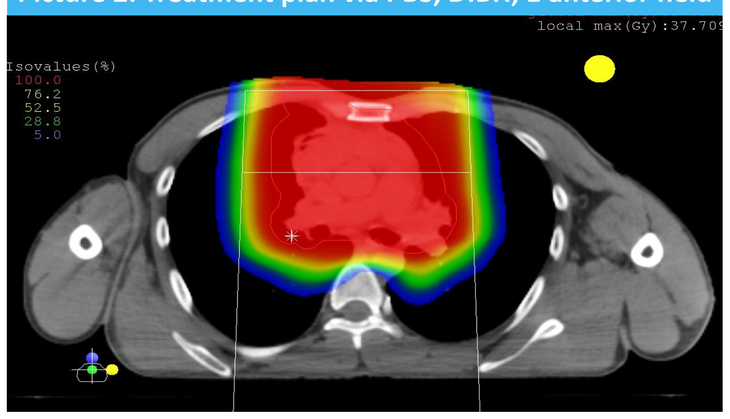
CASE REPORT 1: 36-year old man diagnosed with HL stage IIB in 12/2013

- initial mediastinal bulk with infiltration of lung, bilateral hilar regions, right supraclavicular area
- primary chemoresistant , stable-disease after ABVD (6 cycles), salvage 2xDHAP 11/2014-2/2015 with conditioning BEAM and auto-SCT 2/2015-showed SD with localised PET+ mediastinal residual disease (see Picture 1), photon RT not recommended- high risk of RT toxicity due to the extent of residuum
- PBS in DIBH on PET+ mediastinal involvement 40CGE/20 fractions 4 weeks. (dose distribution, see Picture 2) - achieved local control of mediastinal disease, see Picture 3
- 9/2015 progressed out of target (epigastrium, spleen, liver, lungs)-indicated for 2.auto-SCT, achieved PR, continued with anti-CD30, achieved CR and allo-SCT. 3/2019 lasting CR, pt in good performance status, able to work full-time (baker)

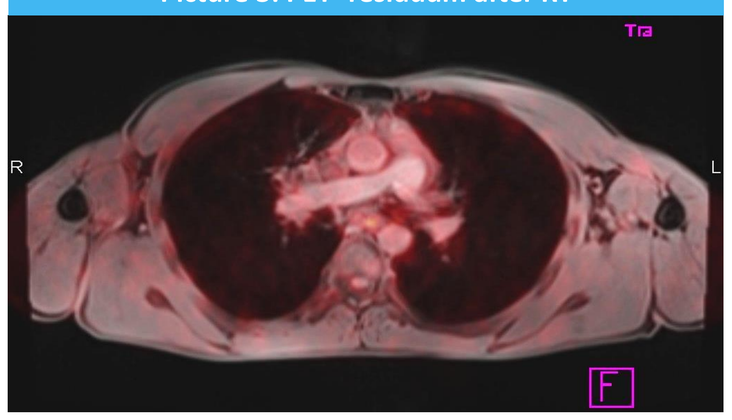
Picture 1: Chemoresistant PET+ residuum before RT



Picture 2: Treatment plan via PBS, DIBH, 1 anterior field



Picture 3: PET- residuum after RT



CASE REPORT 2: 71-year old man diagnosed with NHL, DLBCL st.IIAS 10/2017

- initial infradiaphragmatic involvement : retroperitoneal LNs, bulky disease in liver hilar region (10x5x3cm) (see Picture 1), focal spleen involvement
- systemic treatment 6xR-CHOP+2xR, achieved CR, DS=3 (see Picture 2)
- PBS in DIBH with repainting - initial bulk in liver hilar region 36 CGE/18 fractions (dose distribution, see Picture 3)
- 3/2019 lasting CR, DS=2 (see Picture 4)

Picture 1: PET+ involvement before chemo

Picture 2: PET- after chemo

Picture 3: treatment plan via PBS, DIBH, 2 convergent posterior field

Picture 4: after treatment completed

RESULTS: We have summarized our clinical experience with PBS in a wide spectrum of lymphomas. We have treated 143 patients with different sub-types and locations of lymphomas since 4/2013. The majority of our patients had mediastinal target locations. However, the use of PBS can be a promising option for some patients with non-mediastinal target (subhepatal, craniospinal axis irradiation, neck reirradiation and others). PBS proton therapy was well tolerated, with maximum acute toxicity grade 2 (dysphagia, skin). We observed only 1 possible case of serious symptomatic radiation pneumonitis in an elder comorbid patient with relapsing DLBCL and a large target volume (RT IF 44 CGE in curative setting for mediastinum + bilateral hilar region).

There are some specifics associated with response evaluation. In several patients (4 pts: 3HL, 1 NHL) we have observed a delayed response after PBS. These patients achieved final metabolic response 6-12 months after RT completion. Recently, there are 3 patients with focally Deauville score 4 metabolic response within on-going morphologic response. This type of response has been observed predominantly in centrally necrotic lesions with persistent metabolic active border. Thus, treatment response after PBS could be evaluated with caution and should take into account the possibility of delayed metabolic response . This situation could be judged in correlation with other factors as morphologic response and clinical status.

In some patients, PBS can reverse unfavourable clinical prospects of refractory disease with low toxicity potential. The advanced mediastinal disease progressing under systemic treatment with the need of dose escalation and large volume irradiation is the most common clinical situation. The mediastinal reirradiation is another example of beneficial use of PBS, mostly with no curative treatment alternative.

CONCLUSION: PBS proton therapy for lymphoma patients in different locations represents a meaningful and safe radiotherapy technique with a very favorable toxicity profile.