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Original Article

Proton beam therapy for mediastinal Hodgkin lymphoma: A prospective study of clinical efficacy and safety

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ABSTRACT

Background: Proton beam therapy using pencil beam scanning is an advanced radiotherapy technique that utilises proton beams to precisely target tumours. It is known for its enhanced ability in sparing healthy tissue and potentially reducing toxicity. Clinical experience with pencil beam scanning in the treatment of mediastinal Hodgkin lymphoma remains limited.

Patients and methods: This study aimed to evaluate the toxicity and outcomes of a prospectively observed cohort. A total of 162 patients were irradiated between May 2013 and December 2020, with a median age of 32 years (range: 18.4–79.2) and followed up until April 2024. The median applied dose was 30 GyE (range: 20–40). Deep inspiration breath hold was used in 146 patients to enhance targeting precision.

Results: The disease-free survival, overall survival and local control rates were 95.1 %, 98.8 % and 98.8 %, respectively. The median follow-up was 59.1 months (range: 4–120.1). The most common acute toxicities observed were oesophageal and skin toxicity. Grade 1 oesophageal mucositis occurred in 76 patients (47 %), grade 2 in 16 patients (10 %). Dermatitis of grade 1 and 2 was observed in 65 (40 %) and 4 (3 %) patients respectively. Grade 1 pulmonary toxicity presented in 8 patients (4.9 %), and grade 2 in one patient (0.6 %). The most predominant late toxicity was grade 2 hypothyroidism in 37 patients (23 %). Three patients (1.8 %) underwent coronary interventions during follow-up, and one patient was diagnosed with hepatocellular carcinoma 3 months post-RT. No unexpected acute or late toxicities were observed.

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Conclusion: Proton beam therapy using pencil beam scanning is a safe and effective technique in terms of toxicity and local control, even when irradiating mediastinal targets.

Introduction

Radiotherapy (RT) is a well-established modality in the treatment of Hodgkin lymphoma (HL), usually following systemic treatment with anthracyclines, as part of an effective combined modality treatment (CMT) approach [1,2]. However, mediastinal irradiation may carry a higher risk of morbidity, particularly in the form of radiation-related cardiovascular disease (CVD) and second malignancies (SM) [3–8].

Concerns regarding RT toxicity have led to a reduction in the use of RT in early stage disease and the almost elimination of its use in more advanced disease, typically limited to patients at high risk of locoregional failure or those with persistent disease after systemic therapy. Stratification for RT is usually guided by interim or final PET/CT results [9–14].

The omission of RT is often compensated by intensifying various types of systemic treatments. Regimens incorporating new drugs may be associated with other significant toxicities. For example, the BV-AVD regimen has been linked with an increased risk of long lasting peripheral neuropathy compared to the ABVD regimen [15], while schedules including check point inhibitors carry a risk of immune-related adverse events [16]. Cytotoxic regimens pose additional risks, such as hematopoietic involvement, which can lead to serious complications such as the development of myelodysplastic syndrome and subsequent secondary acute myeloid leukaemia [17]. Further side effects of systemic therapy, including cardiovascular disease [18], second cancers [19], decreased fertility [17] or cognitive decline [20], often significantly affect the quality of life after treatment.

However, there remains a subset of patients who can still benefit from a CMT approach. Consolidation RT remains the standard care of treatment schedules for early and intermediate stage HL according to some guidelines [1,2,21].

Furthermore, there is more evidence that supports the inclusion of consolidation RT for localized HL despite early PET/CT negativity, where the omission of RT could be associated with lower 10-year PFS [22].

Proton beam therapy (PBT) using pencil beam scanning (PBS) is an advanced RT technique which could be used to sustain the disease control benefits of RT whilst reducing risks such as radiation-related CVD and SM [23,24]. Owing to their unique physical properties, protons deliver a dose that steeply drops beyond the target area, thereby minimising radiation exposure to surrounding healthy tissues when compared to photon RT [25–27]. A review of the theoretical assumptions and clinical data from 14 planning studies demonstrated that PBT significantly lowers the radiation load on organs at risk [28]. This becomes particularly relevant in the treatment of mediastinal HL, where the irradiated area contains a number of vital organs such as the heart, lungs and oesophagus and therefore patients are at risk of developing RT associated toxicities.

Consensus guidelines on PBT for adult mediastinal lymphomas identify patient groups that are most likely to benefit from the treatment [29]. The guidelines set stricter limits on the exposure of organs-at-risk compared to previous criteria [30]. Maintaining optimally low doses to the organs at risk (OAR) via advanced photon RT is often possible [23].

However, there is a still group of patients who could benefit more from the inclusion of PBT in their treatment regimen [29,31,32]. For example, patients with lower mediastinal disease or axillary involvement. Another study has estimated that 41–70 % of patients with mediastinal target volumes could benefit from the inclusion of PBT in terms of reducing 30-year absolute mortality risks (AMR_{30}) from radiation-related CVD and second cancers. However, to more accurately determine a more personalised potential benefit of PBT, dual planning using both photon RT and PBT should be considered [33].

The theoretical dosimetric benefits of PBT for mediastinal HL are known and some small studies have demonstrated clinical benefits [34–36], however, clinical studies with long term follow up from a large patient cohort are limited. In this study, we aim to address this gap by evaluating treatment outcomes and toxicities in a large cohort of patients with mediastinal HL treated with PBT-PBS.

Materials and methods

Patient selection criteria and follow up

This prospective single-institution observational study aimed to prospectively monitor the efficacy and toxicity of PBT-PBS and was approved by the local ethics committee (Study Protocol No.2023012). Patients were referred by the Czech comprehensive cancer centre network and treatment was individually approved by the patients' health insurance. Inclusion criteria were histologically proven Hodgkin lymphoma (all subtypes) and indications for RT in mediastinal area following national recommendations, regularly updated and based on current international guidelines.[37].

Indications included:

a. Patients whose organ-at-risk dose limits were exceeded with photon-based RT at their local institutions
b. Large target volumes involving the lung hilum, lower mediastinum (below the level of main left coronary trunk) [29] or upper mediastinum simultaneously with axilla (anticipating high radiation dose to the lungs and/or mammary gland in women)
c. Patients with significant cardiovascular or pulmonary comorbidities

Patient characteristics and disease-related information are summarised in Table 1. The vast majority of patients (95 %) had PET/CT performed initially and for monitoring of response to the systemic treatment. A final PET/CT was performed three months after PBT-PBS. Patients with persistent PET positivity, occasionally seen in bulky central necrotic residues, were examined further on an individual basis. Follow-up examinations after PBT-PBS, including physical examinations, blood count assessments and biochemistry were scheduled every three months for two years, every six months for the subsequent two years, and once per year thereafter. Chest X-rays, abdominal ultrasound, thyroid-stimulating hormone (TSH) and electrocardiogram (ECG) were performed annually. The institutional patient database was periodically updated at two-year intervals. All patients were educated about screening of CVD, thyroid function, mammary screening in women and smoking cessation during long-term follow-up. Patients who stopped attending follow-up clinics were contacted by phone, e-mail, by searching available patient databases [38] or by contacting their attending haemato-oncologist. Data for analysis of OS and PFS were collected up to April 2024 and analysed. Statistical analysis was performed using R software, version 4.4.0 and Kaplan-Meier curve estimations were done using version 3.5–8.

Target volume definition

The involved field RT (IFRT) approach according to German Hodgkin Study Group (GHSG) was used between 2013 and 2015 [39]. From 2015 onwards, the involved site (ISRT) or residual disease target definitions, according to the International Lymphoma Radiation Oncology Group

Table 1
Patients demographics and pre-treatment characteristic.

Sex		**[patients]**
	male	63
	female	99
Age		**[years]**
	min	18.4
	max	79.2
	median	32
Chemotherapy		**[patients]**
	ABVD (2 cycles)	9
	ABVD (4 cycles)	15
	ABVD (2 cycles) + BEACOPP escalated (2 cycles)	108
	BEACOPP escalated (6 cycles)	23
	Other regimens	7
Follow up		**[months]**
	min	4.0
	max	120.1
	average	63.4
	median	59.1
PET post chemotherapy		**[patients]**
	PET negative (Deauville score 1–3)	115
	PET positive (Deauville score 4–5)	30
	unknown	17
Initial staging		**[patients]**
	IA	1
	IB	2
	II	3
	IIA	74
	IIA/B	1
	IIAE	2
	IIB	48
	IIBE	4
	IIEA	2
	IIIA	6
	IIIB	3
	IVA	4
	IVB	12
Staging according to GHSG		**[patients]**
	early	9
	intermediate	123
	advanced	30

(ILROG) guidelines, were adopted [40]. Radiotherapy characteristics including target definition is detailed in Table 2. The margins for target volumes were defined as follows: the clinical target volume (CTV) was expanded by a 5 mm margin to create the internal target volume (ITV) to account for cardiac and great vessels' movement. The ITV was further expanded by 5–7 mm to create the planning treatment volume (PTV). The cardiac substructures were contoured according to a published atlas [41].

Motion management

Initially, the free-breathing technique with 4D-CT was used, with a maximum allowable target motion due to breathing limited to 6 mm. As a result, patients with involvement of the lung hilum or lower mediastinum were frequently excluded due to more extensive respiratory movement. Following the adoption of deep inspiration breath hold (DIBH), using the Dyn'R breath control system (SAS DYN'R Aix-en-Provence FRANCE), the eligibility criteria expanded considerably. The inter-fraction reproducibility of DIBH using DyńR was evaluated prior to its routine use.

Treatment planning

Field configuration depended on the treatment area and is detailed in Table 3. All patients in this study were planned using XIO planning system (Elekta Sweden, Version 4.8 and 5.1).

In 2022, the XIO was replaced by Ray Station (RaySearch, Sweden). The plans were designed with emphasis on minimising the dose to the lungs, heart, breasts and other organs-at-risk, despite potentially

Table 2
Radiotherapy characteristics.

Target volume definition		Patients
	RT involved field	12
	RT involved site	120
	RT residual disease	30
Target regions		
	Waldeyeŕs ring + cervical lymph nodes + mediastinum	1
	Waldeyeŕs ring + cervical lymph nodes + mediastinum + unilateral axilla	1
	Cervical lymph nodes + mediastinum	86
	Cervical lymph nodes + mediastinum + bilateral axilla	7
	Mediastinum	34
	Cervical lymph nodes + mediastinum + unilateral axilla	33
Total dose	**[GyE]**	
	20 (min)	9
	30 (median)	145
	32	1
	34	1
	36	2
	40 (max)	4
	19.8 + 10	1
Breathing control		
	free breathing	16
	deep inspiration breath-hold	146
Reirradiation		
	yes	4
	no	158

Table 3
Treatment planning strategies.

Treated region	Ray Station TPS		XiO TPS	
	Number of fields	Typical gantry angle	Number of fields	Typical gantry angle
Upper mediastinum only	2	5° and 355°	1	0°
Bilateral neck lymph nodes	2 cervical nodes	60° and 300°	2 cervical nodes	60° and 300°
Upper mediastinum close to heart	2 repainted-small field	5° and 355°	1 repainted field for whole upper mediastinum	0°
Lower mediastinum	2	175°and 185°	1	180°
Axillary lymph nodes	1–2 depending on patient lateral size	180° female (prefer) 0°male (prefer)	1–2 depending on patient lateral size	180° female (prefers) 0°male (prefer)
Infradiaphragmatic region	Individually depending on location			

compromised and non-robust PTV coverage, dose constraints can be seen in Table 1 Supplementary materials. Robust optimization was not performed in the treatment plans systematically. Prior to routine use of DIBH, we calculated a scenario of plans shifted by two millimetres in every direction and we used every control CTs to compute and evaluate the quality assurance plans. Rescanning was employed for targets located near the heart and great vessels to supress the interplay effect. The daily X-ray imaging setup was proceeded. A control CT scan was performed once per week. In cases of bulky viable residual tumours, more frequent CT imaging was performed to monitor expected tissue changes during the course of PBT-PBS. A quality assurance plan was required if the target morphology changed by more than 2–3 mm, with individual decisions made for plan adaptation, which was carried out without treatment interruption. The physical dose was multiplied by a relative biological effectiveness factor of 1.1 [42]. An example of a typical dose distribution is shown in Fig. 1.

Results

A total of 162 adult patients with mediastinal HL were irradiated using PBT-PBS between April 2013 and December 2020. The median age was 32.0 years (range: 18.4–79.2), and the median applied dose was 30 GyE (range: 20–40). The dosimetric parameters for all patients can be seen in Table 4. DIBH was utilised in 146 patients for enhanced targeting precision. Compliance with DIBH was excellent, with all patients but one successfully following the technique.

This prospective observational study focused primarily on demonstrating the safety of PBT-PBS in terms of local control. The disease-free survival, overall survival and local control rates were 95.1 %, 98.8 % and 98.8 %, respectively, see Figs. 2-4. The median follow-up was 59.1 months (range 4–120.1).

A total of 6 patients relapsed, 5 patients had distant relapse and 1 patient had simultaneous in-field and distant relapse, (Table 2 Supplementary materials). Two patients died due to COVID-19 complications during the follow-up period, at four and 47 months post PBT-PBS. Hepatocellular carcinoma was detected in one patient during their restaging PET/CT, three months post RT. There were no differences in survival outcomes between patients with PET positivity and those without PET positivity before RT.

The most common toxicity reactions were mucosal toxicity in the upper gastrointestinal (GI) tract and dermatitis. Oesophageal mucositis was observed at grade 1 in 76 patients (47 %) and grade 2 was reported in 16 patients (10 %). Grade 1 dermatitis occurred in 65 patients (40 %), and four patients had grade 2 (3 %). Pulmonary toxicity presented as grade 1 in 8 patients (4.9 %). One patient (0.6 %) developed grade 2 pulmonary toxicity, and required treatment with short course of inhaled corticosteroids. No medical interventions were necessary to adjust haematological parameters during RT. We did not observe any neurological toxicity associated with PRT. For toxicity details see Table 3 Supplementary materials.

The most frequent late toxicity was grade 2 hypothyroidism, observed in 37 patients (23 %), all of whom required hormone replacement therapy. The probability of grade 2 hypothyroidism was 18 %, 15 %, 17 % and 32 % for mean thyroid gland dose groups (0–10) GyE, (10–20) GyE, (20–30) GyE and 30 + GyE respectively. This was followed by grade 1 retrosternal fibrosis, seen in 6 patients (4 %), manifesting as transient retrosternal pain without need for intervention. Three grade 2 coronary events were recorded (2 multiple stenosis, 1 embolization) between 35 to 58 months post PBT-PBS, (Table 4 Supplementary materials). All these patients exhibited multiple pre-existing cardiovascular risk factors, with one individual additionally presenting with hypercoagulability in the early postpartum period. In all three cases, the involved coronary arteries were in close proximity to the target volume and were treated by stent insertion. No other significant cardiac

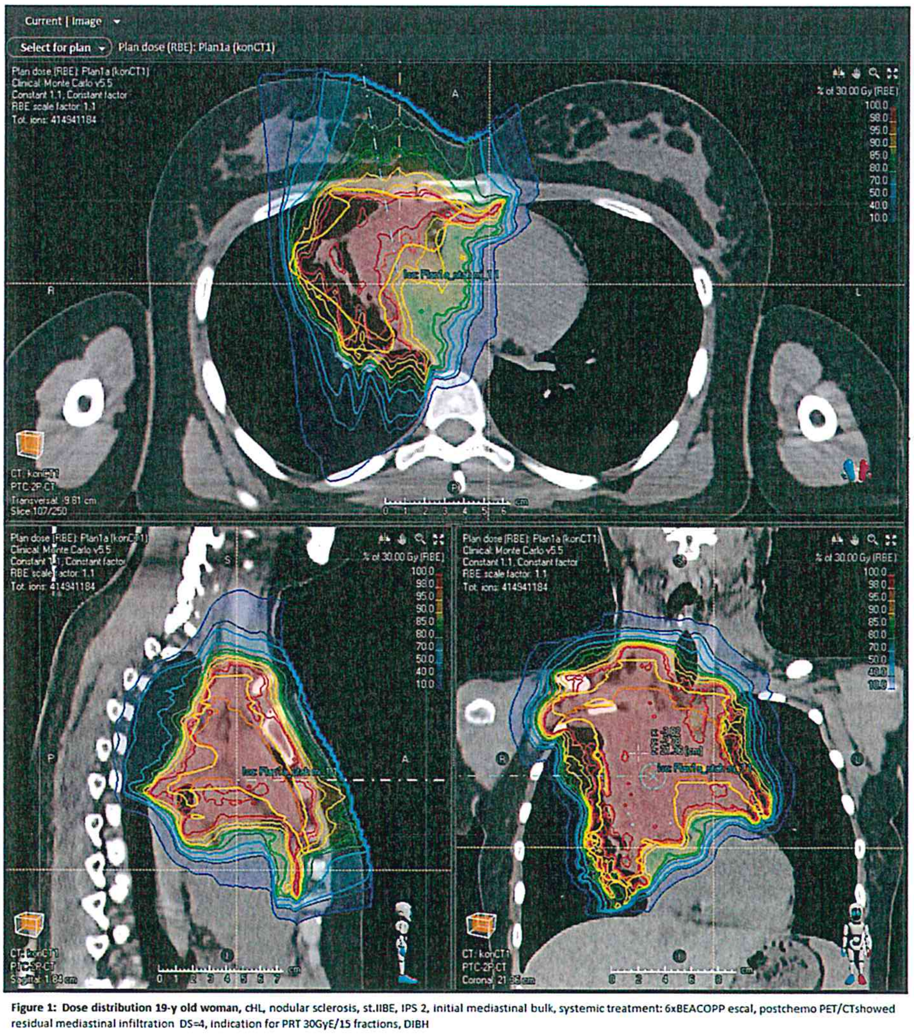

Fig. 1. Dose distribution 19-y old woman, cHL, nodular sclerosis, st.IIBE, IPS 2, initial mediastinal bulk, systemic treatment: 6xBEACOPP escal, postchemo PET/CT showed residual mediastinal infiltration DS = 4, indication for PBT-PBS 30GyE/15 fractions, DIBH.

Table 4
Dosimetric parameters of treatment plans (n = 162).

volume	unit	min	max	mean	median
V_{PTV}	[cm^3]	313.24	4144.67	1538.66	1450.62
PTV $D_{95\%}$	[GyE]	18.15	40.15	29.05	29.44
V_{CTV}	[cm^3]	40.15	1730.96	543.90	502.89
CTV $D_{98\%}$	[GyE]	19.62	40.81	30.00	30.36
Lung L D_{mean}	[GyE]	0.97	12.06	5.93	5.70
Lung L V_{5GyE}	[%]	4.47	54.46	27.85	26.19
Lung L V_{20GyE}	[%]	0.00	40.70	15.47	14.70
Lung R D_{mean}	[GyE]	0.41	12.46	5.26	5.01
Lung R V_{5GyE}	[%]	2.28	55.65	24.18	22.50
Lung R V_{20GyE}	[%]	0.00	34.98	13.23	12.35
Lungs D_{mean}	[GyE]	1.87	10.09	5.56	5.45
Lungs V_{5GyE}	[%]	8.93	46.21	25.67	25.28
Lungs V_{20GyE}	[%]	0.00	31.16	14.30	14.10
Heart D_{mean}	[GyE]	0.08	22.77	6.56	5.78
Left atrium D_{mean}	[GyE]	0.03	29.51	7.25	4.31
Right atrium D_{mean}	[GyE]	0.08	31.37	8.51	7.13
Left ventricle D_{mean}	[GyE]	0.00	17.26	2.53	0.96
Right ventricle D_{mean}	[GyE]	0.00	31.16	6.54	5.04
Aortal valve D_{mean}	[GyE]	0.08	39.96	14.27	12.53
Pulmonal valve D_{mean}	[GyE]	0.00	41.45	23.88	27.71
Mitral valve D_{mean}	[GyE]	0.00	25.23	1.85	0.30
Tricuspid valve D_{mean}	[GyE]	0.00	30.75	2.69	0.24
Right coronary artery D_{mean}	[GyE]	0.00	38.46	13.97	12.94
Left anterior descend artery D_{mean}	[GyE]	0.02	40.21	10.31	7.00
Left circumflex artery D_{mean}	[GyE]	0.01	31.45	7.34	5.52
Left main coronary artery D_{mean}	[GyE]	0.14	41.64	18.68	19.98
Mammary gland L V_{4GyE} [%]	[%]	0.00	43.27	10.08	7.16
Mammary gland R V_{4GyE} [%]	[%]	0.00	35.08	8.36	6.06
Mammary gland L D_{mean}	[GyE]	0.01	7.48	1.68	1.11
Mammary gland R D_{mean}	[GyE]	0.00	18.35	1.40	0.85
Thyroid gland D_{mean}	[GyE]	0.00	36.85	25.25	29.36
Parotid gland L D_{mean}	[GyE]	0.00	30.66	11.42	13.60
Parotid gland R D_{mean}	[GyE]	0.00	28.55	12.86	17.15
Spinal Cord $D_{2\%}$	[GyE]	0.00	25.82	6.51	4.90
Oesophagus D_{mean}	[GyE]	0.03	33.84	18.91	18.51

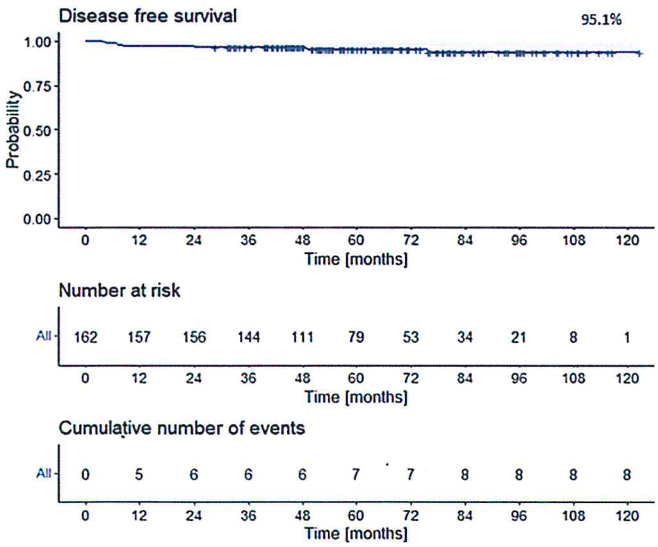

Fig. 2. Disease free survival (DFS).

toxicities, such as valvular disease, arrhythmias or myocardial injury were observed. No second malignancies or unexpected late toxicities were observed.

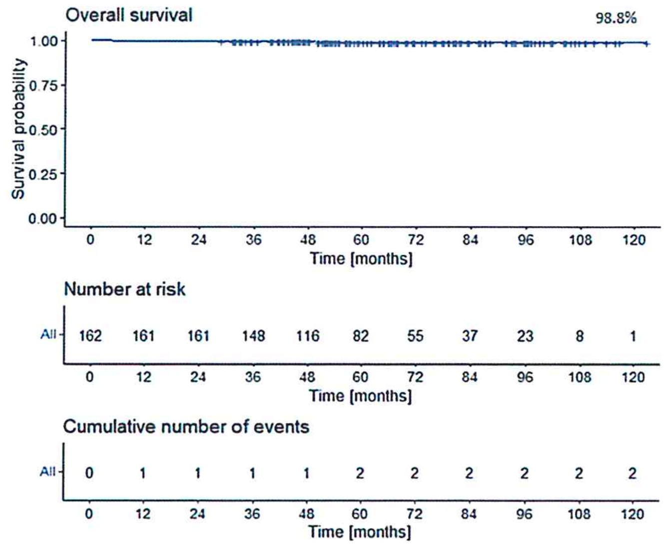

Fig. 3. Overall survival (OS).

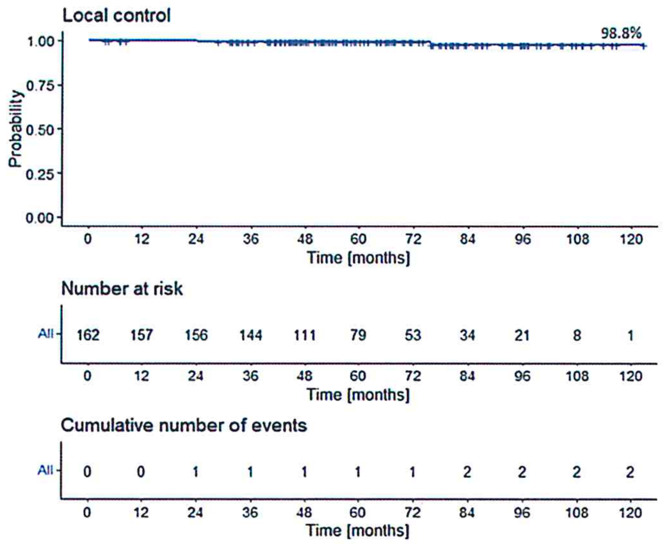

Fig. 4. Local control (LC).

Discussion

This study represents the largest cohort to date reporting long-term outcomes for mediastinal HL patients who received PBT-PBS in DIBH. A previous large study evaluated the therapeutic outcomes of HL patients using a mix of PBT techniques. The majority of patients in that study underwent older PBT techniques such as passive-scattering and uniform-scanning [34]. Advanced PBT-PBS is supposed to have slightly higher efficacy, lower out-of-field dose, it allows real 3D dose modulation compare to double scatter proton therapy (DSPT) and it broadens the spectrum of indications for HL compared to DSPT [43]. Additionally, PBT-PBS is the technique of choice for all new PBT centres worldwide. It is, therefore, crucial to assess its efficacy and safety in a large clinical cohort.

A combined approach that incorporates RT continues to have its place in the treatment of Hodgkin lymphoma. Modern photon techniques for mediastinal RT, such as volumetric modulated arc therapy (VMAT) and intensity modulated radiotherapy using "butterfly" technique (IMRT-BT) with DIBH, may provide comparable dosimetric and clinical outcomes to PBT, especially when proton irradiation cannot be combined with DIBH [23]. While photon-based RT has achieved significant improvements over the last two decades, it has reached its physical limitations. PBT can provide even lower doses to organs at risk offering more precise targeting and likely lower toxicity to organs at risk.

However, when introducing mediastinal PBT-PBS into clinical practice, there are several challenges to overcome. Not addressing these challenges in clinical practice may invalidate the expected dosimetric benefit of protons. PBT is characterized by a different relative biological effectiveness (RBE) and a high conformity with a steep dose gradient. The higher RBE is corrected by a factor of 1.1 compared to the physical dose. However, this factor is not constant throughout the irradiated volume, and in areas of the distal edge of the treatment volume, the RBE increases above 1.1 due to a rising linear energy transfer (LET) [44,45]. The inhomogeneous RBE could be a source of concern for the organs located in the proximity of the distal edge area, which may receive a higher biologic dose than was calculated. This could be significant for organs sensitive to high maximal doses such as the coronary arteries, oesophagus, heart valves and spinal cord. Investigations are being made to incorporate RBE into the dose calculation using different algorithms. One study concluded that a higher RBE at the distal edge was unlikely to outweigh the dosimetric benefits for cardiac substructures.[46] Previous studies encouraged a cautious approach especially when the calculated dose is close to the dose objectives [47,48]. Therefore, careful monitoring of possible unexpected adverse effects of PBT is necessary during and after treatment.

Mediastinal PBT-PBS must account for a range of uncertainty due to the heterogenous composition of tissues with varying water equivalent thicknesses (WET). Even small positional changes in the irradiated area could lead to significant WET uncertainty. This increases the risk of under dosing the target volume (geographic miss) or overdosing the organs at risk located behind the target. The use of DIBH may lead not only to better positional reproducibility but also to greater sparing of organs at risk with further dose reduction to the lungs and heart and possibly breasts [49]. For these reasons, it is always advisable to combine mediastinal PBT-PBS with DIBH [23]. Respiratory movement is not the only source of uncertainty in the accuracy of PBT-PBS. Combining DIBH with rescanning in areas affected by heart motion appears to be the safest treatment strategy when using PBT-PBS in the mediastinal region.

The selection of patients who benefit from PBT is based on various parameters, and the threshold of the absolute dosimetric differences in terms of toxicity risk varies [50]. Radiobiological models that process dosimetric differences can better estimate the clinical advantage of PBT compared to dosimetric differences from photon-based RT alone. Our team performed a risk prediction study in a subset of this cohort (80 patients) which aimed to define those patients that would benefit the most from PBT-PBS compared to photon-based RT. In terms of AMR_{30}, the study concluded that PBT-PBS could reduce cardiovascular AMR_{30} in selected patients with $\geq$ 40 % of the target volume overlapping with the heart in the cranio-caudal direction or in cases with axillary disease. The study did not confirm a significant reduction in the mortality risk from second primary breast cancer despite the breast dose reduction from PBT-PBS, however, PBT-PBS could be recommended for its potential to lower lung doses and risk of second primary lung cancer mortality risk [31].

A planning study from another institution involving 30 patients comparing PBT-PBS to VMAT confirmed significant reduction of mean doses to the heart, left ventricle and the valves. The magnitude of clinical benefit is related not only to dosimetric parameters, but also to the presence of other underlying cardiovascular risk factors. The median composite relative risk reduction (cRRR) of cardiovascular adverse events with PBT-PBS was 4.8 %, ranging from 0.1 % to 30.5 %. The study concluded that only a minority of patients experienced a significant overall reduction in CVD risk, which depended on the clinical scenario and PBT-PBS availability [51]. Toltz et al. compared the risk of cardiac mortality, lung cancer, and breast cancer with two photon-based techniques, helical tomotherapy (HT) and 3D-conformal RT (3DCRT) to PBT-PBS in 20 patients. While the predicted and absolute risks of cardiac mortality were not reduced with HT or PBT-PBS compared to 3DCRT, the predicted risks for second lung and breast cancers were increased for HT and decreased for PBT-PBS [47].

Clinical data on the use of PRT is limited due to a relatively small number of cohorts reported in the literature. In a study of 50 paediatric patients, a 5-year relapse-free-survival (RFS) rate of 90 % was achieved. All recurrences occurred both in- and out-of-field, with a median incidence of 9.2 months post-PBT. At a median follow-up of 5.3 years, no PBT-related grade 3 to 5 toxicities or secondary malignancies were reported [36]. A multicentric study with 138 paediatric and adult HL patients reported a 3-year RFS of 92 % for all patients; with 96 % for adults and 87 % for paediatric patients. No grade 3 radiation-related toxicities occurred [34]. König at al. published results for 20 patients with mediastinal HL. With a median follow-up of 32 (range 21–48) months, the local and distant progression-free survival rates were 95.5 % and 95.0 %, respectively. RT was well tolerated, with only grade 1 and 2 acute and chronic toxicities reported [35]. In our cohort, we have also confirmed excellent outcomes in terms of disease control and low toxicity.

A new potential advantage of PBT is its possible lymphocyte-sparing effect [52,53]. With the growing role of immunotherapy in HL treatment regimens,[54] a synergistic effect is expected when immunotherapy is applied concurrently with RT [55–57]. It is assumed that preserving the patient's immunocompetence as much as possible is essential for the optimal effect of immunotherapy. However, RT is generally known to be a lymphodepleting modality. Highly conformal photon-based techniques such as IMRT, HT or VMAT are associated with a significant risk of inducing severe lymphopenia [58], particularly when large volumes including lymphocyte-rich non-target tissues are irradiated [59]. Proton RT, with its proven ability to minimise damage to lymphocytes, could be an optimal RT technique for combination with immunotherapy [52]. However, these assumptions should be validated further through clinical studies.

Conclusions

Proton beam radiotherapy using PBS is a well-tolerated treatment modality that demonstrates excellent therapeutic outcomes. Replacing standard photon-based RT with PBT-PBS reduces the risk of developing both acute and, potentially, late toxicities — the main factors often leading to the reduction in RT use in modern treatment practices. This study represents the largest cohort to date reporting long-term outcomes of PBT-PBS for mediastinal HL.

Our results demonstrate that PBT-PBS in DIBH is a well-tolerated treatment modality with excellent therapeutic outcomes, at least comparable, or even better than those observed in photon-based RT studies [1,2,14].

There was no evidence to support the frequently raised concerns about potential risks associated with PBT-PBS, such as suboptimal local control or the risk of unexpected acute or late toxicities. However, longer follow-up over several decades is needed to assess late toxicities such as CVD or second cancers more meaningfully. As the number of PBT centres using PBS increases globally, reporting outcomes from clinical experience in PBS use for treating mediastinal HL is crucial and is likely to increase the use of it in this patient group.

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A data sharing statement

Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

CRediT authorship contribution statement

Kateřina Dědečková: Writing – original draft, Methodology, Conceptualization. **Michal Andrlik:** Writing – review & editing, Writing – original draft. **Heidi Mócíková:** Writing – review & editing, Conceptualization. **Lucia Kaliská:** Validation. **Simona Zapletalová:** Writing – review & editing. **Jiří Kubeš:** Writing – review & editing, Supervision, Methodology. **Sarah Al-Hamami:** Writing – review & editing. **David J. Cutter:** Writing – review & editing. **Georgios Ntentas:** Writing – review & editing. **Vladimír Vondráček:** Writing – review & editing. **Barbora Ondrová:** Formal analysis. **Jana Marková:** Validation, Data curation. **Ľubica Gahérová:** Validation, Formal analysis. **Lekaá Mohammadová:** Validation, Formal analysis. **Vít Procházka:** Validation, Formal analysis. **Jozef Michalka:** Validation, Formal analysis. **Alice Sýkorová:** Validation, Formal analysis. **Juraj Ďuraš:** Validation, Formal analysis. **Jan Kořen:** Validation, Formal analysis. **Matěj Navrátil:** Validation, Data curation. **Michaela Vařejková:** Data curation. **Tomáš Doležal:** Data curation. **Jana Prausová:** Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2025.110931.

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