Evidence for external beam radiotherapy in mediastinal Hodgkin and non-Hodgkin lymphoma – systematic review

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▌ Abstract

Introduction and objective. Proton beam therapy (PBT) provides the opportunity for a more localized delivery of high energy protons and may reduce the damage to healthy tissues and vital organs. The aim of this review was to assess the effects of proton therapy for patients diagnosed with Hodgkin or non-Hodgkin lymphoma treated with mediastinal irradiation.
Review methods. A systematic search of EMBASE, MEDLINE via OVID and Cochrane Library was conducted in May 2022 according to PRISMA guidelines to identify relevant data on the efficacy and toxicity of proton beam therapy for patients diagnosed with Hodgkin or non-Hodgkin lymphoma.
Brief description of the state of knowledge. Of 566 screened abstracts (430 after de-duplication) 11 studies with a total of 529 patients were included. All studies were case series published between 2011–2021. Median range of follow-up time was 15–63.6 months. The overall survival (OS) for 2 years varied from 91% – 98% for 5 of the included studies. Three of the included studies had favourable outcomes with 2-year progression-free survival (PFS) ranging from 73% – 94%. Skin reaction, oesophagitis and fatigue were found to be the most common grade 1 and grade 2 toxicities. No acute or late grade 4 and higher toxicities/adverse events were observed.
Summary. There are data indicating that PBT may to be an effective treatment against mediastinal Hodgkin and non-Hodgkin lymphoma. Because all the studies were case series, the authors of this review have little confidence in the evidence. There remains a need for well-designed randomized controlled trials to inform about the optimal approach to proton irradiation in HL and NHL.

▌ Key words

lymphoma, mediastinum, non-Hodgkin, Hodgkin Disease, proton therapy

INTRODUCTION AND OBJECTIVE

Proton therapy, also known as proton beam therapy (PBT), is a type of radiation therapy that uses a beam of high energy protons to treat specific types of cancer. Proton therapy enables a dose of high energy protons to be precisely targeted at a tumour and reduce the damage to surrounding healthy tissues and vital organs [1]. It enables better local tumour control and decreases the risk of complications. The total energy absorbed in the patient's body (integral dose) is 2–3 times lower compared to the photon beam [2, 3]. The clinical practice of this type of radiotherapy focuses on ocular tumours, skull base, paraspinal tumours and unresectable sarcomas, which had poor results when previously treated with photon radiotherapy [4].

Hodgkin lymphoma (HL), formerly called Hodgkin's disease, is a rare monoclonal lymphoid neoplasm with an estimated incidence of 2.7 – 2.8 cases per 100,000 person/year, characterized by a excellent overall prognosis with an approximately 80% cure rate [5]. Hodgkin lymphoma has been divided into two distinct categories: classical Hodgkin lymphoma and nodular lymphocyte-predominant Hodgkin lymphoma (NLP-HL). Classical Hodgkin lymphoma accounts for approximately 95% of all HL [6]. Non-Hodgkin lymphoma (NHL) is a group of malignant neoplasms originating mainly from the lymph nodes. NHL may be associated with various factors, including infections, immunodeficiency states, chronic inflammation and environmental factors. NHL is comprised of various subtypes, each with different aetiologies, immunophenotypic, genetic, clinical features, and response to therapy. Based on the prognosis of the disease, NHL can be divided into two groups: 'indolent' and 'aggressive' [7]. The landmark lymphoma staging classification system for both HL and NHL was originally the Ann Arbor staging system [8] which has subsequently been modified. The currently

most widely-used lymphoma staging system is the Lugano staging classification, which also separately defines criteria for response to treatment assessed by PET-CT or by CT alone [9].

Both HL and NHL belong to the group of neoplasms with the highest radiosensitivity [10]. Treatment of HL depends on the histologic characteristics, stage of the disease and the presence (or absence) of prognostic factors [6]. For many patients with HL, this is chemotherapy (usually 2 – 4 cycles of ABVD) followed by radiation to the initial site of the cancer [11]. The most common treatment for NHL includes chemotherapy, radiotherapy, immunotherapy, stem cell transplant, and in rare cases – surgery [12]. Proton's therapy physical dose distribution is one of the treatment strategies for patients with mediastinal lymphoma which may reduce the risk of radiation-associated late cardiac toxicity, secondary cancers of the breast and lung tissue [13].

Some guidelines indicate that proton therapy can have a positive impact on late complications/side-effects and secondary neoplasms, compared to conventional radiotherapy methods [14, 15, 16]. Also, some of the guidelines do not recommend proton therapy for the treatment of lymphoma because of the absence of high-quality evidence [17, 18, 19]. Thus, the presented review sought to determine what the current literature states about the efficacy and safety of PBT in treating mediastinal Hodgkin lymphoma and non-Hodgkin lymphoma.

REVIEW METHODS

Search strategy and selection criteria. A comprehensive review of the literature was carried out using the EMBASE and MEDLINE via OVID and the Cochrane Library databases. The search was conducted on 30 May 2022 without time limitation, using the following key words: 'proton therapy', 'lymphoma', 'reticulolymphosarcoma', 'germinoblastoma. Inclusion criteria were defined using the Population, Intervention, Control, Outcome, and Study Design (PICOS). Studies selected for inclusion met the following criteria: (1) population – patients diagnosed with Hodgkin or non-Hodgkin lymphoma treated with mediastinal irradiation; (2) intervention – proton therapy; (3) control – not restricted; (4) outcome – overall survival, progression-free survival, local control, distant metastasis-free survival, quality of life and safety profile; (5) study design – randomized controlled trials (RCT), non-randomized controlled trials (nRCT), cohort studies, case-control studies, and case series ≥ 5 patients). Exclusion criteria were: review articles, conference abstracts, study protocols, preclinical animal research, or studies that did not provide the outcomes within the scope of interest. Publications in a language other than Polish and English were excluded from the analysis, as well as publications on dosimetry.

Articles were initially screened by title and abstract for relevance and two independent investigators separately assessed each article that met inclusion criteria. Any disagreement between investigators was resolved by discussion and consensus. A cross-reference search of selected articles was manually reviewed to identify other relevant publications. Data extraction from each study was performed independently and then reviewed by a second author.

A search for clinical trials in proton therapy in Hodgkin and non-Hodgkin lymphoma was performed (ClinicalTrials.gov) on 20 May 2022.

Quality appraisal. Risk of bias was assessed according to the Risk of Bias Tool 2.0 for RCT [20], ROBINS I for nRCT [21] Newcastle Ottawa Scale (NOS) for cohort and case-control study [22], and the Joanna Briggs Institute Critical Appraisal Tool for case series [23]. For case series, the potential risk of bias was specified as high with ≤49% 'yes' answers, moderate when 50% – 69% 'yes', and low when the study reached ≥70% 'yes'. The rating scale was prepared by the authors of this review. Two authors systematically assessed each domain and independently estimated the potential risk of bias for each study. In the case of differences in results, the final grade was selected after discussion with the author(s).

Statistical analysis. Due to the paucity of trials and the high heterogeneity among studies, a quantitative analysis on the effectiveness of radiotherapy was not attempted.

DESCRIPTION OF THE STATE OF KNOWLEDGE

Selection and characteristics of studies. The three search strategies considering clinical studies identified 566 articles, reduced to 430 after the exclusion of duplicates, with another 37 articles excluded for various reasons. Of the 430 records screened on the basis of title and abstracts, 48 were potentially relevant publications. In total, 11 studies met the inclusion criteria (Fig. 1) [24–34]. The characteristics of the included publications are shown in Appendix 1. All studies were case series with total of 529 patients. The studies were published between 2011 and 2022 and included a population of adults and children who had undergone proton therapy. The age range of the patients at the time of diagnosis was 5 – 73 years [27, 33]. The follow-up time varied with a median range of 15 – 63.6 months[25, 32]. Most patients were female (range: 50% – 75%) [34, 26]
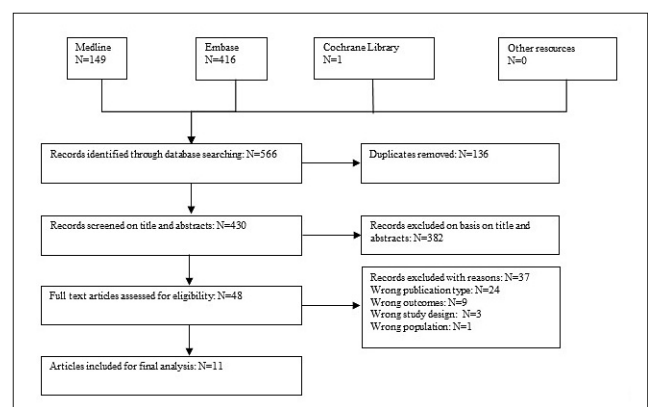
Figure 1. PRISMA flow-diagram of the study selection process

The most common indication was Hodgkin lymphoma (described in all studies), whereas patients with non-Hodgkin lymphoma were described in 5 studies [25, 28, 29, 31, 33]. Most patients had stage 2 according to Lugano/Ann Arbor staging system. For Hodgkin lymphoma, the most commonnly reported histologic subtype was nodular sclerosing lymphoma; for Non-Hodgkin lymphoma – diffuse

Annals of Agricultural and Environmental Medicine 2024, Vol 31, No 1

49

Malwina Kowalska, Ewelina Sitarz-Kilian, Klaudia Jaros, Magdalena Koperny , Paweł Moćko, Jacek Siwiec, Paweł Kawalec. Evidence for external beam radiotherapy…

large B-cell lymphoma (DLBCL). In most cases, the patients, also received chemotherapy, with the chemotherapy regimens varying between both, studies and patients enrolled in the studies (Appendix 1). The main intervention was proton therapy, but patients could receive multiple treatments. There were different proton doses (GyRBE) and protocols for proton therapy in the studies. Paediatric patients received smaller doses (median range: from 21 Gy – 26 Gy [27, 34, 25]. For adults, the most common median dose was 30.6 Gy (highest median dose: 36 Gy [25, 33]). For Non-Hodgkin lymphoma patients, the dose was higher than for Hodgkin lymphoma (Tab. 1).

Table 1. Treatment characteristics

Reference	Protocol of treatment	Proton dose Gy (RBE)
Bates 2021 [24]	Not reported	Proton and photon total: <30 Gy (n=37) >30 Gy (n=54)
Dionisi 2022 [25]	Not reported	Paediatric patients: median: 26 (range 19.8-30) Adult patients: median: 36 (range 30-40)
Hoppe 2014 [26]	3D-CRT and proton therapy IMRT and proton therapy 3D-CRT and IMRT	Radiation prescription dose: Paediatric patients: 15-21 at 1.5 Gy Adult patients: 30.6 Gy at 1.8 Gy Patients with incomplete CT and/or PET response following chemotherapy: an additional 4.5 to 9 Gy
Hoppe 2017 [27]	University of Florida (n=39) University of Pennsylvania (n=54) Proton Collaborative Group (n=45)	Paediatric patients: median: 21 (range 15-36) Adult patients: median: 30.6 (range 20-45)
König 2019 [28]	HL: Study concepts of the German Hodgkin Study Group NHL: Not reported	HL: Median: 30 (range 20-30) NHL: Median: 36 (range 36-39.6)
Li 2011 [29]	3D-PBT at M. D. Anderson Cancer Center	Range of prescribed doses: 30.6-50.4 (CGE) 6 patients received 30–40 CGE
Loap 2021 [30]	Institut Curie, Department of Radiation Oncology (Paris, France)	Total dose: 30.6
Nanda 2017 [31]	Not reported	Median prescription dose: 30.6 (range 15-45)
Tringale 2021 [32]	AHOD0331 (n=20) AHOD0831 (n=3) AHOD1331 (n=13)	21-28 (n=36) 29-34 (n=9) 35-36 (n=5)
Tseng 2020 [33]	University of Florida	Median: 36 (range 20-54): HL: 36 (range 20-45) Aggressive NHL: 40 (range 30-54)
Wray 2016 [34]	Eclipse Workstation (Varian Medical Systems, Palo Alto, California)	Median PT dose: 21 (range 15-36)

3D-CRT – 3-dimensional conformal radiation therapy; 3D-PBT –3-dimensional proton beam therapy; CGE – cobalt gray equivalent; CT – computed tomography; HL – Hodgkin lymphoma; IMRT – intensity modulated radiation therapy; NHL – non-Hodgkin lymphoma; PET – Positron Emission Tomography; RBE – relative biological effectiveness

Clinical Outcomes. Reported endpoints included in total: overall survival, progression-free survival, recurrence-free survival, event-free survival rate, local progression free survival, distant progression free survival, and response to treatment (revised response criteria for lymphoma). The main findings of the studies are summarized in Table 2. Safety was additionally assessed by toxicity (Appendix 2).

Table 2. Clinical outcomes for patients with mediastinal lymphoma

Study	OS	PFS	RFS
Bates 2021 [24]	2-year: 98%	2-year: 94% Proton therapy: 94% vs photon therapy: 86% (p=0.7)	N/A
Dionisi 2022 [25]	100%	N/A	93%
Hoppe 2014 [26]	N/A	3-year: 87% (95% CI: 59-97)*	3-year: 93% (95% CI: 65-99)
Hoppe 2017 [27]	N/A	N/A	3-year: 92% For adults: 96% For children: 87%
König 2019 [28]	N/A	Local: 2-year: 95.5% Distant: 95.0%	N/A
Li 2011 [29]	N/A	N/A	N/A
Loap 2021 [30]	N/A	3-year: 87%*	3-year: 93%
Nanda 2017 [31]	N/A	N/A	-
Tringale 2021 [32]	5-year: 100%	N/A	5-year: 90%
Tseng 2020 [33]	2-year: 91% HL: 96% vs NHL: 81% (p=0,001)	2-year: 73% HL: 84% vs NHL: 52% (p=0,0015)	N/A
Wray 2016 [34]	2-year: 94% 3-year: 94%	2-year: 86% 3-year: 86%	N/A

OS – overall survival; N/A – not applicable; PFS – progression-free survival; RFS – recurrence free survival
*event-free survival

Among the included studies, 5 reported the overall survival (OS), with the overall survival for 2 years varying from 91% – 98% [24, 33, 34]. Tringale et al. 2021 [32] noted that the 5-year OS rate for patients with HL was 100%. The 2-year OS rate of HL was significantly higher than NHL (96% vs 81%, p=0.001 [33]). Wray et al. 2016 [34] noted for both 2- and 3-year OS rate at 94%. The 2-year total progression free survival (PFS) ranged from 73% – 94%, reported by 3 studies [24, 33, 34]. Tseng et al. 2020 [33] observed that the 2-year PFS was higher for HL patients (84% vs 52%), and Bates et al. 2021 [24] also observed higher PFS rate for proton therapy, compared to photon therapy (94% vs 86%; p=0.7). Another study [28] on 2-year local progression free survival and distant progression free survival, reported them to be 95.5% and 95%, respectively. The 3-year recurrence free survival (RFS) were similar in 3 studies (92% – 93%) [26, 27, 30]. Hoppe et al. (2017) noted a better RFS rate for an adult population than in paediatric patients (96% vs 87%). In one study [32] the 5-year RFS rate was 90% and 5 patients had biopsy-proven recurrences, which occurred at a median of 9.2 months after completion of proton treatment (range: 2.5–24.9 months). The 3-year event-free survival rate was the same (87%) in 2 included studies [26, 30]. Six of 11 studies showed the response to treatment (Tab. 3). Complete response was assessed in 4 studies, and ranged from 78% – 86% [25, 26, 27, 29]. Li et al. (2011) [29] focused on complete metabolic response of all 7 patients in the study with refractory disease, indicated by positive findings on PET scans before proton beam therapy. Six of them (86%), with the exception of a patient with disseminated T-cell lymphoblastic lymphoma,

50

Annals of Agricultural and Environmental Medicine 2024, Vol 31, No 1

Malwina Kowalska, Ewelina Sitarz-Kilian, Klaudia Jaros, Magdalena Koperny , Paweł Moćko, Jacek Siwiec, Paweł Kawalec. Evidence for external beam radiotherapy…

Table 3. Treatment response for patients with mediastinal lymphoma

Study	Complete response[1]	Partial response[1]	Other response
Dionisi 2022 [25]	11 (78%)	3 (22%)	N/A
Hoppe 2014 [26]	17 (85%)	3 (15%)	N/A
Hoppe 2017 [27]	115 (83.3%)	15 (10.9%)	Not clearly defined: 8 (5.8%)
König 2019 [28]	N/A	N/A	Outfield relapse after 2 months followed by infield relapse 6 months after proton beam irradiation (n=1)
Li 2011 [29]	6 (86%)[2]		N/A

[1] revised response criteria for lymphoma; [2] complete metabolic response; N/A not applicable

showed a complete metabolic response. Loap et al. 2021 [30] showed that none of the patients in their study relapsed. In another study [27], in-field (4.3%), in-field and out-of-field (0.7%), and out-of-field recurrences immediately adjacent nodal regions (2.1%). König et al. (2019) [28] observed that one patient suffered from an outfield relapse after 2 months, followed by an infield relapse 6 months after PT.

Toxicity. Toxicity was assessed mostly by Common Terminology Criteria for Adverse Events (CTCAE) (versions 3.0–5.0) (Appendix 2). Among the included studies, 9 reported acute toxicity [25, 26–33]. Late toxicity was noted in 2 studies [26, 31]. Toxicities were not specified (acute or late) in only one study [33]. The most commonnly reported grade 1 and grade 2 adverse events were skin reaction/dermatitis, esophagitis and fatigue. Grade 3 toxicity was reported in 2 studies: one patient developed subacute toxicities potentially related to radiation treatment pneumonitis and pleural effusions 7 months post-RT [32], and 2 patients suffered from bleomycin-induced pneumonitis [28].

Methodologic quality assessment. The risk of bias in the studies was assessed by the Checklist for Case Series Joanna Briggs which showed that the quality of studies varied from low to high. The results of the quality assessment are shown in Appendix 3.

Clinical trials. As the result of a search for clinical trials in proton therapy in Hodgkin and non-Hodgkin lymphoma (at ClinicalTrials.gov), 4 studies (as of 20 May 2022) were found, but all of them were completed, suspended or terminated.

DISCUSSION

Since 2011, numerous grade I-IV mediastinal Hodgkin and non-Hodgkin lymphoma case series have been published, adding evidence toward the effectiveness of proton beam radiation therapy in their treatment. No RCTs or other studies with a comparative group were found.

The data from this systematic reviews shows that patients with HL and NHL can achieve survival benefit with no or low-grade late toxicity after proton therapy. Some studies have shown that proton therapy provided similar clinical outcomes when compared with photon therapy [24, 27, 34]. The crucial expected benefit from proton therapy is to reduce late toxicities. Although there were no acute or late grade 4 or higher toxicities, the median length of follow-up in included studies did not exceed 3 years. Thus, the possible effects and

potential risk of development of second cancers or cardiac toxicity 10–30 years after definitive treatment, are not known.

During the scoping review, many systematic reviews were found reporting the effectiveness and safety of proton therapy in several indications, such as meningioma of the brain and spinal cord [35, 36], skull base chordoma [37], nasopharyngeal cancer [38], intracranial benign tumours [39], and gliomas [40]. However, presented systematic review is the first summary of available evidence about patients with HL or NHL.

The study has several limitations that should be considered when interpreting the findings. The number of included studies was small. Each study was case series and most of them were retrospective. The quality of included studies was judged to have low [26, 27], moderate [24, 28, 32, 33] and high [25, 29, 30, 31, 34] risk of bias. Only one study [26] clearly reported the demographics of the participants, but no study indicated the sites/clinics demographic information. In some cases, the criteria for inclusion and information about the use of valid methods for identification of the condition for all participants, were unclear.

Although it is indicated that randomized controlled trials are the gold-standard for studying causal relationships, despite being expensive and time consuming as randomization eliminates much of the bias inherent with other study designs [41], the current systematic search did not reveal any RCTs. In a recently published review, Loap et al. 2021 [5] described the challenges and pitfalls regarding RCTs for Hodgkin lymphoma proton therapy. First, they discussed epidemiological considerations, since mediastinal HL is a rare malignancy, the development of an RCT for HL proton therapy is challenging (compared to the current RCT recruiting for breast cancer PT). An estimated example in the United Kingdom, where only 600 – 700 HL patients per year (from 1,700 new cases in the UK per year, compared to 50,000 breast cancers) would have a localization amenable to proton therapy in a consolidative setting, confirms that the recruitment process for RCTs would be demanding. A similar conclusion was made by Mailhot Vega et al. (2022) [42], that such a trial would be costly and require substantial time and patient numbers to detect a difference between the two. It is therefore that such a trial will probably not be conducted in the USA.

In considering data from ClinicalTrials.gov, there is not much research being carried out in this area; in fact, only one study is currently underway, which has been suspended, two studies terminated, and only one completed. Secondly, statistical hypotheses would be difficult to define *a priori* because treatment may be delivered through outdated techniques (as 2D), or the technique is still new and limits the toxicity of follow-up (as for VMAT or IMRT).

Finally, the ethical aspects of RCTs for PT must be considered. On the one hand there are uncertainties regarding the efficacy of proton therapy, and the importance of a measurable benefit to justify the financial cost of the technique [43]. On the other hand, there is the consideration that since proton therapy is associated with sparing another organ at risk, it would be expected that patients in almost all situations could benefit from the therapy [41], as in the multiple tumour-site proton therapy RCT by Baumann et al. (2020) [44]. In that case, proton chemoradiotherapy was associated with significantly reduced acute adverse events in patients with head and neck, oesophageal, pulmonary, rectal,

Annals of Agricultural and Environmental Medicine 2024, Vol 31, No 1   51

Malwina Kowalska, Ewelina Sitarz-Kilian, Klaudia Jaros, Magdalena Koperny , Paweł Moćko, Jacek Siwiec, Paweł Kawalec. Evidence for external beam radiotherapy…

cerebral, gastric or pancreatic cancer. Besides, Tian et al. 2017 indicate that the use of proton therapy for consolidation following chemotherapy, may be suitable in cases of Hodgkin lymphoma and non-Hodgkin lymphoma [45], especially as proton therapy becomes cheaper and more accessible [46]. However, the availability of proton therapy also remains debatable because of reimbursement restrictions, access to proton therapy centres and patient prioritization (due to the limited number of treatment rooms, as well as other indications with a higher level of the evidence may have been prioritized over HL) [47]. Accordingly, it is considered that international cooperation would be helpful with ensuring that HL patients receive proton therapy when needed. There is also an equally good concept proposed by Loap et al. 2021 [5], that of developing national or international registries of Hodgkin lymphoma patients treated with proton and photon therapies to receive outcomes and toxicities at a longer follow-up. It is assumed that this would also be an acceptable solution for non-Hodgkin lymphoma since it is an equally rare malignancy, and developing an RCT for non-Hodgkin lymphoma proton therapy would be also challenging.

SUMMARY

The current limited data from case series suggest that proton beam therapy is a rapidly developing technique that may to be an effective treatment against mediastinal Hodgkin and non-Hodgkin lymphoma. However, due to the varied quality of the included studies, the effectiveness and safety of proton therapy is uncertain. In addition, more studies should be conducted to quantify the efficacy of proton therapy compared to conventional therapies, and to provide meaningful comparisons of survival rates, long-term outcomes and safety for the patients. At the same time, it is indicated that the implementation of randomized controlled trials is not a simple matter, and other solutions are proposed to obtain long-term results for external beam radiotherapy in mediastinal Hodgkin and non-Hodgkin lymphoma.

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Malwina Kowalska, Ewelina Sitarz-Kilian, Klaudia Jaros, Magdalena Koperny , Paweł Moćko, Jacek Siwiec, Paweł Kawalec. Evidence for external beam radiotherapy…

Appendix 1. Characteristics of the included studies

Reference	Study design	Participants (number)	Age mean/ median (range) [years]	Indication	Histologic subtype	Stage/ Staging	Intervention	Other treatment (type, n)	Follow-up median (range)
Bates 2021 [24]	Retrospective, case series	91	Median: not reported <18 (n=24) 18–30 (n=34) >30 (n=33)	Hodgkin lymphoma: Mediastinal/ hilar (n=74)	Not reported	I (n=12) II (n=79)	Proton therapy (n=48) Photon therapy (n=43)	Chemotherapy (n=not reported)	Proton therapy: 3.7 years Photon therapy: 1.9 years
Dionisi 2022 [25]	Retrospective, case series	14	Median: 29 (15–49)	Mediastinal lymphoma: Hodgkin lymphoma (n=9) Non-Hodgkin lymphoma (n=5)	Not reported	II (n=12) III (n=1) IV (n=1)	Proton therapy	Immunochemotherapy (n=14) regimen: ABVDx2 + BEACOPPx2 (n=1) ABVDx4 (n=2) ABVDx5–6 (n=3) BVDx4 (n=1) R-CHOPx6 (n=3) R-EPOCHx6 (n=1) Other schedules (nivolumab, euronet schedule, OEPA/ CODPACx6) (n=3)	15 months (1–33 months)
Hoppe 2014 [26]	Prospective case series	20	Median: 23 (7–57)	Hodgkin lymphoma with mediastinal involvement	Not reported	IAX (n=1) IBX (n=1) IIA (n=2) IIAX (n=3) IIAEX (n=1) IIBX (n=6) IIIAX (n=1) IVBX (n=0)	Consolidative Involved-Node Proton Therapy	Chemotherapy (n=15) regimen: ABVE-PCx4 (n=4) VAMPx4 (n=1) ABVDx3 (n=1) ABVDx4 (n=2) ABVDx5 (n=1) ABVDx6 (n=6)	37 months (26–55)
Hoppe 2017 [27]	Retrospective, case series	138	Median: 20 (6–57)	Hodgkin lymphoma: Mediastinal (n=132) Other (n=6)	Not reported	I (n=7) II (n=93) III (n=21) IV (n=17)	Consolidative proton therapy	Chemotherapy (n=138) regimen: ABVDx2–3 (n=9) ABVDx4 (n=34) ABVDx5–6 (n=32) ABVE-PCx3–4 (n=39) ABVE-PCx5 (n=7) ABVE-PCx4 + (DECA or IV) (n=6) Other (n=11)	32 months (5–92 months)
König 2019 [28]	Retrospective, case series	20	Median: 31 (18–54)	Mediastinal lymphoma: Hodgkin lymphoma (n=9) Non-Hodgkin lymphoma (n=11)	HL: Nodular sclerosis (n=8) Mixed cellularity (n=1) NHL: DLBCL (n=10) Gray zone (n=1)	HL: I (n=2) II (n=6) IV (n=1) NHL: II (n=7) IV (n=4)	Consolidative proton therapy	Induction Chemotherapy (n=20) HL: ABVD +/− escalated BEACOPP or escalated BEACOPP (n=9) NHL: R-CHOP +/− MTX (n=11)	32 months (21–48 months)
Li 2011 [29]	Retrospective, case series	10	Median: 33 (26–45)	Mediastinal lymphoma: Hodgkin lymphoma (n=8) Non-Hodgkin lymphoma (n=2)	NH: Nodular sclerosing lymphoma (n=8) NHL: DLBCL (n=1) T-cell lymphoblastic lymphoma (n=1)	HL: II (n=8) NHL: II (n=1) Dis-seminated (n=1)	3D-PBT	Chemotherapy: (n=10) Radiotherapy: (n=2) Autologous SCT: (n=3) Chemotherapy regimen: HL: ABVD (n=4) ABVD, ICE, stem cell transplant (n=1) ABVD, IVE, mini BEAM, ESHAP, BEAM/ stem cell transplant, gemcitabine + oxaliplatin, SGN-35 (n=1) AVD, R-ESHAP, IGEV, stem cell transplant, HDAC inhibitor / azacitidine, stem cell transplant (n=1) ABVD, ESHAP, IGEV (n=1) NHL: R-CHOP (n=1) Hyper-CVAD (n=1)	Not reported

Malwina Kowalska, Ewelina Sitarz-Kilian, Klaudia Jaros, Magdalena Koperny , Paweł Moćko, Jacek Siwiec, Paweł Kawalec. Evidence for external beam radiotherapy…

Appendix 1. Characteristics of the included studies (continuation)

Reference	Study design	Participants (number)	Age mean/ median (range) [years]	Indication	Histologic subtype	Stage/ Staging	Intervention	Other treatment (type, n)	Follow-up median (range)
Loap 2021 [30]	Case series	20	Median: 28 (10–40)	Mediastinal Hodgkin lymphoma	Nodular sclerosing (n=20)	Not reported	Proton therapy (n=4) Other (n=16)	Not reported	2 years (1.1–3.1)
Nanda 2017 [31]	Case series	59	Not reported	Mediastinal lymphoma: Hodgkin lymphoma (n=50) Non-Hodgkin lymphoma (n=9)	Not reported	Not reported	Proton therapy	Chemotherapy (n=59) SCT (n=7) Chemotherapy regimen: ABVD (n=29) ABVE-PC (n=24) R-CHOP (n=4) Other (n=2) Second or third line (n=11)	24.1 months (6–82 months)
Tringale 2021 [32]	Retrospective, case series	50	Mean: 17 (11–21)	Hodgkin lymphoma	Nodular sclerosing (n=49) Lymphocyte-predominant (n=1)	II (n=23) III (n=13) IV (n=13) Relapsed (n=1)	Proton therapy	Chemotherapy (n=50) Photon therapy (n=1) Chemotherapy regimen: ABVD (n=15) ABVE-PC (n=34) BEACOPP (n=9) Other (n=7)	5.3 years (2–8.4 years)
Tseng 2020 [33]	Retrospective, case series	85	Median: 28 (8-73)	Mediastinal relapsed/ refractory lymphoma: Hodgkin lymphoma (n=56) Non-Hodgkin lymphoma (n=29)	HL: Nodular sclerosing (n=50) Mixed cellularity (n=1) Unknown or unclassifiable (n=5) NHL: DLBCL (n=10) PMBCL (n=13) Grey zone lymphoma (n=2) High-grade NHL (n=1) T-cell lymphoblastic lymphoma (n=1) T-cell peripheral lymphoma (n=1) Unclassifiable NHL (n=1)	HL: I (n=3) II (n=40) III (n=5) IV (n=8) NHL: I (n=9) II (n=10) III (n=4) IV (n=6)	Proton therapy	Salvage systemic therapy (n=59) Transplant (ie, peritransplant radiation) (n=40) SCT (n=45) Chemotherapy Chemotherapy regimen: ABVD-based (n=41) ABVE-PC (n=10) R-CHOP or R-CHP (n=19) R-EPOCH (n=6) Other (n=8) Unknown (n=1)	ntire cohort: 25.6 months (0.9–113.4) Among living patients: 26.3 months (2.3–113.4)
Wray 2016 [34]	Retrospective, case series	22	Median: Not reported Range: 6–18	Hodgkin lymphoma	Not reported	II (n=6) III (n=8) IV (n=4) Relapsed (n=4)	Proton therapy	Chemotherapy (n=22) ASCT (n=4) Chemotherapy in *de novo* patients prior to PT: ABVE-PC (n=16) ABVE-PC + IE (n=1) VAMP (n=1)	36 months (10–79 months)

3D-PBT – three-dimensional proton beam therapy; ABVD – adriamycin, bleomycin, vinblastine, dacarbazine; ABVE-PC – adriamycin, bleomycin, vincristine sulfate, etoposide, prednisone, cyclophosphamide; ASCT – autologous stem cell transplant; AVD – adriamycin, vinblastine, dacarbazine; BEACOPP – bleomycin sulfate, etoposide phosphate, adriamycin, cyclophosphamide, oncovin, procarbazine hydrochloride, prednisone; BEAM – carmustine, etoposide, cytarabine, melphalan; DECA – dexamethasone, etoposide, cisplatin, cytarabine; DLBCL – diffuse large B-cell lymphoma; ESHAP – etoposide, solu-medrone, high-dose cytarabine, cisplatin; HDAC – histone deacetylase inhibitor; HL – Hodgkin lymphoma; Hyper-CVAD – cyclophosphamide, vincristine, doxorubicin, dexamethasone, methotrexate cytarabine; ICE – ifosfamide, carboplatin, etoposide; IE – ifosfamide, etoposide; IGEV – ifosfamide, gemcitabine, vinorelbine, prednisone; IVE – ifosfamide, etoposide, epirubicin; MTX – methotrexate; n – number of patients; NHL – Non-Hodgkin lymphoma; PMBCL – primary mediastinal B-cell lymphoma; PT – proton therapy; R-CHOP – rituximab, cychlophosphamide, hydroxydaunorubicin, oncovin, prednisone; R-EPOCH – rituximab, etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin; R-ESHAP – rituximab, etoposide, solu-medrone, high-dose cytarabine, cisplatin; SCT – stem cell transplant; SGN-35 – CD30 immunotoxin; VAMP – vincristine, adriamycin, methotrexate, prednisone.

Malwina Kowalska, Ewelina Sitarz-Kilian, Klaudia Jaros, Magdalena Koperny , Paweł Moćko, Jacek Siwiec, Paweł Kawalec. Evidence for external beam radiotherapy…

Appendix 2. Toxicity

Study	Toxicity	
	Acute	Late
Bates 2021 [24]	Not reported	Not reported
Dionisi 2022 [25]	Grade 1/Grade 2 (No. of patients): Skin reaction:10 (71%) Fatigue: 3 (21%) Esophagitis and/or dysphagia: 13 (92%) No grade 2+ toxicities (CTCAE version 5.0)	No late toxicities (CTCAE version 5.0)
Hoppe 2014 [26]	Grade 1/Grade 2 (No. of events) Anxiety/ depression (No. of events unclear) Performance status (2/0) Fatigue (4/0) Pulmonary toxicity (8/0) Esophagitis (10/3) Chest pain (3/0) Xerostomia (5/0) Skin toxicity (14/10) No acute grade 3 non-haematologic toxicities (CTCAE version 3.0)	Grade 1/Grade 2 (No. of events) Anxiety/ depression (5/0) Performance status (2/0) Fatigue (8/0) Pulmonary toxicity (13/0) Esophagitis (4/0) Chest pain (5/0) Xerostomia (3/0) Skin toxicity (11/0) No late grade 3 non-haematologic toxicities (CTCAE version 3.0)
Hoppe 2017 [27]	Grade 1/Grade 2 (cumulative result from: University of Florida, University of Pennsylvania and Proton Collaborative Group) Anorexia: 16/4 Anxiety/ depression/ agitation: 19/1 Constipation: 12/0 Cough: 53/2 Diarrhoea: 3/0 Dry Mouth: 18/1 Dyspepsia: 11/2 Dyspnoea: 30/0 Oesophagitis: 48/25 Fatigue: 68/7 Hoarseness: 16/0 Hypothyroidism:0/3 Mucositis: 2/0 Nausea: 29/4 Pain: 22/1 Performance status: 7/1 Pulmonary (fibrosis/ pneumonitis/ effusion): 6/0 Radiation dermatitis: 95/8 Vomiting: 8/2 No acute grade 3 toxicities (CTCAE version 4.0)	No late toxicities (CTCAE version 4.0)
König 2019 [28]	Grade 1 and Grade 2 radiation-induced (No. of patients) Dermatitis: 12 (60%) Oesophagitis: 11 (55%) Pneumonitis: 12 (60%) Grade 3 bleomycin-induced (No. of patients): Pneumonitis: 2 (9%) No grade 3+ radiation-induced toxicities (CTCAE version 4.03)	Not reported
Li 2011 [29]	Grade 1 (No. of patients): Radiation dermatitis: 10 (100%) Hoarseness: 1 (10%) Grade 2 No. of patients): Dysphagia/ odynophagia: 2 (20%)	Not reported
Loap 2021 [30]	Grade 1 (No. of patients): Radiodermitis: 3 (15%) Acute dysphagia: 1 (5%) Grade 2 (No. of patients): Acute dysphagia: 1 (5%) No grade 3+ acute toxicities	No late adverse events (pulmonary, cardiac, digestive)
Nanda 2017 [31]	Grade 1 (No. of patients): Cough: 21 (36%) Dyspnoea: 12 (20%) Thoracic pain: 15 (25%) Grade 2 (No. of patients): Cough: 3 (5%) Dyspnoea: 2 (3%) Pneumonitis: 1 (2%) No grade 3+ toxicities (CTCAE version 4.0)	Grade 1 (No. of patients): Cough: 22 (37%) Dyspnoea: 19 (32%) No grade 2+ toxicities (CTCAE version 4.0)
Tringale 2021 [32]	Grade 1 (No. of patients): 37 (74%) Grade 2 (No. of patients): 2 (4%) Grade 1-2 (No. of events): Dermatitis: 24 (48%) Esophagitis: 16 (32%) Fatigue: 5 (10%) Dysphagia: 3 (6%) Odynophagia: 2 (4%) Nausea: 1 (2%) Laryngitis: 1 (2%) Dyspnoea: 1 (2%) Subacute toxicities potentially related to radiation treatment (number of patients): Grade 1: substernal chest pain with panic attacks: 1 (2%) Grade 2: pneumonitis 2 months post-PT: 1 (2%) Grade 2: left-ventricular strain: 1 (2%) Grade 3: pneumonitis and pleural effusions 7 months post-RT: 1 (2%) No PT-related grade 3+toxicities (CTCAE version 5.0)	No late toxicities (CTCAE version 5.0)
Tseng 2020 [33]	Toxicities not specified (acute or late) Grade 1 (No. of patients): Pneumonitis: 11 (13%) (HL: 7 (8%); NHL: 4 (5%)) Grade 2 (NO. of patients): Pneumonitis: 11 (13%) (HL: 5 (6%); NHL: 6 (7%)) No grade 3+ pneumonitis (CTCAE version 4.0)	
Wray 2016 [34]	Acute toxicities Grade 2 (No. of patients): Oesophagitis: 2 (9%) Nausea and vomiting: 2 (9%) Temporary toxicities (number of patients): Grade 2: Fatigue for 1 week: 1 (4.5%) Chronic toxicities (No. of patients): Grade 2: Hypothyroidism: 1 (4.5%) No PT-related grade 3+ acute toxicities No cardiac complications or secondary malignancies attributed to radiation (CTCAE version 4.0)	No grade 3+ late toxicities (CTCAE version 4.0)

Abbreviations: CTCAE – Common Terminology Criteria for Adverse Events; HL – Hodgkin lymphoma; n – number; N/A – not applicable; NHL – Non-Hodgkin lymphoma; PT – proton therapy.

Malwina Kowalska, Ewelina Sitarz-Kilian, Klaudia Jaros, Magdalena Koperny , Paweł Moćko, Jacek Siwiec, Paweł Kawalec. Evidence for external beam radiotherapy…

Appendix 3. Risk of bias

Question	Bates 2021	Dionisi 2022	Hoppe 2014	Hoppe 2017	König 2019	Li 2011	Loap 2021	Nanda 2017	Tringale 2021	Tseng 2020	Wray 2016
Were there clear criteria for inclusion in the case series?	Yes	Unclear	Yes	Yes	Yes	Unclear	Yes	Yes	No	Yes	Unclear
Was the condition measured in a standard, reliable way for all participants included in the case series?	Yes	No	Yes	Yes	Yes	Yes	No	Unclear	No	Yes	Unclear
Were valid methods used for identification of the condition for all participants included in the case series?	Yes	No	Yes	Yes	Yes	Unclear	Unclear	Unclear	Unclear	No	Yes
Did the case series have consecutive inclusion of participants?	Yes	Yes	Unclear	Yes	Unclear	Yes	Unclear	Yes	Yes	Yes	Yes
Did the case series have complete inclusion of participants?	No	Yes	Yes	No	No	Unclear	No	No	Yes	No	No
Was there clear reporting of the demographics of the participants in the study?	No	No	Yes	No	No	No	No	No	Yes	No	No
Was there clear reporting of clinical information of the participants?	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Were the outcomes or follow up results of cases clearly reported?	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes
Was there clear reporting of the presenting site(s) / clinic(s) demographic information?	No	No	No	No	No	No	No	No	No	No	No
Was statistical analysis appropriate?	Unclear	Unclear	N/A	Yes	Yes	Unclear	N/A	N/A	Unclear	Yes	Yes
% Yes	50%	40%	77.78%	70%	60%	30%	33.33%	44.44%	50%	60%	40%
Risk	Moderate	High	Low	Low	Moderate	High	High	High	Moderate	Moderate	High

Answers: Yes; No; Unclear; N/A – Not applicable.