

# Residual Site Radiotherapy After Immunochemotherapy in Primary Mediastinal B-Cell Lymphoma: A Monoinstitutional Retrospective Study

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**1407Abstract.** *Aim: To evaluate the efficacy of residual site radiation therapy (RSRT) on local control (LC), progression-free (PFS) and overall (OS) survival in patients with primary mediastinal lymphoma (PMBCL), following rituximab and chemotherapy treatment (ICHT). Patients and Methods: The study included 34 patients with PMBCL treated between 2006 and 2014 with ICHT with/without autologous stem cell transplantation and RSRT. Between the end of ICHT/stem cell transplantation and RSRT, patients were evaluated with <sup>18</sup>F-fluorodeoxyglucose positron-emission tomography. The gross tumor volume included morphological mediastinal residual disease after ICHT/SCT. The percentage of LC, PFS and OS were assessed. Results: All patients received RSRT with a median dose of 30 Gy. Median follow-up was 82 months. One patient out of 34 (3%) showed progressive disease 9 months from diagnosis. The 10-year PFS and OS were 97% and 97% respectively. Conclusion: RSRT in*

*patients with PMBCL treated with ICHT did not impact unfavorably on LC and patient survival.*

Primary mediastinal B-cell lymphoma (PMBCL) is a distinct clinicopathological entity that accounts for 2-4% of non-Hodgkin's lymphomas. It is characterized by a locally aggressive presentation with a large mediastinal mass, more frequently in young women between the third and the fourth decade (1, 2). The presence of bulky mediastinal disease >10 cm is not uncommon, with extension into the contiguous chest wall, lung and pericardium. A combined approach with doxorubicin-based chemotherapy and adjuvant mediastinal radiotherapy (RT) has been evaluated in retrospective series, most of them performed in the pre-rituximab era, showing a 5-10 years progression-free survival (PFS) of 57-81% (2-5). More recently, the addition of rituximab to the doxorubicin-based chemotherapy schedules (ICHT) and adjuvant RT demonstrated survival improvement, with 3- to 5-year PFS of 80% and overall survival (OS) 83%-88% (1, 2, 6, 7). Although there is a lack of randomized studies, ICHT and adjuvant RT are considered part of the standard of care in the treatment of PMBCL in Italy (2). However, a high cure rate with a 5-year PFS of 93% has been also reported following treatment based on the R-DA-EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin and rituximab) schedule, without adjuvant RT, but these results, similarly, lack validation by randomized multicentric studies

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(8, 9). The major concern about the use of adjuvant RT, especially in the setting of young patients, is due to worries about the potential incremental occurrence of late treatment-related toxicities, such as coronary heart disease, valvular heart disorders, and risk of secondary cancer (10, 11). Total RT dose and the target radiation volume are the two most relevant risk factors that may contribute to late toxicities. The high variability of target volume contours still represents a significant issue for RT planning in PMBCL (12). However, among different approaches, moving from involved-field radiation therapy (IFRT) to involved-site radiation therapy (ISRT) as target volume represents that most frequently used in PMBCL for RT, since it comprises the original mediastinal tumor volume and all the other nodal localizations at the outset, taking into account the healthy surrounding structures after tumor shrinkage (2, 13).

We retrospectively evaluated a consecutive series of patients with PMBCL in which only the residual disease of the bulky mediastinal mass (residual site radiation therapy, RSRT) after ICHT was considered as the target radiation volume, in order to verify whether this de-escalated consolidative RT approach has a non-detrimental impact on local control (LC) and survival outcomes.

**Patients and Methods**

Between June 2006 and October 2014, 34 consecutive previously untreated patients with PMBCL were diagnosed according to the WHO criteria (14). All patients were treated with ICHT. Nine patients underwent high-dose chemotherapy and stem cell transplantation (SCT) according to the Deauville scoring system (DS) score  $Sup > 3$  based on clinical judgment (15). All patients underwent positron-emission tomography/computed tomography (PET/CT) with  $^{18}F$ -fluorodeoxyglucose (FDG) as treatment response assessment/restaging according to the Deauville scoring system, after 5 weeks from the end of ICHT (15). At the beginning of the study, metabolic complete response was defined as DS 1-2, and was modified according to the latest Lugano response assessment criteria thereafter as DS 1-3, DS 4 or 5 being considered only as inadequate response (15-17). Patients who did not achieve metabolic complete response after ICHT (DS 3-5) underwent early intensification with SCT. All patients underwent repeat PET/CT assessment after 30-40 days from the SCT.

All the PET scans were centrally reviewed by two expert Nuclear Medicine Specialists (DP and PP).

RSRT was planned within 30-40 days after the completion of ICHT or SCT. The patients were immobilized with wing board with the arms up and CT without contrast was acquired with slices of 25 mm. The residual mediastinal mass after chemotherapy was morphologically identified by CT PET and/or CT with *i.v.* contrast and, after rigid merging procedures, was contoured as gross tumor volume (GTV) by two expert Radiotherapist Oncologists (VDS and MFO). The planning target volume (PTV) was created by the 5 mm isotropic expansion of the GTV, taking into account the healthy surrounding structures. The median total RT dose was 30 Gy (range=28-40 Gy) delivered with conventional fractionation (daily fractions: 2.0 Gy) 5 days per week by 6-MV linear accelerator.

Table I. *Characteristics at diagnosis of all 34 patients.*

Characteristic		Value
Age, years	Median (range)	34 (16-67)
Gender, n (%)	Male	10 (29)
	Female	24 (71)
Stage, n (%)	I-II	22 (64.5)
	III	2 (6)
	IV	10 (29.5)
	Bulky mass, n (%)	No
	Yes	34 (100)
Superior vena cava syndrome, n (%)	No	3 (9)
	Yes	31 (91)
Chemotherapy, n (%)	R-MACOP-B	23 (67.5)
	R-CHOP14	6 (17.5)
	R-CHOP21	5 (15)

R-MACOP-B: Rituximab, methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisone and bleomycin R-CHOP; rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone. According to WHO criteria (14).

Three-dimensional conformal radiotherapy (3D-CRT) treatment was employed in 31 patients. Intensity-modulated radiation therapy (IMRT) planning was chosen for three patients. No deep inspiration breath hold procedure was used.

FDG-PET was planned for patients at 3 months after the completion of mediastinal RT. All patients were evaluated every 3 months for the first 2 years and every 6 months afterwards for a period of at least 5 years with clinical and radiological procedures as required. Subsequently, all patients started annual follow-up and the patients who did not attend a periodic clinical check up in the previous 2 years were contacted by phone.

The Kaplan-Meier estimator was used to calculate survival curve estimates. OS was calculated from the date of diagnosis to the date of death from any cause or to date of the last follow-up. PFS was calculated from the date of diagnosis to the time of progression or relapse or to date of the last follow-up.

**Results**

The median age at diagnosis was 36 years (range=16-67 years). Twenty-four patients were females and 10 were males. All but three showed symptoms at disease onset, above all superior vena cava syndrome, night sweats, chest pain and dyspnea. The main clinical characteristics are summarized in Table I. Twenty-two patients had supradiaphragmatic disease, in particular eight and thirteen were stage I and II, respectively. More advanced disease was diagnosed in 12 patients, with stage III and IV in two and 10 (visceral localizations: kidney, pancreas, lungs, liver, gastric, adrenal glands), respectively. All patients had bulky mediastinal disease, with median longitudinal and transverse lengths of 10 cm (range of 5-18 cm and 3-14 cm, respectively). All patients were treated with standard ICHT: 23 with R-MACOP-B (rituximab, methotrexate, doxorubicin, cyclophosphamide,

Table II. *Deauville score (15) according to treatment and radiation dose/technique.*

Case	DS post ICHT	Therapy post ICHT	DS post SCT and pre RSRT	RT dose (2 Gy/fr)	RT technique	DS 3 months after RSRT
1	3	ISRT		30	3D	3
2	4	SCT	4	36	3D	3
3	2	ISRT		30	3D	2
4	2	ISRT		30	3D	2
5	2	ISRT		30	3D	2
6	3	ISRT		30	3D	3
7	2	ISRT		30	3D	2
8	3	ISRT		30	3D	3
9	3	ISRT		30	3D	3
10	2	ISRT		30	3D	2
11	2	ISRT		30	3D	2
12	4	SCT	4	40	IMRT	4
13	3	ISRT		40	IMRT	3
14	3	ISRT		30	3D	3
15	2	ISRT		30	3D	2
16	3	ISRT		30	3D	3
17	3	ISRT		30	3D	3
18	3	ISRT		30	3D	3
19	5	SCT	3	30	3D	NA
20	4	SCT	4	30	3D	3
21	2	ISRT		30	3D	2
22	3	SCT	3	30	3D	3
23	3	ISRT		30	3D	3
24	3	ISRT		40	3D	3
25	3	ISRT		30	3D	3
26	4	ISRT		30	3D	4
27	3	ISRT		40	3D	3
28	3	SCT	3	30	3D	3
29	3	SCT	3	30	3D	3
30	4	ISRT		30	3D	4
31	5	SCT	5	28	3D	NA
32	3	ISRT		30	3D	3
33	4	SCT	4	40	IMRT	4
34	3	ISRT		30	3D	3

DS: Deauville score; ICHT: rituximab and chemotherapy treatment; SCT: autologous stem cell transplantation; ISRT: involved-site radiation therapy; RSRT: residual site radiation therapy; RT: radiotherapy; IMRT: intensity-modulated radiation therapy; NA: not assessed.

vincristine, prednisone and bleomycin); six with R-CHOP14 (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone); and five with R-CHOP21.

Nine patients were considered non-responders or partially responders to ICHT, switching therefore to SCT. The metabolic response after ICHT for these patients was: DS 5, DS 4 and DS 3 in two, four and three patients, respectively (Table II). The metabolic response after SCT was DS 5, DS 4 and DS 3 in one, four and four patients, respectively. These nine patients underwent RSRT after a median of 61 days (range=51-113 days) from SCT, with a median total radiation dose of 30 Gy (range=28-40). In particular, one received 28 Gy (prematurely stopped the planned 40 Gy), five 30 Gy, one 36 Gy and two 40 Gy. The DS score assessed at 3 months from the end of RT was assessed in 7/9 patients.

Among these, the score evaluation was of DS 4 and DS 3 for two and five patients, respectively. Two patients did not undergo the PET assessment after RT because one patient showed progressive disease and the other underwent only CT evaluation.

In the other 25 patients, the metabolic response after ICHT was: DS 4, DS 3 and DS 2 in two, 15 and eight patients, respectively. All these patients underwent RSRT after a median of 63 days (range=27-148 days) and median radiation dose of 30 Gy (range=30-40 Gy). Twenty-three patients received 30 Gy and two patients 40 Gy (Table II).

At the time of RT, all 34 patients exhibited residual mediastinal disease with a median longitudinal length of 8.33 cm (range=4.04-13.42 cm) and transverse length of 5.55 cm (range=3.61-7.88 cm).

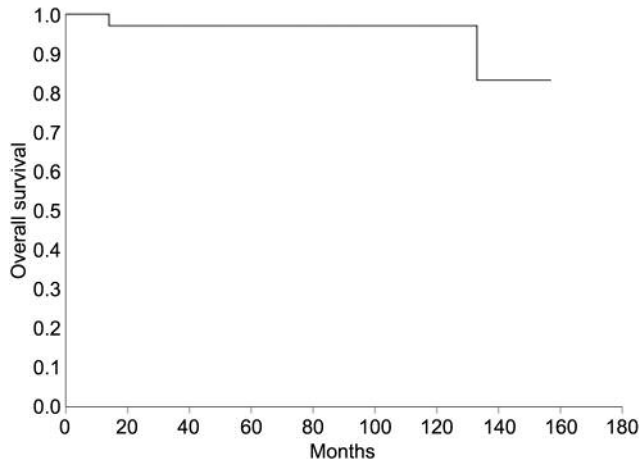


Figure 1. Overall survival of 34 patients with primary mediastinal B-cell lymphoma.

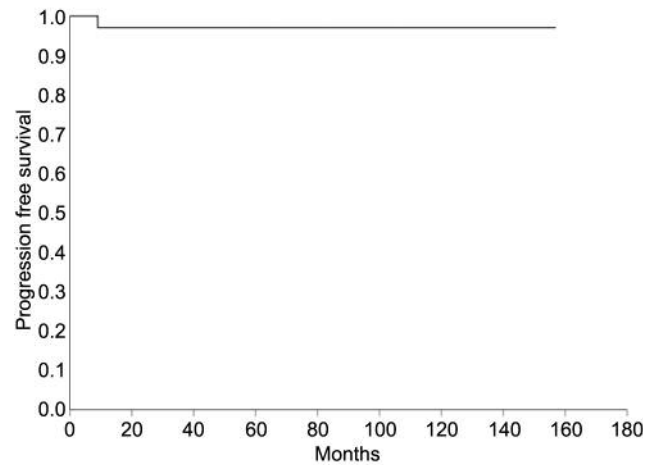


Figure 2. Progression-free survival of 34 patients with primary mediastinal B-cell lymphoma.

The median CTV was 84.52 cm<sup>3</sup> (range=25.41-208.38 cm<sup>3</sup>) and median cc of the PTV were 236.24 cm<sup>3</sup> (range=86.46-757.49 cm<sup>3</sup>).

Thirty-one patients were treated with conventional 3D-CRT and three patients with IMRT technique. During RT, portal vision was planned every 2 days in 31 patients treated with 3D-CRT, while daily on-board imaging with cone-CT was planned for three treated with IMRT technique. No deep inspiration breath-hold technique was adopted in our series of patients.

After a median follow-up of 82 months (range=14-157 months), only one patient died due to lymphoma progression during RT, with infield and outfield progression. The patient had a DS of 5 after ICHT, then underwent SCT without any benefit on the DS score. The patient underwent RT, which was discontinued at a total dose of 28 Gy, because of infield and outfield progression, therefore dying shortly thereafter from their disease. No local relapse (in-field or marginal field) or systemic recurrence occurred in any of the remaining 33 patients with PMBCL, but one died from ischemic cardiac disease after 123 months from the end of RT (this patient was treated with eight cycles of R-CHOP21 and RSRT of 30 Gy).

The 10-year OS and PFS rates were 97.1% and 97.1%, respectively (Figures 1 and 2).

## Discussion

The aim of our study was to retrospectively evaluate whether the concept of RSRT can be safely applied to patients with PMBCL. As shown by Piva *et al.*, significant interobserver variability exists in the delineation of target volumes in PMBCL (12). Nonetheless, the target radiation volume most frequently applied in PMBCL in ISRT, namely a target volume comprising

the mediastinal disease and all the nodal sites affected by lymphoma at onset. In the past decade, the reduction of the target radiation volume known as involved nodal RT or ISRT, has been explored mostly in patients with early-stage Hodgkin's and nodal non-Hodgkin's lymphoma, with satisfactory results in term of dose distribution to organs at risk in the absence of detrimental effects on LC and patient survival (13, 18, 19). Further reduction of the target radiation volume is recently explored by Pinnix *et al.* (20) in early-stage Hodgkin's lymphoma, and aimed to reduce the RT dose to organs at risk by omitting the cardio-phrenic lymph nodes (even when these nodes were involved at diagnosis) from the radiation volume or lower the dose on the latter. In fact, they reported only one relapse in 20 patients treated by sparing the cardio-phrenic region, which resulted in a significant reduction of the radiation dose to the total heart, left ventricle, coronary arteries and left breast. For several decades, IFRT was employed after full-course chemotherapy in advanced stage Hodgkin's lymphoma (21). Recently, a reduction of the target radiation volume was explored in this setting of patients enrolled in the HD15 trial (22). After 6-8 cycles of BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisolone) based chemotherapy, patients with advanced-stage Hodgkin's lymphoma with residual disease >2.5 cm and PET-positive results were irradiated with 30 Gy only to the site of residual disease. A relapse analysis within the patients enrolled in the HD15 showed 16% of relapse among the treated patients (20/123) when adequate radiation volume and contouring was applied, while this percentage increased to 24% (7/29) when the definition of the radiation volume was incorrect. The authors concluded that irradiation of residual disease is feasible and not detrimental for this setting of patients. Moreover, in the International Lymphoma Radiation Oncology

Group (ILROG) guidelines, the target in advanced Hodgkin's lymphoma is represented by the residual mass (GTV) after chemotherapy with an additional margin of 1 cm (13). IFRT (pre or post SCT) has been used in patients with (non)-Hodgkin's lymphoma with refractory/progressive disease in the past series, while the recent ILROG guidelines indicated that the RT volume should encompass the site(s) of disease recurrence, without prophylactic inclusion of adjacent lymph nodal stations (23, 24).

As previously discussed, despite the large variability in target volume contouring in PMBCL, ISRT represents the most frequently radiation target volume chosen in the clinical trials and in daily clinical practice. With this radiation volume, since it must include all the sites affected by lymphoma at diagnosis, there is a large amount of normal tissue without morphological/metabolic residual disease (1, 2, 6, 7). The introduction of rituximab into the combined chemotherapy era has improved clinical results by better systemic control, whereas the presence of a bulky mediastinal mass is still at high risk of progression/relapse.

The aim of our study was therefore to verify if this de-escalated consolidative RT approach had a non-detrimental impact on LC and survival outcomes in patients with PMBCL treated with ICHT. The RSRT volume target is inclusive only of morphological residual disease after completing ICHT or after SCT and represents the GTV. For RT delivery, the GTV encompassed an additional safety margin of 0.5 cm, the PTV, unlike the ILROG guidelines and the HD15 methods, where the safety margins for PTV were 1.0 cm and 1.5 cm, respectively.

In our consecutive series of 34 patients with PMBCL, we recorded only one case of progression during RT that experienced premature RT interruption at 28/40 Gy. We consider that this patient had never obtained a metabolic response, neither after ICHT (DS 5) nor after SCT (persistence of DS 5) and the persistence of or progression to DS 5 after treatments is itself considered a negative prognostic factor (5, 25). Moreover, our patient showed both infield and outfield progressive disease, which required an unsuccessful third-line therapy.

The other 33 patients with PMBCL remained disease-free after a median of 72 months (range=11-145 months). Therefore, these results seem to suggest that RSRT can be safely applied in patients with PMBCL, without detriment in local relapse and, consequently, for the survival outcomes.

Although the role of adjuvant RT in PMBCL is still debated, ICHT and adjuvant RT is largely adopted in daily clinical practice in our country. The ongoing randomized study IELSG 37 will establish the role of adjuvant RT in patients with PMBCL with complete metabolic response (26). Moreover, in patients with PMBCL without complete metabolic response after ICHT, RT represents an advantageous and safe approach (15, 25, 27).

Reducing the target radiation volume without affecting the survival outcome for patients with PMBCL requiring RT may represent an attractive updated approach that fits into the scenario of modern RT. However, we must note that one patient died from ischemic cardiac disease 123 months from the end of RT. She was treated with eight cycles of R-CHOP21 and RSRT of 30 Gy with 3D-CRT technique.

Several studies have focused their attention on the reduction of the RT dose to organs at risk and on the other important issue of secondary malignancy, comparing ISRT, INRT or residual volume RT to IFRT in mediastinal lymphomas (28, 29). When the residual radiation volume, contoured according to ILROG guidelines, was specifically considered, it should be noted that the mean doses to the right breast, left breast, lung, esophagus and thyroid were lower than those obtained with ISRT and INRT. This dosimetric advantage was also demonstrated for risk of secondary cancer. Bearing in mind that the reduction of the target volume can represent a main factor for the reduction of late RT-related toxicities, efforts should also be made to offer these patients other RT techniques or procedures capable of lowering the dose to organs at risk and second cancer occurrence (IMRT/deep inspiration breath-hold technique) (30).

However, we are aware of the major limitation of our study represented by the single-center cohort of 34 consecutive patients with PMBCL not homogeneously treated. Moreover, an additional limitation is the different PET-based therapeutic approaches used for our patients, quite different for patients with DS 3 or DS 4 after ICHT. These differences were due to the modification of the criteria of assessment of metabolic response that was changed during the accrual of our patients that were treated accordingly. Moreover, 9/34 patients underwent early intensification with SCT, and this may be considered a clinical bias with respect to the results of the survival outcomes of the other patients treated with ICHT alone. Finally, considering the large variability of target volume contouring in PMBCL that is often related to the individual skills, we can only suggest RSRT as an explorable approach for RT in PMBCL.

In conclusion, our study seems to suggest that a reduction of radiation volume in PMBCL can be feasible without compromising survival outcomes. Our study should prompt larger prospective and multi-institutional series to better confirm the role and the advantage of this RT approach in PMBCL.

### Conflicts of Interest

The Authors state that they have no conflicts of interest in regard to this study.

## Authors' Contributions

V. De Sanctis: Made substantial contributions to conception of the study, analyzed the data and drafted the article. A. Di Rocco, M.C. Cox, M. Valeriani, D. Prosperi, P. Pizzichini, S. Pelliccia, A. Tafuri, M. Martelli and M.F. Osti: Made substantial contributions to conception of the study, analyzed the data and drafted the article. F. Perrone Congedi, D. Anzellini, M. Massaro and F. de Giacomo: Helped to draft and revise the article; G. Vullo and G. Facondo: Made substantial contributions to revising the article critically for important intellectual content, helped to draft the article; M. Alfò: Made substantial contributions to analyzing the data and drafted the article. All Authors critically revised the article, approved the final version to be published, and agree to be accountable for all aspects of the work.

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