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Primary mediastinal B-cell lymphoma: a nationwide real-life retrospective study of first-line treatment approaches in Italy

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Primary mediastinal B-cell lymphoma: a nationwide real-life retrospective study of first-line treatment approaches in Italy

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A list of FIL sites and investigators participating in the study is reported in Appendix 1 of Data Supplement.

AUTHORSHIP CONTRIBUTION

E.I. and U.C. conceived and designed the research, identified eligible patients, provided patients to the study, conducted the research, analyzed and interpreted the data, and wrote the manuscript; L.D. provided patients to the study, and analyzed and interpreted the data, and wrote the manuscript; M.B., and C.I. provided patients to the study, and analyzed and interpreted the data; A.D.R. provided patients to the study, and analyzed and interpreted the data; A.E. performed statistical analyses; M.S., and R.D.C., collected the data provided by the sites in the study database; A.L.P. served as Project Manager of the study at FIL Operational Offices; P.L.Z., and M.M. provided patients to the study, and supported the manuscript drafting; F.M. and C.V. contributed to the study design, and provided patients to the study. All other authors provided patients to the study; and all authors reviewed the manuscript before submission.

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All other authors declare no competing interest.

Short Title for running head: PMBCL first-line therapy in real-life in Italy

Data sharing: Qualified researchers may contact the Fondazione Italiana Linfomi board at segreteriadirezione@filinf.it for individual-level patients' clinical data reported in this manuscript (pseudonymized). Requests will be reviewed based on scientific merit. The study protocol and statistical analysis plan will be available to requesters for what is not already available in the appendix/supplemental data by contacting Fondazione Italiana Linfomi at segreteriadirezione@filinf.it.

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ABSTRACT

Primary mediastinal large B-cell lymphoma (PMBCL) is a rare and aggressive cancer predominantly affecting young adults. Although a consensus on the optimal regimen has not yet been reached, anthracycline-rituximab backbone chemo-immunotherapy (CIT) regimens are the mainstay. We retrospectively analyzed 931 PMBCL patients from 37 Fondazione Italiana Linfomi (FIL) centers to compare front-line treatments (R-CHOP-21, R-CHOP-14, R-MegaCHOP, R-MACOP-B, R-VACOP-B, DA-EPOCH-R). The overall and complete response rates after CIT were 92% and 62%, respectively. Mediastinal radiotherapy (RT) was administered as consolidation to 66% of patients. The 5-year progression-free survival (PFS) and overall survival (OS) rates for the entire cohort were 84% and 92%, respectively. Among patients treated with R-MACOP-B (reference group), 5-year PFS and OS rates were 86% and 91%. In multivariable analysis, R-CHOP-21 was associated with worse PFS (HR = 2.05, P = .019), while R-CHOP-14 was associated with improved OS (HR = .41, P = .034); other regimens showed time-to-event outcomes not significantly different from those of R-MACOP-B. DA-EPOCH-R had a 5-year PFS of 77%; although this rate was lower than reported in the literature, it did not differ significantly from R-MACOP-B in multivariable analysis (HR 1.66, 95% CI: 0.92-3.01). Patients with Deauville scores of 1–3 after CIT showed no difference in 5-year PFS, regardless of whether they received RT consolidation. Our findings suggest that R-CHOP-21 is a suboptimal regimen as a first-line therapy for PMBCL patients and that R-CHOP-14 may be preferable due to its improved efficacy and tolerability.

INTRODUCTION

Primary mediastinal B-cell lymphoma (PMBCL) is an aggressive extranodal neoplasm originating from the thymus, characterized by distinctive clinical and pathologic features and a unique molecular signature.[2,3] PMBCL accounts for 2-4% of non-Hodgkin lymphomas, primarily affecting adolescents and young adults, particularly females in their twenties and thirties.[2,3] Typically, the disease presents as a rapidly growing voluminous mediastinal mass in the upper anterior mediastinum. The tumor progression tends to remain localized in the thorax, and extrathoracic spread occurs in fewer than 20% of cases. At onset, in approximately half of the patients, compression of the large airways and/or mediastinal vessels may occur, requiring urgent intervention.[4–6] Particularly in cases of disease recurrence, extranodal sites may be involved. From a molecular standpoint, the PMBCL signature is different from that of other nodal DLBCLs and is more similar to that of classical Hodgkin's Lymphoma.[7] This distinction involves the deregulation of the JAK-STAT pathway, leading to increased expression of PDL1 and PDL2.[8,9] Due to the rarity of the disease, most of the available evidences on treatment comes from small retrospective trials,[4,10,11] and unplanned subgroup analyses in prospective studies dedicated to diffuse large B-cell lymphoma (DLBCL).[12–15] Chemo-immunotherapy (CIT) with anthracycline and rituximab-containing regimens is the current mainstay of first-line approaches, historically followed by mediastinal radiotherapy (RT).[16] In 2016, the European Society for Medical Oncology (ESMO) published guidelines recommending several CIT options as first-line therapy for PMBCL patients.[17] These options include: 1) R-CHOP21 (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone); 2) R-CHOP14 (a dose-dense R-CHOP); 3) R-MACOP-B (a weekly regimen with rituximab, methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisone, and bleomycin); 4) R-VACOP-B, a MACOP-B like weekly regimen, except for the substitution of methotrexate for etoposide (VP-16); 5) DA-EPOCH-R (dose-adjusted etoposide, prednisolone, vincristine,

cyclophosphamide, doxorubicin, and rituximab); 6) R-MegaCHOP, 3 Q21d cycles of high-dose R-CHOP followed by 3 Q21d cycles of R-ESHAP (rituximab, etoposide, methylprednisolone, cisplatin, cytarabine) and autologous stem cell transplantation. In the past decade, concerns regarding late toxicities have fueled a debate about the safety of mediastinal RT in younger patients. A recent prospective randomized trial addressing this issue has shown that RT can be safely omitted in patients who achieve a complete metabolic response (CMR) with a Deauville score (DS) of 1-3 after induction CIT, using a PET-guided approach.[18]

However, the lack of randomized trials has made it challenging to reach a consensus on the optimal CIT regimen, and debates persist regarding the best first-line therapeutic strategies.[4,10,11,14,15,19,20] A recent systematic review and meta-analysis[21] involving 4,068 patients with PMBCL compared dose-intensified chemo-immunotherapy (DI-CIT) with standard-dose chemo-immunotherapy (S-CIT) for first-line treatment of PMBCL. Interestingly, the study showed a significant 5-year OS advantage for DI-CIT compared with S-CIT (88% vs 80%, respectively). The S-CIT group included only the R-CHOP21 regimen, whereas the DI-CIT cohort comprised several regimens with increased frequency, dose, and/or the number of systemic agents, such as R-ACVBP (rituximab, doxorubicin, cyclophosphamide, vindesine, bleomycin, prednisone), DA-EPOCH-R, R-V/MACOP-B, and R-CHOP14. In line with the finding of a benefit for intensified therapies over R-CHOP21, the recent LYSA recommendations also favor dose-dense immunochemotherapy (e.g., R-CHOP14, DA-EPOCH-R, R-ACVBP).[22]

Considering this scientific context, we conducted a comprehensive multicenter retrospective study across Italy in centers of the Fondazione Italiana Linfomi (FIL). We aimed to analyze the first-line treatment strategies adopted for patients with PMBCL in a real-world setting. Additionally, we sought to compare outcomes and toxicity profiles associated with different CIT regimens.

METHODS

We retrospectively analyzed data from 37 centers affiliated with FIL. Eligible patients were adult subjects with a new diagnosis of PMBCL rendered between 2007 and 2019 and treated upfront with CIT (rituximab-anthracycline combination). The study adhered to the Declaration of Helsinki, was approved by the bioethics committees of all participating centers, and each patient provided a statement of non-opposition.

Investigators at each center conducted retrospective reviews of medical records or local clinical databases, including baseline demographic, clinical, laboratory, pathology, treatment, and outcome data which were pseudo-anonymized and collected in a study-specific database. Local investigators were responsible for assessing diagnostic criteria, stage, and response according to international criteria and recommendations[23–26] and institutional guidelines and practices of the enrollment period. Response was assessed using CT-based criteria for complete response (CR) (IWG)[23], Cheson criteria (IWG)[24], and, subsequently, the Lugano revision (IWG)[25], which were considered the standard at the time of evaluation. Since our data collection started before PET response criteria were broadly incorporated into real-world practice, end-of-therapy PET-based response and DS were not available for some patients. Diagnoses, staging, and response assessments were performed locally at each center according to international criteria and institutional practice during the enrollment period. No centralized pathology review or adjudication of response/progression was performed. In suspected persistent or progressive mediastinal disease, the use of repeated imaging and biopsy confirmation was performed inconsistently across centers and were not systematically captured in the study database.

Statistical analysis

The primary objective was to analyze the outcomes associated with different approaches, particularly the type of CIT regimen and the adoption of consolidative RT and/or ASCT. Primary study outcomes were as follows: primary early refractory disease (RD) rate,

defined as a clinical response of less than partial response (PR) at the end of CIT or progression during treatment or within three months after treatment completion; overall response rate (ORR), defined as the sum of PR and CR; complete response rate (CRR), defined as the rate of CR; progression-free survival (PFS), defined as the time from the start of therapy to progression, relapse, or death from any cause, whichever occurred first; overall survival (OS), calculated as the time from the start of therapy to death from any cause or the last follow-up. The secondary objectives were to evaluate both acute and late toxicity profiles associated with treatment strategies.

Baseline characteristics were compared using the Kruskal-Wallis test for continuous variables and the chi-squared test for categorical variables. Time-to-event outcomes, not influenced by competing risks, were estimated using the Kaplan-Meier method and compared using Cox proportional hazards models, which incorporated shared frailty terms to account for clustering by center. Disease-specific mortality was analyzed using cumulative incidence functions estimated with the Gooley method,[27] treating non-lymphoma deaths as competing events. Comparisons were performed using Fine & Gray's model.[28] The impact of RT on PFS was assessed using a 6-month landmark analysis; this was restricted to patients with stage I–II disease who had an end-of-treatment PET with a documented DS, achieved CMR (DS 1–3) or PR (DS4) after induction CIT, had available data on RT consolidation, and were alive and progression-free at 6 months from treatment initiation. Multivariable analyses of time-to-event outcomes were conducted using 20 multiple imputed datasets to account for missing covariates. In these models, the effects of composite scores were evaluated without including their component covariates. The incidence of adverse events was compared using random-effects logistic regression models to account for clustering by center.

The R-MACOP-B and R-VACOP-B groups accounted for approximately half of the cohort, and their outcomes were nearly identical and closely comparable to those reported in the

literature. Therefore, R-MACOP-B was used as the baseline treatment comparator in the Cox multivariable analysis.

Analyses were performed using STATA version 15 (StataCorp LLC, College Station, TX, USA).

RESULTS

A total of 931 patients were enrolled across 37 FIL centers (Figure 1). Of these, 40 patients were excluded from the analysis: one patient died before treatment initiation, 22 patients received unconventional treatments that did not include the rituximab-anthracycline backbone, and 18 patients were enrolled in the high-dose consolidation therapy with the ASCT arm of a prospective randomized study in DLBCL.[29]

Baseline patient characteristics at diagnosis for the entire cohort, stratified by treatment group, are reported in Table 1. The median age at diagnosis was 35 years (IQR 28-44), with a prevalence of females (61.6%). Most patients (72.4%) presented with a bulky mediastinal mass and LDH value above the normal range (75.3%). Pericardial and pleural effusions were present in 38.5% and 44.3% of cases, respectively. Approximately one-fifth of patients had an advanced Ann Arbor Stage III-IV (21.6%) and a poor ECOG PS (21.8%). Thirty-four patients (3.8%) were aged ≥ 60 years, and 8 of them (23.5%) received R-CHOP21. In this age group, the proportion of patients treated with R-CHOP21 was more than double that observed in the overall study population (96/891, 10.8%). Compared with the younger cohort, older patients had a significantly higher incidence of pleural effusion (71.5% vs 41.0%; $P < .003$).

Treatment analysis

Of the 891 patients analyzed, treatment regimens included R-CHOP21 (n = 96), R-CHOP14 (n = 181), R-MegaCHOP (a dose-intensified CHOP) (n = 31),[30] R-V/MACOP-B (n = 404), and DA-EPOCH-R (n = 179). While most patients (95.0%) completed all 6

planned treatment cycles, information on dose intensity for each group and on dose escalation in the DA-EPOCH-R group was unavailable.

The frequency of clinical features at diagnosis varied significantly among treatment groups, except for LDH levels above the normal value and sex (Table 1). The DA-EPOCH-R and R-CHOP21 groups exhibited higher proportions of advanced-stage disease (34.6% and 33.3%, respectively), with extranodal involvement observed in over one-third of patients. The R-CHOP21 group also had a higher median age of 39.5 years (IQR 30-49). In keeping with these baseline characteristics, 17.7% of the R-CHOP21 patients had a poor-risk IPI score (≥3). The R-MACOP-B and R-VACOP-B cohorts exhibited the highest frequency of bulky mediastinal mass (74.2% and 76.0%, respectively).

Table 2 summarizes data on consolidation treatments. Sixty-six percent (589/891) of patients received mediastinal RT at a median dose of 30 Gy (IQR 30-36). The rates of consolidation for RT varied significantly across the treatment groups ($P < .001$). As expected from the treatment strategy, the DA-EPOCH-R group had a substantially lower rate of consolidative RT compared with all other treatment groups (31.3% vs 59.4%–90.3%), whereas the highest rate was observed in the R-MegaCHOP group (90.3%).

ASCT consolidation rates varied significantly across CIT groups ($P < .001$), with the highest rates observed in patients treated with R-VACOP-B. Overall, 66 patients (7.4%) received consolidation ASCT after completion of the CIT program, 44 in CR and 22 in PR. After the ASCT procedure, 41 of 66 (62.1%) patients also underwent mediastinal RT. Notably, 76% (50 patients) of all ASCTs were performed before 2014.

Patient outcomes

Treatment response rates after CIT are listed in Table 3. The clinical response was lacking for six patients (0.6%); three experienced premature death, and for the remaining three, no information was provided to help understand why the response was not recorded. After induction CIT, 552 patients (62%) attained a CR, 267 (30%) achieved a PR, and 66 (7.4%)

exhibited RD. Therefore, the ORR was 92% with no notable differences among the treatment groups. Of the 799 patients (90%) who underwent end of therapy PET scan evaluation, only 401 (51%) had a documented DS.

With a median follow-up of 5.4 years (IQR 3.6-7.8), the 5-year PFS (Figure 2A) and OS (Figure 2B) of the entire series were 83% (95%CI: 80-85) and 92% (95%CI: 89-94), respectively. During the study, there were 153 PFS events, comprising 34 relapses (22.2%), 104 progressions (68%), and 15 deaths (9.8%). The 5-year PFS for R-MegaCHOP, R-CHOP14, R-VACOP-B, R-MACOP-B, DA-EPOCH-R, and R-CHOP21 were 93% (95%CI: 75-98), 89% (95%CI: 83-93), 86% (95%CI: 81-90), 86% (95%CI: 80-90), 76% (95%CI: 69-82), and 70% (95%CI: 59-78%), respectively (Figure 2C). The 5-year OS for R-MegaCHOP, R-CHOP14, R-VACOP-B, R-MACOP-B, DA-EPOCH-R, and R-CHOP21 were 96% (95%CI: 78-99), 95% (95%CI: 91-98), 92% (95%CI: 87-95), 91% (95%CI: 86-94), 90% (95%CI: 84-93), 86% (95%CI: 77-92) (Figure 2D). The largest group was R-MACOP-B, which, along with the similar R-VACOP-B group, having comparable outcomes, included a total of 404 patients, accounting for 45% of the study population.

A total of 72 patients died, from deaths related to lymphoma (n = 57), toxicity (n = 3), secondary malignancy (n = 3), and nine to other unspecified causes. Nearly all lymphoma-related deaths occurred within the first 24 months of follow-up, regardless of the CIT group. Figure S1A (Data Supplement) illustrates the cumulative incidence of lymphoma-related mortality starting from the initiation of first-line therapy. Figure S1B shows that age is associated with a higher risk of death from non-lymphoma causes (HR per year 1.07, 95% CI 1.03–1.11, P < 0.001), whereas age is not significantly associated with lymphoma-specific mortality (HR per year 1.00, 95% CI 0.97–1.02, P = 0.804). These findings were estimated using Fine and Gray's competing-risk model.[27]

Regarding PFS, by univariate analysis, two regimens, DA-EPOCH-R and R-CHOP21, performed worse than the reference R-MACOP-B. However, in the multivariable Cox

model (Table S1, Supplementary Data), only the R-CHOP21 cohort had a significantly higher HR for progression compared to the R-MACOP-B cohort (HR = 2.05; 95%CI: 1.12–3.74). Univariate analysis did not reveal significant differences in OS among the different treatment groups. However, the multivariable analysis (Table S2, Supplementary Data) showed that the HR for survival of the R-CHOP14 group was significantly lower than that in the R-MACOP-B cohort (HR = 0.41, 95%CI: 0.18-0.93, *P* = .034).

Among the baseline covariates, multivariable analysis indicated that a one-point increase in IPI score, advanced stage (III-IV), >1 extranodal site, and the presence of B-symptoms were associated with a worse PFS. For OS, the significant parameters associated with poorer survival were a one-point increase in IPI score and involvement of more than one extranodal site. Additionally, B-symptoms and bulky mediastinum were associated with a higher risk of poor survival, of borderline significance. Furthermore, having more than one extranodal site had a greater negative prognostic impact than other IPI parameters for both PFS and OS, with HR of 2.03 and 2.07, respectively.

The role of RT on PFS was investigated in 129 patients with stage I-II disease, who achieved a PET-documented CMR (DS 1-3) following induction CIT. A landmark analysis at 6 months (Figure S2, Supplementary Data) showed no statistically significant difference in 5-year PFS rates between patients who received consolidation RT and those who did not (*P* = .124). This subgroup of patients had characteristics similar to the inclusion criteria of the IELSG37 study.[18] The same analysis was performed in patients with a DS 4 after induction CIT. Although the analysis was limited by the relatively small and unbalanced sample size (116 patients: 100 receiving RT consolidation and 16 not receiving RT consolidation), a landmark analysis at 6 months showed no statistically significant difference in 5-year PFS between patients who received consolidation RT and those who did not (P = .133) (Figure S3, Data Supplement).

Acute and late toxicity

Table 4 reports both acute and late toxicities. Regarding acute toxicities, febrile neutropenia occurred in 11.4% of patients, and pneumonia in 6%. The incidence of acute toxicity classified as grade ≥3 varied significantly ($P < .001$) among the different CIT regimens. Grade 3 or higher hematological and non-hematological toxicities were recorded in 31.7%, and 18.9% of the entire cohort, respectively. The highest rate of non-hematological toxicity was observed with the R-MegaCHOP regimen (40%). In contrast, the highest rate of hematological toxicity was reported for the DA-EPOCH-R regimen (51.5%).

Information on late toxicity was unavailable for 246 patients, accounting for 27.6% of the total. Of the 645 patients evaluated for late toxicities, 104 (16.1%) experienced at least one late effect. Among these patients, cardiotoxicity accounted for 8.4%, secondary malignancies for 3.6%, and other events for 4.8%. Of the 54 (8.4%) late cardiac events, 40 (74.1%) involved mild mitral regurgitation and/or a reduced ejection fraction graded as 1 or 2. Secondary malignancies were reported in 23 patients (3.6%): four hematological (one acute myeloid leukemia, one acute lymphoid leukemia, two Hodgkin lymphoma), three breast cancer, two thyroid cancer, two urinary tract cancer, one lung cancer, one mesenchymal cancer, one esophageal cancer, one dermoid cyst; the type of malignancy was not specified for the remaining 8 patients. Among the 645 patients evaluated for late toxicities, 440 (68.2%) had received RT (Table S3, Data Supplement). Among patients who experienced any late effect, 65/104 (62.5%) had received RT, compared with 375/541 (69.3%) of those without late effects. Among patients with a cardiovascular event, 32/54 (59.3%) had received RT versus 408/591 (69%) of those without a cardiovascular event. Among patients with a secondary malignancy, 16/23 (69.6%) had received RT, similar to the proportion among those without (424/622, 68.2%). The same was true for other late events (21/31, 67.7% vs 419/614, 68.2%). The combination of DA-EPOCH-R and RT

(n=34) was more frequent among patients with late effects than without: 12/104 (11.5%) vs 22/541 (4.1%) for any late effect, and 9/54 (16.7%) vs 25/591 (4.2%) for cardiovascular events, specifically.

DISCUSSION

Our retrospective analysis of a large cohort of 891 patients represents the most extensive retrospective study to date with the longest follow-up and provides insights into the real-world effectiveness and comparative performance of various CIT regimens for PMBCL. Our findings challenge some previous assumptions about treatment outcomes after R-CHOP21 and DA-EPOCH-R regimens. Notably, they provide real-life evidence supporting the selective omission of mediastinal RT consolidation in patients who achieve CMR.[18]

This study analyzed the outcomes of patients with newly diagnosed PMBCL treated with rituximab-anthracycline backbone CIT at 37 FIL centers. Notably, all enrolled patients had a minimum follow-up of 2 years, encompassing the timeframe in which over 90% of PFS events occur. With a median follow-up of 5.4 years, the 5-year PFS and OS rates for the entire cohort were 83% and 92%, respectively, approaching the most favorable outcomes documented in the literature for this neoplasm.

Among the six CIT groups investigated, patients who received R-MACOP-B achieved 5-year PFS and OS rates of 86% and 91%, respectively. These temporal outcomes are consistent with those reported in the literature for R-MACOP-B/R-VACOP-B.[16] Among the other treatment groups, R-CHOP14 and R-MegaCHOP achieved PFS similar to that of R-MACOP-B, while R-CHOP21 and DA-EPOCH-R showed worse than expected outcomes. Specifically, multivariable analysis adjusted for strata (including bulky disease, B-symptoms, sex, and all IPI covariates), indicated that R-CHOP21 was associated with a significantly shorter PFS (HR = 2.05, 95%CI: 1.12-3.74). Though data on R-CHOP21 in the literature are rather conflicting,[15],[31] our findings are consistent with the 2025 LYSA recommendations[22], and the conclusions of a large LYSA retrospective study[11] and the

prospective IELSG37 study.[18],[31] In the LYSA study, conducted across 25 centers in France and Belgium, 313 patients were enrolled. Of these, 180 received R-ACVBP as first-line treatment, 76 received R-CHOP14, and 57 received R-CHOP21. The three-year PFS and OS rates for R-ACVBP, R-CHOP14, and R-CHOP21 were 89.4%, 89.4%, 74.7% and 92.4%, 100%, 87.5%, respectively.[11] The prospective IELSG37 study analyzed 545 patients with early-stage disease (I-II) who were treated with various regimens, including R-V/MACOP-B, R-CHOP14, R-CHOP21, DA-EPOCH-R, R-MegaCHOP, and other DI-CIT treatments. The study showed that the 5-year PFS rate was 87.6% for R-CHOP21, with an HR of 1.82 (95%CI: 0.78-4.25) compared to the reference regimen R-V/MACOP-B. The study also highlighted an uneven distribution of DS, with patients scoring DS = 5 being twice as common with R-CHOP21, suggesting that this treatment regimen produces less profound responses.[31] In our study, the higher median age and the higher proportions of advanced-stage disease and extranodal involvement in the R-CHOP21 cohort suggest that treatment assignment may have been influenced by patient age and fitness in standard clinical practice. Consistent with these baseline characteristics, the proportion of patients with a poor-risk IPI score (≥3) was higher in the R-CHOP21 group (17.7%) than in the other treatment groups. Thirty-four patients (3.8%) were aged ≥60 years, of whom 8 (23.5%) received R-CHOP21 – more than twice that observed in the overall study population (10.8%). An age of ≥ 60 years is uncommon in PMBCL patients, and given local diagnostic practices without central pathology review, some diagnostic overlap with DLBCL in this older population cannot be excluded.

Regarding DA-EPOCH-R, the 5-year PFS rate, although lower than reported in the literature,[13] did not show a statistically significant difference compared with R-MACOP-B in multivariable analysis (HR 1.66, 95%CI: 0.92-3.01). The DA-EPOCH-R regimen is designed to increase dose intensity by adjusting the doses of etoposide, cyclophosphamide, and doxorubicin – administered as a 96-hour continuous infusion –

based on hematological nadirs at each cycle, thereby enhancing the regimen's complexity.[32],[33] However, our study lacks data on dose escalation, so this hypothesis remains speculative. Our results outline that, outside the highly controlled setting of a single-institution trial,[13] dose escalations not correctly applied could negatively impact outcomes. Another plausible explanation is an adverse patient selection. Actually, the DA-EPOCH-R cohort included a high proportion of patients with advanced disease (34.6%), with over one-third exhibiting >1 extranodal involvement, suggesting that the regimen was likely administered to individuals deemed at elevated risk of treatment failure.

Given the young age and female predominance of PMBCL patients, reducing the need for mediastinal RT remains a major therapeutic goal to minimize late toxicities. The high rate of consolidative mediastinal RT (90.3%) in the R-MegaCHOP cohort, in contrast to other treatments, likely reflects historical, center-specific practice patterns related to adherence to a clinical protocol from an earlier treatment era, rather than a strategy consistent with contemporary PET-guided and RT-sparing approaches. In our cohort, DA-EPOCH-R was associated with a substantially lower use of consolidative RT (31.3%) compared with other CIT regimens (59.4-90.3%), reflecting its potential as an RT-sparing approach. Therefore, the lower PFS observed, although not statistically significant, may partly reflect the different consolidation strategies adopted.

In our study, DA-EPOCH-R was also associated with significant acute and late toxicities. Outside the highly controlled setting of a single-institution trial,[13] the logistical complexity of this regimen may contribute to increased hematological complications and infections. With regard to late toxicities, it should be noted that 31.3% of the patients also underwent RT. Given the retrospective design of the study, the non-random allocation of RT, and potential confounding factors, these findings on toxicity should be interpreted with caution.

In addition to comparing chemotherapy regimens, our study highlighted and confirmed the prognostic value of IPI parameters at diagnosis. Furthermore, it provided real-world data

supporting the omission of RT in patients with CMR, as suggested by the IELSG37 study.[18] In our real-life experience, 66% of patients (589 of 891) received mediastinal RT. There was no statistically significant difference in PFS between patients who received RT and those who did not among those who had PET evaluation and obtained a DS of 1-3 at the end of CIT, which is indicative of a CMR. These findings are in line with the IELSG37 study, which showed that patients who obtain a CMR (DS 1-3) after conventional first-line immunochemotherapy can safely omit mediastinal RT.[18] It is noteworthy that the results of a controlled clinical trial with centralized PET review, such as IELSG37, can be reproduced in a real-world setting. Therefore, current evidence supports omission of consolidation RT in patients with DS 1–3 after first-line CIT. In contrast, the role of RT in patients with DS 4 remains uncertain, with conflicting evidence in the literature. Although no statistically significant difference in 5-year PFS was observed in our DS 4 subgroup, this result should be interpreted with caution given the retrospective design, the limited and unbalanced sample size, and the consequent limited statistical power. Furthermore, the decision to deliver RT was based on local practice; therefore, potential imbalances in baseline prognostic variables and induction chemotherapy regimens between patients treated with RT and those not receiving RT cannot be excluded.

We acknowledge that this study has several limitations due to its retrospective nature and lengthy enrollment period. Indeed, cases of PMBCL were identified using local databases, which could have introduced selection bias. Furthermore, local treatment policies varied among the participating centers, and the criteria for response have evolved since the time our patients were assessed, leading to inconsistencies in patient management and evaluation. The widespread use of RT (66%) and the use of consolidation with ASCT (7.4%) reflect historical treatment approaches that are no longer adopted and may represent potential sources of confounding in outcome comparisons among regimens. Notably, most ASCT procedures (50/66, 76%) were performed before 2014, mainly in

patients enrolled in DLBCL clinical trials or treated according to center-specific historical approaches. Current guidelines[22] do not recommend routine consolidative ASCT as first-line therapy for PMBCL; therefore, these outcomes should be interpreted with caution.

Additional limitations include the lack of centralized histopathologic and imaging review. Consequently, diagnostic classification and response assessment relied on local practice, and the absence of systematic biopsy confirmation in suspected cases of persistent or progressive disease may have introduced inter-center variability and potential misclassification of refractory/progressive disease. Additionally, not all patients underwent FDG-PET scans, and only half of them had an available DS, which might have impacted the consistency of staging and response evaluations. Considering the above limitations, we conclude that R-CHOP21 yields inferior results compared with other CIT regimens and is not recommended as first-line therapy in patients without contraindications to DI-CIT regimens.

Due to the comparable outcomes, the choice among various DI-CIT regimens may depend on an institution's expertise, experience and logistical factors, with R-CHOP14 potentially preferred for its favorable balance of effectiveness and tolerability.

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Tables

Table 1. Patients' characteristics at baseline according to treatment group.

	All patients N=891	R-CHOP21 N=96	R-VACOPB N=179	R-MACOPB N=225	DA-EPOCH-R N=179	R-CHOP14 N=181	R-MegaCHOP N=31	P-value	*Missing*
Age at diagnosis, years, median (IQR)	35.0 (28.0-44.0)	39.5 (30.0-49.0)	34.0 (27.0-43.0)	33.0 (27.0-42.0)	34.0 (28.0-41.0)	37.0 (30.0-47.0)	33.0 (30.0-46.0)	0.002	
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)		
Sex, Female	549 (61.6%)	58 (60.4%)	105 (58.7%)	154 (68.4%)	100 (55.9%)	115 (63.5%)	17 (54.8%)	0.13	
Patient previously included or reported for IELSG37 study	230 (26.9%)	18 (18.9%)	42 (23.9%)	68 (34.5%)	13 (7.4%)	71 (39.2%)	18 (58.1%)	<0.001	*35*
ECOG PS, ≥ 2	188 (21.8%)	22 (23.2%)	54 (31.2%)	37 (16.5%)	44 (26.8%)	24 (13.8%)	7 (22.6%)	<0.001	*30*
LDH, above Upper Limit of Normal	658 (75.3%)	76 (80.0%)	141 (79.2%)	162 (73.6%)	125 (70.6%)	129 (74.6%)	25 (80.6%)	0.35	*17*
Ann Arbor Stage, III-IV	192 (21.6%)	32 (33.3%)	31 (17.4%)	33 (14.7%)	62 (34.6%)	31 (17.2%)	3 (9.7%)	<0.001	*3*
IPI Score, ≥ 3	97 (11.5%)	17 (17.7%)	22 (12.9%)	13 (6.0%)	24 (14.8%)	20 (11.8%)	1 (3.2%)	0.014	*45*
Systemic symptoms, presence	341 (40.2%)	37 (38.9%)	57 (38.8%)	88 (39.3%)	86 (49.1%)	59 (33.1%)	14 (46.7%)	0.067	*42*
Bulky mediastinum, > 10 cm	637 (72.4%)	67 (69.8%)	136 (79.5%)	167 (74.9%)	124 (69.7%)	127 (70.2%)	16 (51.6%)	0.022	*11*
Extra nodal sites, any, presence	259 (29.6%)	34 (35.4%)	58 (34.9%)	35 (15.6%)	61 (34.5%)	63 (35.0%)	8 (25.8%)	<0.001	*17*
Pericardial effusion, presence	330 (38.5%)	37 (38.9%)	64 (39.0%)	57 (26.5%)	80 (45.2%)	81 (46.0%)	11 (35.5%)	<0.001	*33*
Pleural effusion, presence	379 (44.3%)	49 (51.6%)	63 (38.9%)	93 (43.5%)	81 (46.0%)	81 (45.8%)	12 (38.7%)	0.44	*36*
Follow-up, median (IQR)	5.4 (3.5-7.8)	4.9 (3.4-7.0)	6.4 (4.3-9.5)	5.8 (4.5-8.4)	3.8 (2.6-5.8)	5.5 (3.9-7.8)	4.7 (3.2-5.7)	<0.001	

Table 2. Consolidation treatments

	All patients	R-CHOP21	R-VACOP-B	R-MACOP-B	DA-EPOCH-R	R-CHOP14	R-MegaCHOP	P-value
	N=891	N=96	N=179	N=225	N=179	N=181	N=31	
RT	589 (66.1%)	57 (59.4%)	139 (77.7%)	167 (74.2%)	56 (31.3%)	142 (78.5%)	28 (90.3%)	<0.001
ASCT	66 (7.4%)	8 (8.3%)	29 (16.2%)	8 (3.6%)	13 (7.3%)	6 (3.3%)	2 (6.5%)	<0.001
ASCT and RT	41 (4.6%)	3 (3.1%)	26 (14.5%)	3 (1.3%)	7 (3.9%)	0	2 (6.5%)	<0.001

Table 3. Response rate after CIT

	All patients	R-CHOP21	R-VACOP-B	R-MACOP-B	DA-EPOCH-R	R-CHOP14	R-MegaCHOP	p-value
	N=891	N=96	N=179	N=225	N=179	N=181	N=31	
CR	552 (62%)	61 (63.5%)	104 (58.1%)	134 (59.6%)	128 (71.5%)	106 (58.6%)	19 (61.3%)	0.028
PR	267 (30%)	25 (26%)	62 (34.6%)	68 (30.2%)	33 (18.4%)	67 (37%)	12 (38.7%)	
ORR	*819 (92%)*	*86 (89.5%)*	*166 (92.7%)*	*202 (89.8%)*	*161 (89.9%)*	*173 (95.6%)*	*31 (100%)*	
RD (SD+PD)	66 (7.4%)	9 (9.4%)	12 (6.7%)	22 (9.8%)	16 (9%)	7 (3.9%)	0	
NA	6 (0.6%)	1 (1.1%)	1 (0.6%)	1 (0.4%)	2 (1.1%)	1 (0.5%)	0	

Table 4. Acute and late toxicities in PMBCL patients

	All patients	R-CHOP21	R-VACOP-B	R-MACOP-B	DA-EPOCH-R	R-CHOP14	R-megaCHOP	p-value	Missing
During Treatment	N=891	N=96	N=179	N=225	N=179	N=181	N=31		
Febrile neutropenia	93 (11.4%)	13 (14.0%)	10 (7.4%)	26 (11.6%)	29 (17.8%)	11 (6.3%)	4 (13.3%)	0.016	72
Pneumonia	49 (6.0%)	9 (9.7%)	10 (7.3%)	14 (6.3%)	7 (4.2%)	7 (4.0%)	2 (6.7%)	0.44	68
Hematological ≥3	258 (31.7%)	36 (39.1%)	34 (25.8%)	63 (28.5%)	85 (51.5%)	33 (19.1%)	7 (23.3%)	<0.001	78
Extra-hematological ≥3	151 (18.9%)	9 (9.9%)	30 (22.9%)	49 (22.1%)	31 (20.0%)	20 (11.8%)	12 (40.0%)	<0.001	93
Late toxicity	104 (16.1%)	10 (13.9%)	19 (18.6%)	21 (11.7%)	34 (30.4%)	19 (12.1%)	1 (4.5%)	<0.001	246
Cardiotoxicity	54 (8.4%)	4 (5.6%)	7 (6.9%)	8 (4.4%)	26 (23.2%)	9 (5.7%)	0 (0.0%)	<0.001	246
Secondary Malignancy	23 (3.6%)	3 (4.2%)	5 (4.9%)	6 (3.3%)	2 (1.8%)	6 (3.8%)	1 (4.5%)	0.88	246
Other	31 (4.8%)	3 (4.2%)	10 (9.8%)	8 (4.4%)	6 (5.4%)	4 (2.5%)	0 (0.0%)	0.13	246

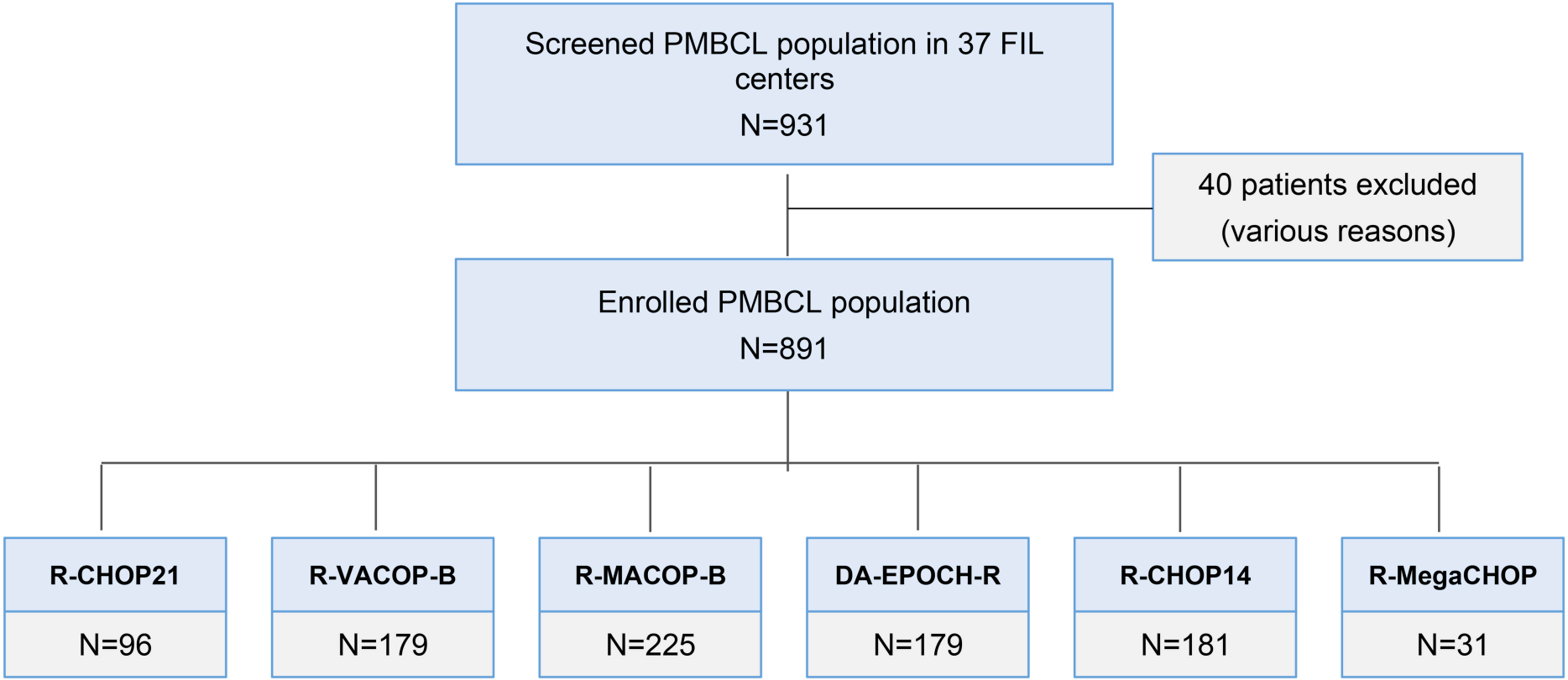
Figure Legends

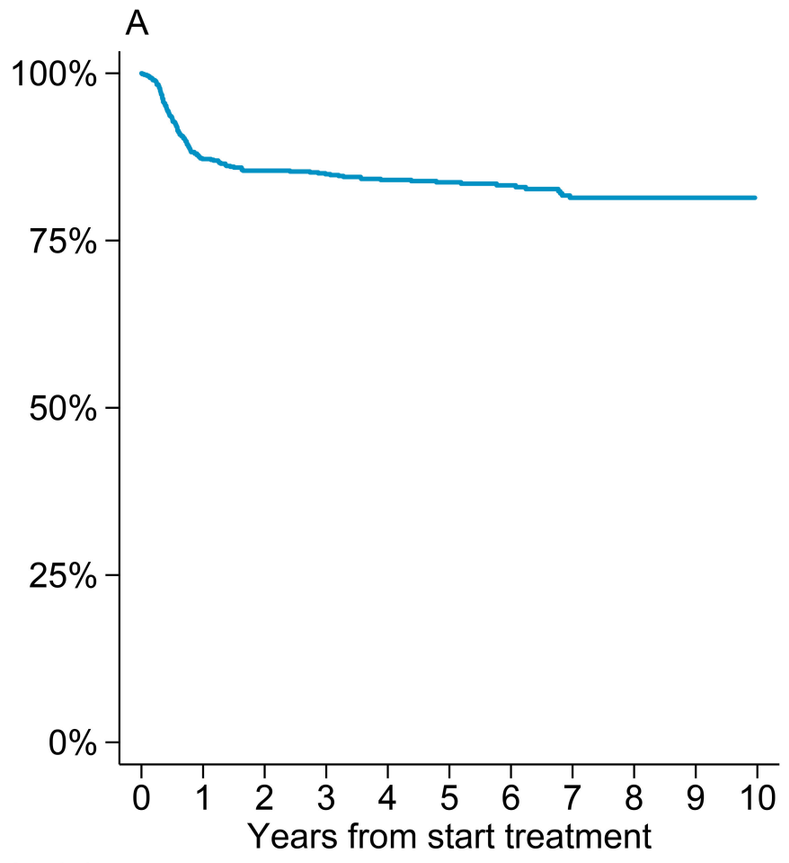
Figure 1. Patient distribution by treatment.

Patients screened for and patients included in the study by treatment groups. Abbreviation: PMBCL=primary mediastinal B-cell lymphoma; R-CHOP21=rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone, Q21d; R-CHOP14=dose-dense R-CHOP, Q14d; R-MACOP-B=rituximab, methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisone, and bleomycin, weekly administration; R-VACOP-B=MACOP-B-like, replacing methotrexate with etoposide (VP-16), weekly administration; DA-EPOCH-R=dose-adjusted etoposide, prednisolone, vincristine, cyclophosphamide, doxorubicin, and rituximab; R-MegaCHOP=3 Q21d cycles of high-dose R-CHOP followed by 3 Q21d cycles of R-ESHAP (rituximab, etoposide, methylprednisolone, cisplatin, cytarabine) and autologous stem cell transplantation.

Figure 2. Survival curves.

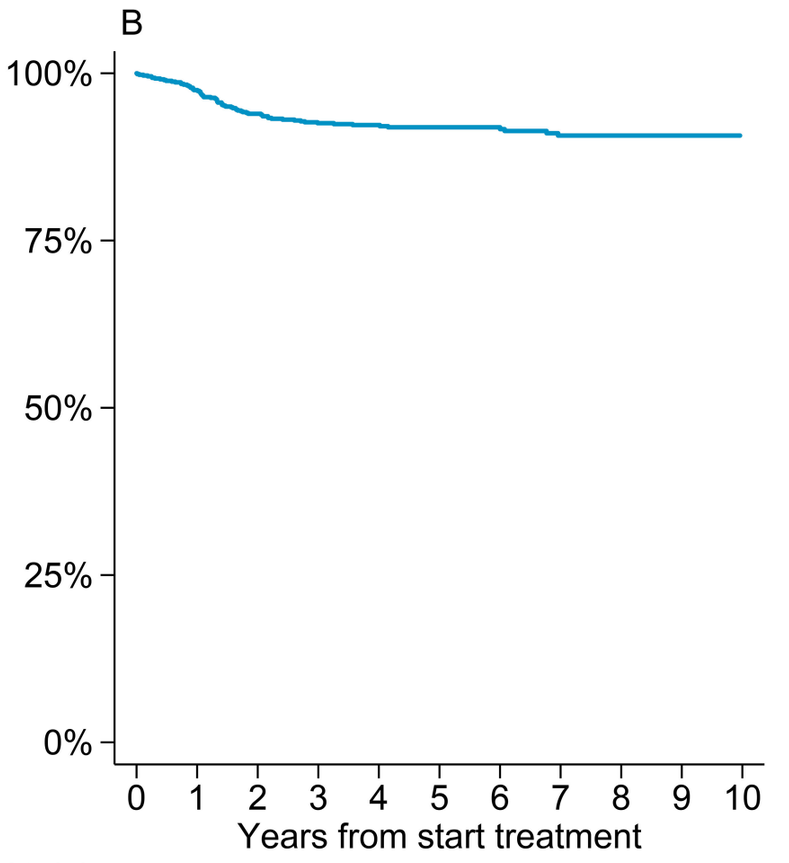
Entire population of enrolled patients n = 891; median follow-up, 5.4 years (interquartile ranges, IQR 3.6-7.8 years). **A:** progression-free survival (PFS) of the entire population of enrolled patients (5-year PFS 83%, 95%CI: 80-85); **B.** Overall survival (OS) of the entire population of enrolled patients (5-year OS 92%, 95%CI: 89-94); **C.** 5-year PFS for R-MegaCHOP, R-CHOP14, R-VACOP-B, R-MACOP-B, DA-EPOCH-R, and R-CHOP21 were 93% (95%CI: 75-98), 89% (95%CI: 83-93), 86% (95%CI: 81-90), 86% (95%CI: 80-90), 76% (95%CI: 69-82), and 70% (95%CI: 59-78%), respectively; **D.** 5-year OS for R-MegaCHOP, R-CHOP14, R-VACOP-B, R-MACOP-B, DA-EPOCH-R, and R-CHOP21 were 96% (95%CI: 78-99), 95% (95%CI: 91-98), 92% (95%CI: 87-95), 91% (95%CI: 86-94), 90% (95%CI: 84-93), 86% (95%CI: 77-92).


Screened PMBCL population in 37 FIL centers
N=931
40 patients excluded (various reasons)
Enrolled PMBCL population
N=891
R-CHOP21
N=96
R-VACOP-B
N=179
R-MACOP-B
N=225
DA-EPOCH-R
N=179
R-CHOP14
N=181
R-MegaCHOP
N=31



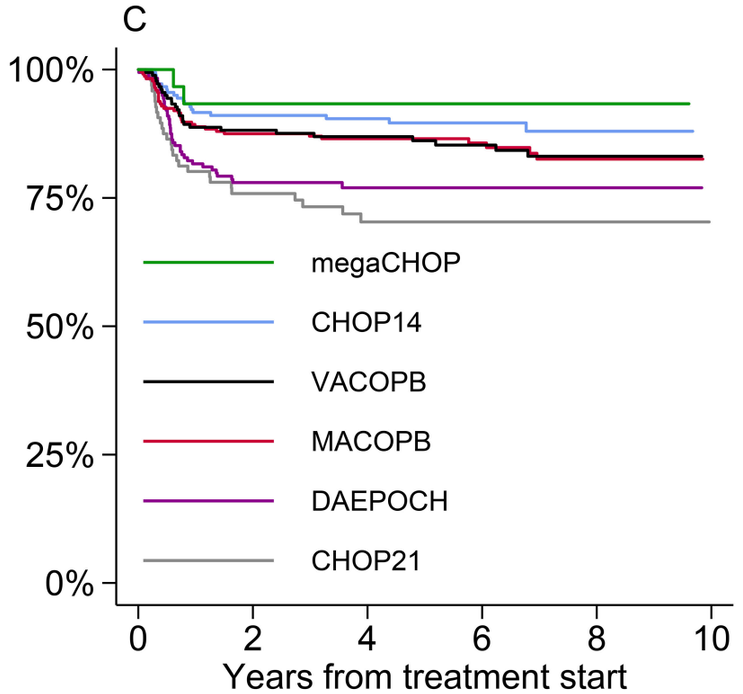
At risk:

891	700	527	313	179	97



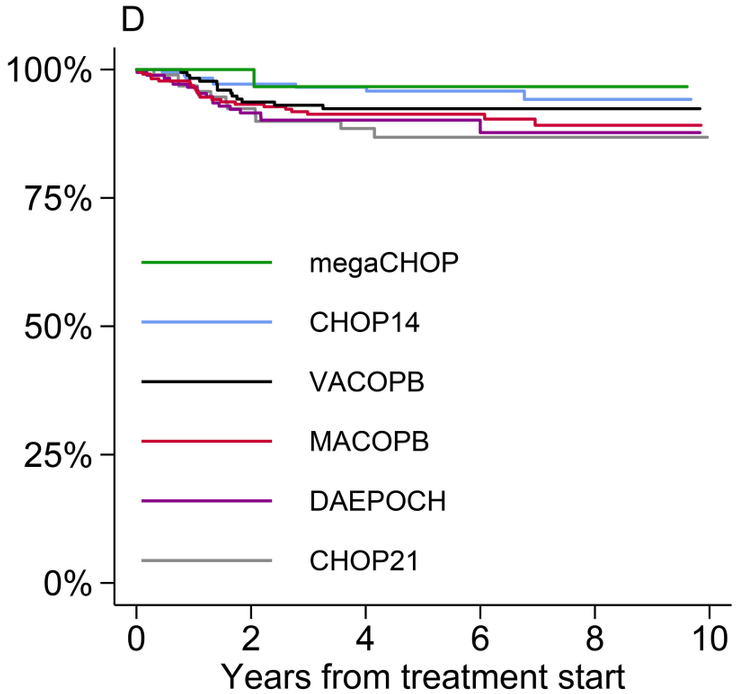
At risk:

891	758	566	334	191	102



At risk:

megaCHOP	31	28	16	6	2	0
CHOP14	181	158	121	65	37	17
VACOPB	179	150	122	87	56	33
MACOPB	225	186	158	98	56	36
DAEPOCH	179	114	67	33	18	7
CHOP21	96	64	43	24	10	4



At risk:

megaCHOP	31	30	16	6	2	0
CHOP14	181	168	129	70	40	18
VACOPB	179	158	128	92	61	37
MACOPB	225	196	164	99	57	36
DAEPOCH	179	131	76	37	21	7
CHOP21	96	75	53	30	10	4

DATA SUPPLEMENT

Primary Mediastinal B-cell Lymphoma: A Nationwide Real-Life Retrospective Study

by Iannitto, Donzelli et al. On behalf of Fondazione Italiana Linfomi

- **APPENDIX 1**

  List of Participating Sites and Investigators

Site Name	First/Last name
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Humanitas Research Hospital IRCCS, Unità Operativa di Oncologia Medica ed Ematologia, Rozzano (MI)	Monica Balzarotti Ciro Maria Improta
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Ospedale Businco, Struttura Complessa di Ematologia e Centro Trapianto di Midollo osseo, Cagliari;	Sara Veronica Usai Brunella Mola

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Ospedale San Giuseppe Moscati, Struttura Complessa di Ematologia, Taranto	Patrizio Mazza
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Azienda Ospedaliero Universitaria delle Marche - Università Politecnica delle Marche, Azienda Ospedaliero Universitaria Ospedali Riuniti, Clinica Ematologica, Ancona	Guido Gini
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- **SUPPLEMENTARY METHODS**

We analyzed data from PMBCL patients treated in 37 hematology centers affiliated with FIL. The focus was on adult patients with newly diagnosed PMBCL between January 2007 and December 2019, according to *2008 and/or 2016 WHO classification criteria*. There were no specific exclusion criteria.

The data of eligible patients were pseudo-anonymized and shared in a study-specific database located at the trial office within the Hematology Unit of Garibaldi National and Highly Specialized Hospital in Catania, Sicily, Italy.

A total of 931 PMBCL medical records were retrieved. Patient-level data included age, sex, disease stage, systemic symptoms (B-symptoms: fever ≥38°C, weight loss of ten percent or more over the past 6 months, and night sweats), bulky disease (defined as mediastinal mass ≥10 cm in axial diameter), International Prognostic Index (IPI) score, lactate dehydrogenase (LDH) above normal levels, number of extranodal sites involved, presence of pericardial and pleural effusions, and the Eastern Cooperative Oncology Group (ECOG) performance status (PS). Patients were clinically staged and scored according to the Ann-Arbor staging system. Cases of PMBCL that involved extranodal distant sites were classified as stage IV. However, if the spread of lymphoma was confined to the thoracic areas, such as the chest wall, lungs, pleura, or pericardium, it was classified as infiltration by contiguity, and these patients were recorded as stage I-II.

The primary objective of this study was to analyze treatment strategies, the choice of CIT regimen, and the adoption of consolidative RT and/or ASCT, and to compare the outcomes associated with these different approaches.

Clinical outcomes included the rate of primary-early refractory disease (RD), overall response rate (ORR), complete response rate (CRR), proportion of patients receiving mediastinal RT consolidation, progression-free survival (PFS), and overall survival (OS).

The secondary objectives were to evaluate both acute and long-term toxicity profiles associated with the various treatment strategies.

Baseline characteristics were compared using the Kruskal-Wallis test for continuous variables and the chi-squared test for categorical variables. Time-to-event outcomes, not influenced by competing risks, were estimated using the Kaplan-Meier method and compared using Cox proportional hazards models, which incorporated shared frailty terms to account for clustering by center. Disease-specific mortality was analyzed using cumulative incidence functions estimated with the Gooley method, treating non-lymphoma deaths as competing events. Comparisons were performed using Fine & Gray's model. The impact of RT on PFS was assessed using a 6-month landmark analysis starting from the initiation of first-line CIT and was evaluated only in patients with an available DS at the end of CIT. Multivariable analyses of time-to-event outcomes were conducted using 20 multiple imputed datasets to account for missing covariates. In these models, the effects of composite scores were evaluated without including their component covariates. The incidence of adverse events was compared using random-effects logistic regression models to account for clustering by center.

The R-MACOP-B and R-VACOP-B groups accounted for approximately half of the cohort, and their outcomes were nearly identical and closely comparable to those reported in the literature. Therefore, R-MACOP-B was used as the baseline treatment comparator in the Cox multivariable analysis.

All analyses were done at the Section of Statistics of the Study Management Unit of the FIL Operational Offices, which also contributed to the design. Analyses were performed using STATA version 15 (StataCorp LLC, College Station, TX, USA). Data and statistical analyses were fully available to all authors, who checked their accuracy, completion, integrity, and adhesion to protocol. This trial was registered at ClinicalTrials.gov as #NCT05162170.

- **SUPPLEMENTARY FIGURES AND TABLES**

Figure S1A: Cumulative incidence of lymphoma-related mortality starting from the initiation of first-line treatment. Lymphoma-specific mortality was analyzed using cumulative incidence functions estimated with the *Gooley method*, treating non-lymphoma deaths as competing events. Comparisons were performed using a *Fine & Gray's competing-risks model*.

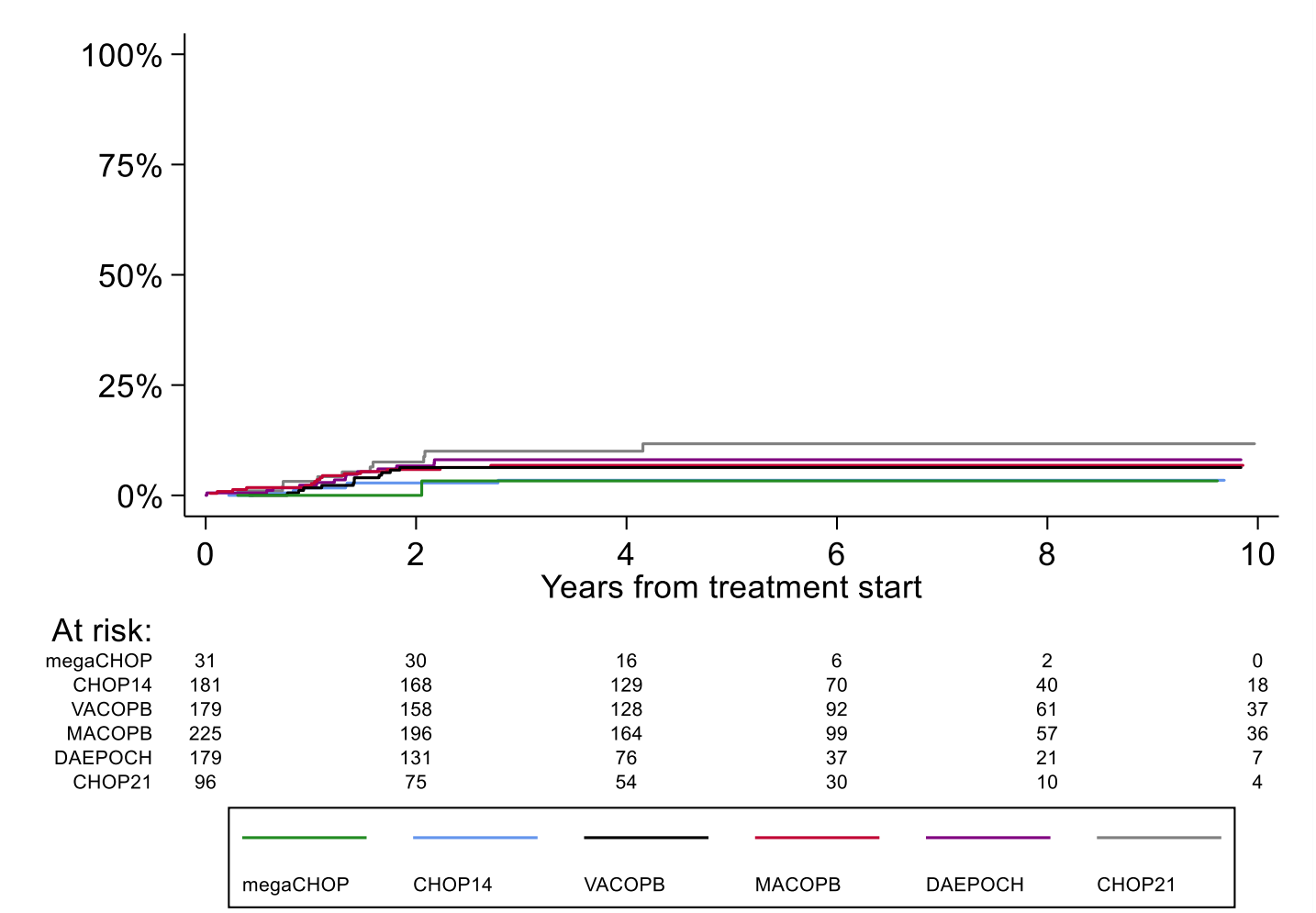
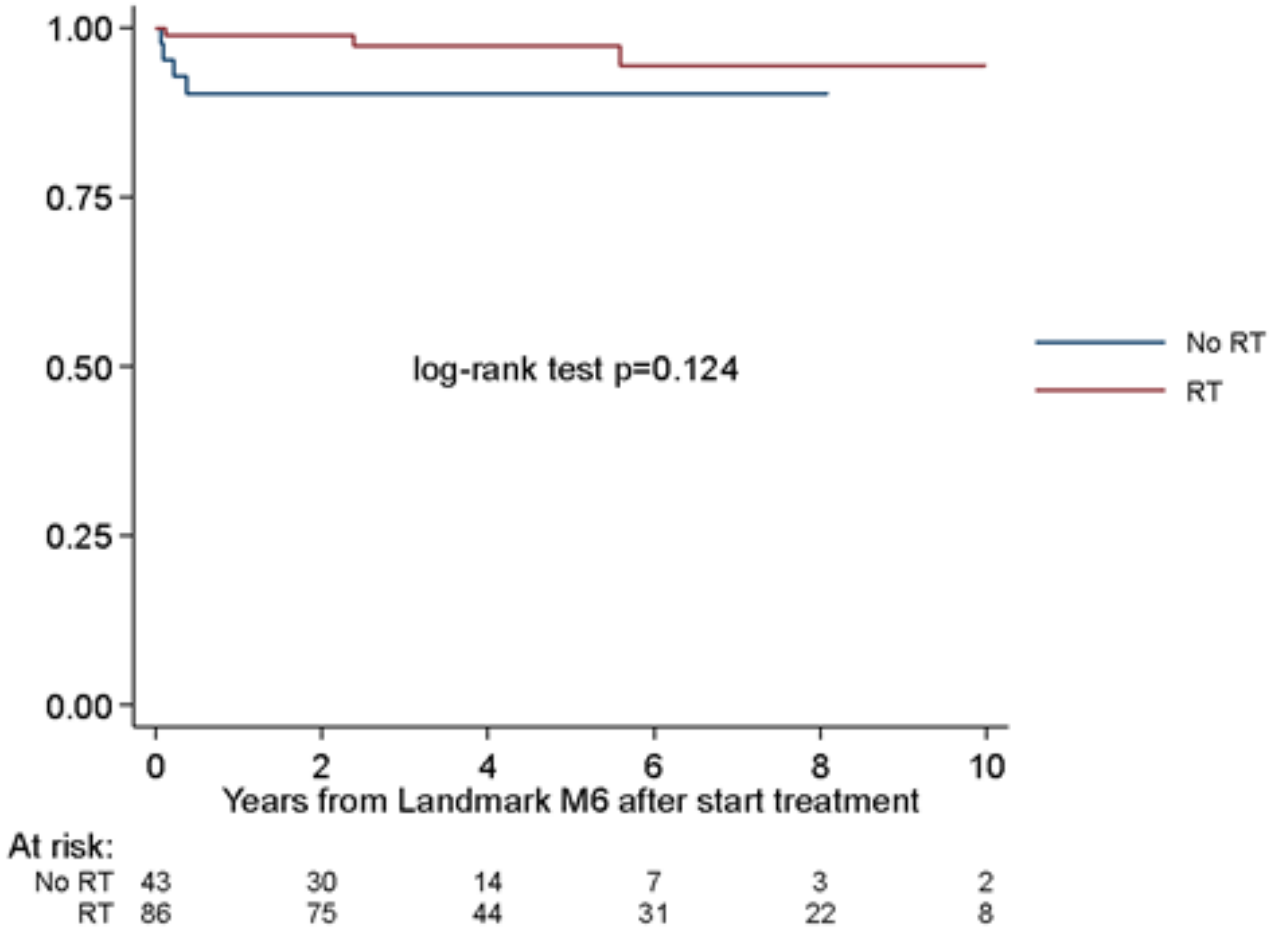


Figure S1B: Treatment and effect of age on cause specific mortality. Lymphoma-specific mortality was analyzed using cumulative incidence functions estimated with the *Gooley method*, treating non-lymphoma deaths as competing events. Comparisons were performed using a *Fine & Gray's competing-risks model*.

	HR per 1-year increase	**95%CI**	**P value**
Lymphoma specific mortality	1.00	0.97,1.02	0.804
Other cause mortality	1.07	1.03,1.11	<0.001

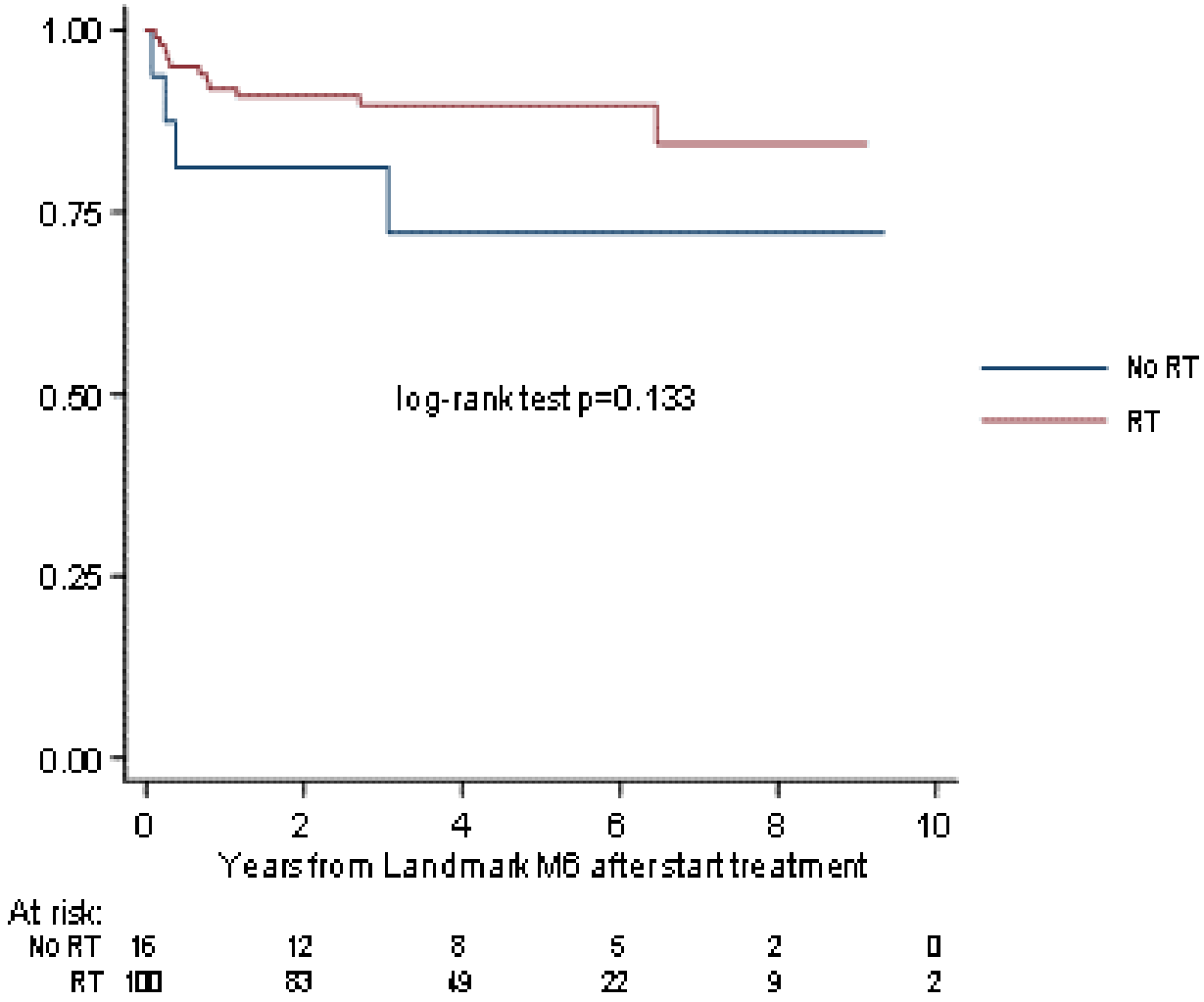
Abbreviations: HR=hazard ratio; 95%CI=95% confidence interval.

Figure S2: Six-month landmark analysis of the impact of radiotherapy on progression-free survival in patients with a Deauville score of 1-3.



Abbreviations: RT=radiotherapy; M6=months 6.

Figure S3: Six-month landmark analysis of the impact of radiotherapy on progression-free survival in patients with a Deauville score of 4.



Abbreviations: RT=radiotherapy; M6=months 6.

Table S1. Univariate and multivariable analyses of prognostic factors associated with progression-free survival.

	HR	95%CI	*P value*
Univariable			
R-CHOP21	2.35	1.30-4.24	.005
R-VACOP-B	1.08	0.58-2.02	.814
R-MACOP-B	1.00	1.00-1.00	.
DA-EPOCH-R	2.00	1.10-3.64	.024
R-CHOP14	0.76	0.39-1.47	.414
R-MegaCHOP	0.37	0.07,1.86	.228
Multivariable			
R-CHOP21	2.05	1.12,3.74	.019
R-VACOP-B	1.01	0.55,1.87	.973
R-MACOP-B (reference)	1.00	.,.	.
DA-EPOCH-R	1.66	0.92,3.01	.092
R-CHOP14	0.72	0.38,1.39	.329
R-MegaCHOP	0.40	0.08,2.00	.267
IPI score (1-point increase)	1.56	1.28-1.89	<.001
Stage III-IV	1.52	1.01-2.29	.042
ECOG PS≥2	1.34	0.89-2.01	.156
Elevated LDH	0.81	0.54-1.19	.280
Extranodal site >1	2.03	1.30-3.18	.002
Extranodal localization			
None (reference)	1.00	1.00,1.00	.
Only thorax	0.77	0.46-1.28	.312
Only extra-thorax	1.31	0.70-2.45	.395
Both	1.53	0.80-2.90	.195
Age, (5-year increase)	1.00	0.93-1.06	.891
Male sex	1.21	0.87-1.68	.265
Systemic symptoms	1.54	1.11-2.15	.011
Bulky mass > 10 cm	1.46	0.94-2.27	.090
Pericardial or pleural effusion	1.22	0.85-1.76	.288

Abbreviations: HR=hazard ratio; IPI=international prognostic index; ECOG PS=Eastern Cooperative Oncology Group performance status; LDH=lactate dehydrogenase.

Table S2. Univariate and multivariable analyses of prognostic factors associated with overall survival

	HR	95%CI	*P value*
Univariable			
R-CHOP21	1.37	0.65,2.87	.410
R-VACOP-B	0.84	0.42,1.68	.621
R-MACOP-B	1.00	1.00,1.00	.
DA-EPOCH-R	1.24	0.64,2.39	.528
R-CHOP14	0.47	0.21,1.07	.073
R-MegaCHOP	0.36	0.05,2.75	.325
Multivariable			
R-CHOP21	0.95	0.44,2.05	.900
R-VACOP-B	0.64	0.32,1.28	.211
R-MACOP-B (reference)	1.00	...	.
DA-EPOCH-R	0.92	0.48,1.78	.810
R-CHOP14	0.41	0.18-0.93	.034
R-MegaCHOP	0.36	0.05-2.67	.315
IPI score (1-point increase)	1.62	1.25-2.12	<.001
Stage III-IV	1.62	0.92-2.85	.096
ECOG PS≥2	1.53	0.90-2.62	.116
Elevated LDH	0.86	0.48-1.53	.605
Extranodal site >1	2.07	1.10-3.87	.023
Extranodal localization			
None (reference)	1.00	.-.	
Only thorax	0.60	0.27-1.31	.200
Only extra-thorax	1.41	0.57-3.45	.459
Both	1.53	0.63-3.75	.349
Age, (5-year increase)	1.06	0.97-1.16	.213
Male sex	1.35	0.85-2.17	.207
Systemic symptoms	1.60	0.99-2.60	.054
Bulky mass > 10 cm	1.97	0.99-3.90	.053
Pericardial and pleural effusion	1.32	0.76-2.29	.318

Abbreviations: HR=hazard ratio; IPI=international prognostic index; ECOG PS=Eastern Cooperative Oncology Group performance status; LDH=lactate dehydrogenase.

Table S3. Distribution of RT overall and DA-EPOCH-R +RT exposure among patients with and without late toxicity.

Event type	Event N	RT with event n (%)	RT with no event n (%)	DAEPOCHR+RT with event n (%)	DAEPOCHR+RT with no event n (%)
Any late event	104	65 (62.5)	375 (69.3)	12 (11.5)	22 (4.1)
Cardiovascular event	54	32 (59.3)	408 (69.0)	9 (16.7)	25 (4.2)
Secondary malignancy	23	16 (69.6)	424 (68.2)	-	34 (5.5)
Other late events	31	21 (67.7)	419 (68.2)	3 (9.7)	31 (5.1)

Patients evaluable for late toxicities n = 625; radiotherapy given n = 440 (68.2%).
RT=radiotherapy.