Management of Primary Mediastinal B cell Lymphoma in the Position-Emission Tomography Era:
American Radium Society™ Appropriate Use Criteria

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Running title: PET-response Management of PMBCL

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ABSTRACT
Primary mediastinal B cell lymphoma is a highly curable subtype of non-Hodgkin lymphoma that is diagnosed predominantly in adolescents and young adults. Consequently, long-term treatment-related morbidity is critical to consider when devising treatment strategies. End-of-chemotherapy positron emission tomography (PET)/computed tomography (CT) scanning has been shown to be a strong prognostic factor for treatment outcomes and, thus, may help determine which patients may benefit from additional therapies (e.g., radiotherapy). When radiotherapy is used, several modern treatment techniques have become available to help minimize the risk of late toxicity, including intensity-modulated radiotherapy, deep-inspiration breath hold, and proton therapy. Herein, we describe those studies on primary mediastinal B cell lymphoma in the relevant PET/CT era and provide evidence-based criteria for treatment of this cohort.

Methodology
An analysis of the medical literature from peer-reviewed journals was conducted on September 9, 2018 to retrieve a comprehensive set of relevant articles. The bibliographies of full articles were reviewed to exclude studies which were not relevant. The literature was reviewed for quality of study design, cohort size, selection bias, evaluation of participants in relation to time from exposure, and methods of assessments. A well-established methodology was used by the expert panel to rate the appropriate use of procedures (1). The multidisciplinary expert panel is composed of radiation, medical, and surgical oncologists, as well as additional members with subject-specific expertise.
Introduction

Primary mediastinal B cell lymphoma (PMBCL) is a unique subtype of non-Hodgkin lymphoma (NHL) that typically affects adolescents and young adults. Progression-free survival (PFS) and overall survival (OS) rates at 5 years have been favorable (80-90% PFS; 90-95% OS) utilizing anthracycline-based systemic therapy with or without radiotherapy; however, late effects from combined modality therapy can compromise quality of life and survival. Consequently, oncologists strive for a delicate balance between maintaining excellent cure rates while minimizing the risks of late treatment toxicity. Approaches include omitting radiation therapy (RT) in exchange for more intensive chemotherapy regimens or based on end-of-chemotherapy (EOC) evaluation with positron emission tomography (PET)/computed tomography (CT) response, or limiting late radiation toxicities by using highly conformal radiotherapy techniques to minimize radiation dose to the organs at risk. This American Radium Society (ARS) Appropriate Use Criteria systematic review provides an evidence-based summary of the literature on patients with PMBCL with EOC PET/CT scans, recommendations for consolidative RT, and expected outcomes.

Epidemiology, Pathology, and Staging

PMBCL comprises 2% of all non-Hodgkin lymphomas diagnosed in the U.S., often classified under diffuse large B cell NHL (DLBCL) and is a distinct entity in the WHO classification (2, 3). The mean age at presentation is in the mid-30’s, with more than 60% of patients presenting under the age of 40 years, and there is a predilection for female sex (4). Furthermore, most patients (80%) present with stage I/II disease (4). Involvement of extranodal sites is commonly observed among patients who have advanced disease or who relapse (3, 5). Patients may present with superior vena cava symptoms, and occasionally have pleural or pericardial effusions.
PMBCL has a unique genetic fingerprint, that differentiates it from germinal center B-cell or activated B-cell subtypes (6). Recent data using the Lymph-cx assay defined a molecular signature distinct from DLBCL (7). PMBCL is often CD30-positive, leading to misclassification as a classic Hodgkin lymphoma (cHL). PMBCL can also be confused with gray zone lymphoma. While treatment approaches are similar between PMBCL and gray zone or composite lymphoma, PMBCL has a superior prognosis than the latter (8).

Work-up for PMBCL resembles that of any other DLBCL and should include a PET/CT scan and diagnostic CT of the neck, chest, abdomen, and pelvis with contrast. Pre-treatment imaging is critical for staging and for radiation treatment planning. To minimize uncertainties when fusing the staging scans with later radiation treatment plans, imaging should be done with the patient’s chin in a neutral position or with arms slightly extended in a comfortable position. Ideally, keeping the arms down for the PET/CT scan and arms above the head for the diagnostic CT allows radiation oncologists to choose the best arm position for the patient.

First-line Treatment Approaches

First-line management of PMBCL includes several options with favorable outcomes. Rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone (R-CHOP) regimen is typically given every 14 or 21 days for 6 cycles followed by RT (9, 10). On the other hand, intensive chemotherapy regimens i.e. dose-adjusted rituximab plus etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin (DA-R-EPOCH) and R-CHOP/R-ICE (ifosfamide, carboplatin, etoposide) are frequently administered without RT (11-13). In recent years, DA-R-EPOCH has emerged as a favored approach in many US centers due to excellent disease control rates (11, 12). While the cumulative doxorubicin dose, if therapy is escalated, is higher with DA-R-EPOCH than with R-CHOP, no increase in cardiac toxicity has been
reported (14). In contrast, DA-R-EPOCH is associated with increased rates of grade 3 and 4 hematologic toxicity and mucositis and is typically delivered in an inpatient setting (9).

Balancing the risk of treatment-related toxicities with excellent disease-specific outcomes is paramount. End-of-chemotherapy (EOC) PET/CT scans are useful in assessing prognosis among patients with cHL and DLBCL using the 5-point Deauville scale (D5PS). While studies differ in defining a partial response or “positive” scan as a minimum Deauville score of 3 versus 4 for cHL, the debate has differed for PMBCL. Studies in PMBCL show that EOC PET/CT response using a Deauville 1-3 as a “negative” scan has a very high negative predictive value following R-CHOP and DA-R-EPOCH. On the other hand, a Deauville 4 following DA-R-EPOCH has a low positive predictive value and these patients often are considered to be in remission and further therapy is withheld with close observation (15). This unique response in PMBCL patients has made developing PET/CT-based treatment algorithms difficult.

Other PET imaging factors may also be predictive for response to treatment. These include total lesion glycolysis (TLG) and metabolic heterogeneity as defined on the baseline PET/CT scan. However, discussion of these parameters is beyond the scope of this article (16).

**PET/CT-guided Therapy**

Nine studies have investigated outcomes in patients with PMBCL in relation to the EOC PET/CT scan response using the D5PS. The studies, described in detail below and in Table 1, include prospective clinical trials and single- and multi-institutional retrospective studies wherein patients were treated with DA-R-EPOCH +/- RT (n=3), R-CHOP +/- RT (n=1), or multiagent chemotherapy regimens (n=5) including DA-R-EPOCH, R-CHOP, R-MACOPB (methotrexate, leucovorin, doxorubicin, cyclophosphamide, vincristine, prednisone, and bleomycin), R-VACOPB (etoposide, leucovorin, doxorubicin, cyclophosphamide, vincristine, prednisone, bleomycin), R-HCVAD (rituximab-cyclophosphamide, vincristine, dexamethasone, and doxorubicin) +/- RT, and R-CHOP/R-ICE.
**Clinical Condition 1: Do patients with EOC PET/CT-determined Deauville 1-3 require consolidation RT?**

Based on the outcomes published from three studies including a phase II prospective clinical trial and three retrospective studies with a cumulative 189 patients with PMBCL receiving DA-R-EPOCH (only 12 receiving RT), an EOC PET/CT D1-3 predicted excellent outcomes. Only 5 patients relapsed leading to negative predictive value (NPV) of 96-100%, regardless of the addition of RT (15, 17, 18). These data suggest that RT can be safely omitted from DA-R-EPOCH when patients have an EOC PET/CT response of D1-3.

While several studies have evaluated rituximab + less-intensive chemotherapy (not DA-R-EPOCH), the majority of patients received RT regardless of EOC PET response. Vassilakopoulos et al reported on 75 patients with an EOC PET/CT of D1-3 following R-CHOP and compared outcomes between those who received RT (n=42) with those who did not (n=33) (19). All 3 relapses occurred in patients not receiving RT, yielding a 3-year EFS rate of 92% versus 100% for those treated without versus with RT, respectively.

Among 143 patients from 4 studies in which patients received consolidative RT following R-chemotherapy (non-DA-R-EPOCH) and had an EOC D1-3, only 1 patient relapsed. Taken together these studies demonstrate a NPV of D1-3 EOC PET/CT of 94-100% following R-chemotherapy (excluding DA-R-EPOCH) followed by consolidative RT, while the NPV appears somewhat lower at 83-93% following R-chemotherapy alone (excluding DA-R-EPOCH). Based on the limited published data on omitting RT for R-chemotherapy (not DA-R-EPOCH), RT should be considered for consolidative therapy even when the EOC PET/CT demonstrates a D1-3. The IELSG37 (NCT01599559) study, which evaluated rituximab-anthracycline containing chemotherapy regimens (investigator choice) followed by randomization to no further treatment versus 30 Gy of RT in patients with a D1-3 on EOC PET/CT unfortunately closed early due to fewer events than anticipated among the patients with a D1-3 response on both arms.
Clinical Condition 2: Do patients with PMBCL with an EOC of Deauville 4 require consolidative RT?

From the studies including patients receiving DA-R-EPOCH, 50 patients had an EOC PET/CT D4 response and 9 patients relapsed. While the rate of recurrence was higher than what was observed for EOC D1-3, the overall recurrence rate was reasonably low despite the majority of patients not receiving any further therapy. This finding suggests that EOC D4 may be due to a post chemotherapy inflammatory response, leading to a high false positive rate. Controversy exists as to the appropriate management of patients treated with DA-R-EPOCH who have an EOC D4 PET response. While some investigators recommend consolidative RT due to the higher incidence of relapse compared with D1-3 patients, others suggest a more conservative approach of continued PET/CT surveillance or biopsy before adding further treatment (20).

In contrast, there is more agreement on giving consolidative RT for patients receiving standard R-chemotherapy with EOC D4 due to the lack of published data on the outcome for these patients if RT is omitted. Among 72 patients from the studies reviewed with an EOC D4 after R-chemotherapy followed by RT, 13 patients relapsed. No prospective clinical trial in PMBCL is currently investigating omission of RT among patients with an EOC PET/CT D4 response. In the IELSG37 study, these patients all receive RT.

Clinical Condition 3: Do patients with PMBCL with an EOC Deauville 5 respond well to RT?

Patients with an EOC D5 response are a heterogenous group that can include those with a partial or stable response to chemotherapy or those with progressive disease. In the Melani study, all 4 patients with an EOC D5 response to DA-R-EPOCH with no radiotherapy developed a relapse by biopsy (n=2) or imaging (n=2). Two of these relapses were salvaged with radiotherapy, while two other patients died of progressive disease 7 and 17 months after multiple salvage regimens (15). In the Giulino-Roth study, 14 patients had an EOC D5 response after DA-R-EPOCH and 9 patients relapsed (17). It is not clear how many of these patients received RT. In a study by Pinnix et al, of 65 patients treated with DA-R-EPOCH at
MD Anderson Cancer Center (n=49) and Dana Farber Cancer Institute (n=16), 9 patients had an EOC D5 response and 7 of these patients experienced disease relapse. Most patients in this study with relapsed and refractory PMBCL received RT as part of salvage therapy but the number that were salvaged with RT alone was not reported (21). At present, there are insufficient data to determine the response to RT following a D5 EOC response to DA-R-EPOCH.

Vassilakopoulos et al. (19) reported on 15 patients with D5 disease following R-CHOP. Three patients were suspected to have progressive disease and treated with aggressive second-line therapy, while 12 were treated with consolidative RT. Among these 12 patients treated with RT, 5 relapsed. In the Filippi study, 6 patients with a D5 following R-chemotherapy went on to receive RT and 5 developed a relapse (22) with an in-field component in all 5 patients. In a retrospective study reporting on outcomes after immunochemotherapy by Pinnix et al, 1 patient treated with R-CHOP and 1 treated with R-HCVAD had EOC PET/CT D5 responses, and were treated with RT and ASCT for suspicion of progressive disease; both patients achieved a remission (18). Finally, Martelli analyzed 10 patients with a D5 response after R-chemo among whom 4 were treated with further chemotherapy and ASCT for suspicion of disease progression, while the remaining 6 patients received RT (23). Among the 6 patients who received RT, 2 developed a relapse.

The most appropriate regimen for a patient with D5 response depends, in part, on whether the disease appears to be stable or progressing. RT, second-line chemotherapy, checkpoint inhibitors, and/or high-dose chemotherapy and transplant may all be appropriate considerations.

**Clinical Condition 4: Relapsed and refractory disease**

Patients with relapsed or refractory disease to first line therapy have a much worse prognosis. Among six patients with relapsed or refractory disease following R-chemotherapy and salvage RT, five of the patients died of their disease after receiving aggressive second-line therapy (22). Relapses generally
occur within 12 months of completing first line therapy. Patterns of relapse are not always clearly described among the different studies. However, the data available suggest that local relapses within the mediastinum are a common site of relapse (13, 18, 19, 22). When distant relapses occur, these are often found within the central nervous system (13, 19, 24).

No standard approach exists for managing patients with relapsed or refractory disease. RT alone can be effective among some patients with biopsy confirmed refractory disease that has not progressed by PET or CT to first line chemotherapy. However, in most situations treatment utilizes second-line chemotherapy regimens followed by autologous stem cell transplantation. Outcomes with the latter are particularly poor for patients with disease that is refractory to DA-REPOCH, and alternative approaches such as radiotherapy and novel agents should be considered in this population. Outcomes also depend on the stage and disease status at relapse (25).

Salvage therapy frequently includes RT, if it was not previously administered and may improve outcomes in patients with a partial response (26). There are data, however, that suggest that RT alone may be inadequate. In the study by Filippi et al, among the 5 patients with 5PS of 5 after immunochemotherapy treated with salvage RT to doses of 36-44 Gy, all 5 patients eventually progressed after RT either exclusively in the RT field (n=1) or in and out of field (n=4) at a median of 4 months from the end of RT (range, 2-6 months) (22). More recently, novel treatments have been approved by regulatory agencies, including the PD-1 inhibitor pembrolizumab and chimeric antigen receptor T (CAR T) cell therapy (27, 28) for patients not responding to second line chemotherapy. Although PMBCL frequently express CD30, the anti-CD30 antibody drug conjugate brentuximab vedotin is less effective compared with classical Hodgkin lymphoma, with response rates of only 15-17% (29, 30).

**Treatment-related Late Effects**
Doxorubicin has both acute and late cardiotoxicities, and an increase in dose is correlated with an increased risk of cardiac disease (31). After 20 years of follow-up, investigators of SWOG 8736 reported a 5-fold increase in deaths caused by congestive heart failure or myocardial infarction with a doxorubicin dose of 400 mg/m2 compared to patients receiving 150 mg/m2 doxorubicin with RT (10 events versus 2 events) (32). In the Childhood Cancer Survivor Study (CCSS), any anthracycline dose (>1 mg/m2) led to an increased risk of any cardiac disease, with doses >250 mg/m2 associated with an 8.4% 30-year cumulative risk (33, 34). Cardiotoxicity may also occur after mediastinal RT. In the same CCSS study, increasing mean radiation dose to the heart also was associated with cardiac disease, including a statistically significant increase in risk at mean heart doses of >10 Gy (30-year cumulative risk, 5.4% for 10-20 Gy), while mean heart doses of 20-30 Gy had a 30-year cumulative incidence of cardiac disease of 7.7%. (35).

Another concerning late effect in young patients receiving RT are second cancers. A recent report analyzed second cancers among 90 patients with PMBCL treated with involved-field radiotherapy with a median follow-up of >10 years showed only 2 patients developed a second cancer, both of which were thyroid cancers that were successfully resected (36); however, data from mediastinal Hodgkin lymphoma survivors have demonstrated increased incidences of breast cancer, lung cancer, thyroid cancer, and soft-tissue and bone sarcomas (37).

**Special Technical Considerations**

*Radiotherapy*

When RT is recommended, best practices should be considered to minimize the radiation dose to the organs at risk (OARs) while maintaining appropriate target coverage. The radiation simulation process should ideally reproduce the patient’s positioning from the initial staging scans prior to starting
chemotherapy. Motion management strategies should be considered prior to simulation. Depending on the planned radiation technique and the initial disease distribution, deep-inspiration breath hold technique may help reduce the radiation dose to the heart and lungs for patients with superior mediastinal disease. Alternatively, gating or planning with a 4-dimensional CT scan with an added margin for the internal target volume (ITV) can be performed. Planning target volume (PTV) margins will depend on the use of immobilization devices and image-guided RT (IGRT). Daily IGRT is encouraged to minimize the required PTV margin to 5 to 8 mm. Involved-site RT (ISRT) treatment volumes are guided by the International Lymphoma Radiation Oncology Group guidelines, although substantial variations in interpretation exist with ISRT (38-40). Given these variations, the radiation oncologist developing the radiation treatment plan should be knowledgeable and experienced in ISRT field design. Patients with stage I/II disease should receive radiation to all sites of initial involvement. Patients with stage III/IV disease receiving full-dose chemotherapy should receive RT to the primary bulky mediastinal mass and any incompletely responding sites based on EOC PET/CT scan, with additional sites considered depending on treatment response and toxicity profile.

In general, when using RT for consolidation for PMBCL patients that achieve a complete response on the EOC PET/CT (5PS of 1-3), the standard dose is 30 to 36 Gy at 1.5 to 2 Gy per fraction. While clinical data do not support the need for higher doses, in cases of partial response (Deauville 4-5) following chemotherapy, additional doses delivered through reduced fields (to residual disease only) should be considered for a total dose of 40 to 50 Gy (41).

RT should be delivered using radiation techniques that best spare the OARs, including the heart, lungs, and breasts (in women and girls), with additional consideration given to the esophagus, thyroid, and total body dose. Patients with superior mediastinal disease only, lying completely above the level of the heart, may be treated with 3-dimensional conformal RT or intensity-modulated RT (IMRT) using fixed
anterior-posterior/posterior-anterior field arrangements since the heart should be outside of the radiation field and the beam arrangement should minimize the breast dose in women. When IMRT or VMAT is used, optimized beam arrangements should be considered, including the butterfly technique, to minimize low-dose exposure to the breast and lungs (42, 43). For patients with lower mediastinal disease, proton therapy may better spare the heart and other OARs (44-46). When advanced forms of radiotherapy are available, the treatment modality that best spares the OARs should be considered. Even small dose differences of 2-3 Gy to the heart, breast, or lung may have significant impact on survivors 30 years following treatment (47).

Radiotherapy Plan Evaluation

When evaluating a radiation treatment plan, coverage of the ITV (internal target volume) or for breath hold non-moving targets, CTV (clinical target volume) and PTV (planning target volume) should be considered in the context of both the potential increased dose to the adjacent OARs as well as the potential benefit of radiation. For patients who demonstrate an excellent response to chemotherapy (Deauville 1-3), coverage of the target volume can be compromised to reduce radiation exposure to the OARs [32]. Conversely, patients with an incomplete response to chemotherapy (Deauville 4 or 5) may require less strict dose constraints in order to obtain appropriate target coverage. Table 2 provides the dosimetric criteria that should be considered when evaluating the treatment plan. For all OARs, the lowest dose achievable is preferred; therefore, dosimetrists, physicists, and physicians should not abandon plan optimization once OARs are within an acceptable range. Rather, plans should be pushed to achieve the goal doses. For patients who have responded poorly to systemic therapy and have limited treatment options available, exceeding the OAR dose constraint may be appropriate to maximize the likelihood of disease control.
**Summary of Recommendations**

1) The committee strongly recommends 6 cycles of DA-R-EPOCH or R-CHOP as usually appropriate systemic therapy for patients with PMBCL.

2) For a Deauville 1-3 response at the end of chemotherapy, the panel strongly recommends no further treatment as usually appropriate after DA-R-EPOCH, and strongly recommends ISRT to 30 Gy using IMRT or proton therapy as usually appropriate after R-CHOP.

3) For a Deauville 4 response at the end of chemotherapy, the panel strongly recommends a short interval PET/CT as usually appropriate after DA-R-EPOCH, and strongly recommends ISRT to 36-40 Gy as usually appropriate after R-CHOP.

4) For a Deauville 5 response at the end of chemotherapy, the panel strongly recommends a biopsy as usually appropriate after either R-CHOP or DA-R-EPOCH. If the biopsy is negative for disease, ISRT may be appropriate; if given, the panel strongly recommends a dose of 40-50 Gy. Alternatively, a short-interval PET-CT scan may be appropriate after DA-R-EPOCH. If the biopsy is positive for disease, the panel strongly recommends ISRT if the disease can be encompassed in a tolerable field, followed by HDC/ASCT if disease has responded favorably. The panel conditionally recommends that alternative regimens, including CAR T cell therapy or checkpoint inhibitors, may be appropriate. The panel strongly recommends that Brentuximab Vedotin monotherapy is usually not appropriate.

**Summary of Evidence**

A pubmed search was conducted on September 5, 2018, to identify articles on the management of PMBCL during the PET era. In total, 50 papers were identified with the search “primary mediastinal[title] and PET” and the resulting abstracts were reviewed. Abstracts were excluded for the following reasons: other mediastinal cancer (n=6), review article (n=11), letters regarding a study (n=7), case report (n=2), no clinical outcomes (n=2), evaluated baseline PET (N=2), interim PET only (n=3), PET
in follow-up (n=1), and PET glycolysis (n=1), leaving 13 abstracts selected for further review in full manuscript format. Among these 13 articles, 6 were excluded because the investigators did not evaluate disease by Deauville score, and 1 was excluded as an earlier version of a more recent study, leaving 6 single or multicenter retrospective studies that reported outcomes by the 5-point Deauville score and 2 prospective multicenter clinical trials.
**Clinical Condition:** Management of Primary Mediastinal B cell Lymphoma in the PET Era
ARS Appropriate Use Criteria

**Variant 1:** Young adult female with stage IIA bulky PMBCL

<table>
<thead>
<tr>
<th>Frontline Chemotherapy Option (Prior to Response Assessment)</th>
<th>Rating Category</th>
<th>Final Tabulations</th>
<th>Group Median Rating</th>
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<th>Reference</th>
<th>SQ</th>
<th>SOE</th>
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<td>1 7 6</td>
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<td>2 3</td>
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<tr>
<td>R-CHOP x 6</td>
<td>A</td>
<td>1 10 2</td>
<td>7</td>
<td></td>
<td>Martelli Vasilokopolous</td>
<td>2 3</td>
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<tr>
<td>R-CHOP x 4</td>
<td>U</td>
<td>9 2</td>
<td>3</td>
<td></td>
<td></td>
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<tr>
<td>RVACOP-B x 12 weeks</td>
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<td>2 1 7 3</td>
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<td>2</td>
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Rating: A-Usually appropriate; M-May be appropriate; U-Usually not appropriate

* Disagreement, i.e., the variation of the individual ratings from the median rating indicates panel disagreement on the final recommendation (see narrative text). Group median rating is set automatically to 5.

Strength of Evidence: S-Strong; M-Moderate; L-Limited; EC-Expert consensus; EO-Expert opinion

Strength of Recommendation: ↑ Strong Recommendation; ↓ Weak Recommendation; - Additional considerations do not strengthen or weaken the panel’s recommendation
**Variant 2:** Following 6 cycles of rituximab + chemotherapy, she undergoes a PET/CT scan showing a Deauville 3 response

<table>
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<tr>
<th>Chemotherapy Regimen</th>
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<th>Final Tabulations</th>
<th>Group Median Rating</th>
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<td>Roth</td>
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<td>6 5</td>
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<tr>
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<td>M*</td>
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<td>If ISRT is given then</td>
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<tr>
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</table>

If ISRT is given then

| 3D-CRT | M | 1 1 4 5 1 1 | 5 | - |
| IMRT/VMAT | A | 1 4 7 | 8 | ↑ |
| Proton therapy | A | 1 2 8 1 1 | 7 | ↑ |

**Rating:** A-Usually appropriate; M-May be appropriate; U-Usually not appropriate

* Disagreement, i.e., the variation of the individual ratings from the median rating indicates panel disagreement on the final recommendation (see narrative text). Group median rating is set automatically to 5.

**Strength of Evidence:** S-Strong; M-Moderate; L-Limited; EC-Expert consensus; EO-Expert opinion

**Strength of Recommendation:** ↑ Strong Recommendation; ↓ Weak Recommendation; - Additional considerations do not strengthen or weaken the panel’s recommendation
### Variant 3:
Following 6 cycles of rituximab + chemotherapy, she undergoes a PET/CT scan showing a Deauville 4 response

<table>
<thead>
<tr>
<th>Chemotherapy Regimen</th>
<th>Rating Category</th>
<th>Final Tabulations</th>
<th>Group Median Rating</th>
<th>Disagree</th>
<th>Reference</th>
<th>SQ</th>
<th>SOE</th>
<th>SOR</th>
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<tbody>
<tr>
<td>If chemo given was DA-R-EPOCH</td>
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<tr>
<td>Repeat short-interval PET/CT?</td>
<td>A</td>
<td>2 10 1</td>
<td>7</td>
<td>Melani Roth</td>
<td>3 4 Expert Opinion</td>
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<td>Biopsy?</td>
<td>M</td>
<td>2 3 4 4</td>
<td>5</td>
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<td>-</td>
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<tr>
<td>ISRT</td>
<td>M</td>
<td>1 4 4 2 2</td>
<td>5</td>
<td>Pinnix Roth</td>
<td>3 3 Limited Limited</td>
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<td>If chemo given was R-CHOP or other</td>
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<tr>
<td>Repeat short-interval PET/CT?</td>
<td>M</td>
<td>1 1 4 3 4 1</td>
<td>5</td>
<td>None</td>
<td>N/A</td>
<td>-</td>
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<tr>
<td>Biopsy?</td>
<td>M</td>
<td>5 6 2</td>
<td>6</td>
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<td>N/A</td>
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<tr>
<td>No further treatment</td>
<td>U</td>
<td>3 4 4 3</td>
<td>2.5</td>
<td>None</td>
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<td>ISRT</td>
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<td>8</td>
<td>Martelli Fillipi Vasilokopolos</td>
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<td>If ISRT is given then</td>
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<td>ISRT 30 Gy</td>
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<td>ISRT 40-50 Gy</td>
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</table>

**Rating:** A-Usually appropriate; M-May be appropriate; U-Usually not appropriate

* Disagreement, i.e., the variation of the individual ratings from the median rating indicates panel disagreement on the final recommendation (see narrative text). Group median rating is set automatically to 5.

**Strength of Evidence:** S-Strong; M-Moderate; L-Limited; EC-Expert consensus; EO-Expert opinion

**Strength of Recommendation:** ↑ Strong Recommendation; ↓ Weak Recommendation; - Additional considerations do not strengthen or weaken the panel’s recommendation

* If biopsy performed and positive, then see variant 5
**Variant 4:** Following 6 cycles of chemotherapy, she undergoes a PET/CT scan showing partial response with reduction in tumor size but residual Deauville 5

<table>
<thead>
<tr>
<th>Chemotherapy Regimen</th>
<th>Rating Category</th>
<th>Final Tabulations</th>
<th>Group Median Rating</th>
<th>Disagree</th>
<th>Reference</th>
<th>SQ</th>
<th>SOE</th>
<th>SOR</th>
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<tr>
<td>If chemo given was DA-R-EPOCH</td>
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<tr>
<td>Repeat short-interval PET/CT?</td>
<td>M</td>
<td>1 2 2 6 2 1</td>
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<td>Biopsy?</td>
<td>A</td>
<td>2 6 5 1 7</td>
<td>Melani 3</td>
<td>Expert Consensus</td>
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<td>U</td>
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<td>↑</td>
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<td>ISRT</td>
<td>M*</td>
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<td>5*</td>
<td>X</td>
<td>Roth Pinnix 4</td>
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<td>If chemo given was R-CHOP or other</td>
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<tr>
<td>Repeat short-interval PET/CT?</td>
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<td>5*</td>
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<td>M*</td>
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<td>If ISRT is given then</td>
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<td>ISRT 30 Gy</td>
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<td>ISRT 36-40 Gy</td>
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<tr>
<td>ISRT 40-50 Gy</td>
<td>A</td>
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<td>Filipi 3</td>
<td>Expert Consensus</td>
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</tbody>
</table>

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Strength of Recommendation: ↑ Strong Recommendation; ↓ Weak Recommendation; - Additional considerations do not strengthen or weaken the panel’s recommendation

* If biopsy performed and positive, then see variant 5
Variant 5: Following 3 cycles of DA-R-EPOCH the patient has a Deauville 4 response and after 6 cycles, she undergoes a PET/CT scan showing increase in mediastinal tumor size and Deauville 5 (primary refractory disease) but no other systemic disease

<table>
<thead>
<tr>
<th>Treatment Approach</th>
<th>Rating Category</th>
<th>Final Tabulations</th>
<th>Group Median Rating</th>
<th>Disagree</th>
<th>Reference</th>
<th>SQ</th>
<th>SOE</th>
<th>SOR</th>
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<tr>
<td>Biopsy</td>
<td>A</td>
<td>2 1 3 3 5 8</td>
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<td>ISRT alone</td>
<td>M*</td>
<td>4 6 1 1</td>
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<td>Melani</td>
<td>4</td>
<td>Expert Opinion ↑</td>
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<tr>
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<td>5*</td>
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<td>Salvage chemo, if response then HDC/ASCT + ISRT</td>
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<td>6 7</td>
<td>5</td>
<td>Pinnix Melani</td>
<td>4</td>
<td>Expert Opinion ↑</td>
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<tr>
<td>ISRT, if response then HDC/ASCT</td>
<td>A</td>
<td>8 5 7</td>
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<td>Expert Opinion -</td>
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<td>CAR T Cell</td>
<td>M</td>
<td>1 10 1</td>
<td>6</td>
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<td>Checkpoint Inhibitor</td>
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<td>1 5 5 2 1 6</td>
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<td>Brentuximab Vedotin alone</td>
<td>U</td>
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<td>2</td>
<td>Zinzani</td>
<td>Expert Opinion -</td>
<td></td>
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</tr>
</tbody>
</table>

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Strength of Recommendation: ↑ Strong Recommendation; ↓ Weak Recommendation; - Additional considerations do not strengthen or weaken the panel’s recommendation

Please refer to the supporting documentation for a more complete discussion of the concepts and their definitions below.

Rating Categories: U-Usually not appropriate; M-May be appropriate; A-Usually appropriate

Final Tabulations: A histogram of the number of panel members who rated the recommendation as noted in the column heading (ie, 1, 2, 3, ... etc.)

Disagree: The variation of the individual ratings from the median rating indicates panel disagreement on the final recommendation.

References: Lists the references associated with the recommendation.

SQ: Study Quality (1, 2, 3, or 4) of the references listed

SOE: S-Strong; M-Moderate; L-Limited; EC-Expert consensus; EO-Expert opinion

SOR: ↑ Strong Recommendation; ↓ Weak Recommendation; - Not strong, not weak
References


23. Martelli M, Ceriani L, Zucca E, et al. [18F]fluorodeoxyglucose positron emission tomography predicts survival after chemoimmunotherapy for primary mediastinal large B-cell lymphoma:


