Radiation therapy has an essential role for certain patients with DLBCL. It is hoped that ongoing and future trials will identify the patients who will benefit from this treatment and those for whom it is unnecessary.

Dr. Kelsey and colleagues have done an admirable job in their review of radiation therapy for patients with diffuse large B-cell lymphoma (DLBCL). There are certain situations in which the role of radiation therapy in the management of these patients is defined. For example, in patients with testicular lymphoma, prophylactic radiation to the contralateral testis decreases the risk of relapse and appears to improve survival.[1,2] Radiotherapy is often used when DLBCL occurs at other extranodal sites, such as the eye, sinus, and skin.

Nevertheless, indications for the use of radiation therapy in the majority of DLBCL patients are not well defined, and there are situations in which radiotherapy is not necessary. As noted by Dr. Kelsey and his coauthors, much of our knowledge predates the use of rituximab and functional imaging with fluorodeoxyglucose (FDG)-positron emission tomography (PET). Furthermore, there were major differences in the way radiotherapy was utilized in the prospective trials that evaluated the use of rituximab in DLBCL. For example, French and US Intergroup trials comparing CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) with R-CHOP (rituximab plus cyclophosphamide, doxorubicin, vincristine, prednisone) prohibited the use of radiation therapy following chemotherapy.[3,4] In contrast, radiation to initial sites of bulky disease or extranodal disease was part of the treatment plan in trials conducted by the MabThera International Trial (MInT) Group and the German High-Grade non-Hodgkin Lymphoma Study Group (DSHNHL).[5,6]

The use of radiation therapy for DLBCL has been best studied in patients with stage I and stage II disease. Results from randomized trials and treatment recommendations are presented in the article by Kelsey and colleagues. It is important to recognize that not all patients with stage I-II disease are the same, as indicated by the different terms used to describe this population—for example, “limited stage,” “early-stage,” “low-stage,” and “localized.”[7] Stage I-II patients can be separated into different groups on the basis of prognostic factors such as age, performance status, lactate dehydrogenase level, and tumor bulk (which has no standard definition). A stage-modified International Prognostic Index (IPI) has been proposed in which the presence of stage II or IIE disease replaces the stage III-IV risk factor in the IPI.[7] Patients with stage I disease, non-bulky tumors, and a performance status of 0 or 1 have an extremely good prognosis. These patients constitute approximately 30% of those with stage I-II DLBCL, and the 5-year overall survival for such patients was 94% following three cycles of CHOP with involved-field radiotherapy.[8] In the MInT trial, the 3-year event-free survival was 97%, and the 3-year overall survival was 100% after six cycles of R-CHOP without radiotherapy in a similar population of DLBCL patients with an age-adjusted IPI score of 0 and no bulky disease.[5] This population has an extremely good prognosis and does not require radiation. These results provide the rationale for the DSHNHL phase III FLYER study that is testing whether four cycles of CHOP with rituximab are equivalent to six cycles of R-CHOP for this “very favorable” subgroup.

Functional imaging is likely to play a larger role in the management of patients with low-stage DLBCL. The use of PET scanning allows for response-adapted therapy and individualized treatment that may eliminate the need for additional radiotherapy. Investigators from British Columbia have reported results of a standardized treatment approach for patients with non-bulky (smaller than 10 cm) stage I-II DLBCL.[9] Patients who were PET-negative after three cycles of R-CHOP received one additional cycle of R-CHOP and no radiation. The 2-year progression-free survival and overall survival were 97%. A similar approach for patients with stage I-II non-bulky (smaller than 7 cm) DLBCL and an IPI score of 0 is being tested in the phase III Groupe Ouest d’tude des Leucmies et Autre Maladies du Sang (GOELAMS) 02 03 protocol. In this trial, patients with a negative PET scan following four
cycles of R-CHOP-14 are randomly assigned to either radiation therapy or observation. A DSHNHL trial provides additional information regarding the value of radiation in elderly patients with DLBCL. Patients in this prospective study received six cycles of R-CHOP-14, but without additional radiotherapy. Results were compared to those in patients in the RICOVER-60 trial who received the same chemotherapy along with radiotherapy to sites of extranodal disease or bulk (7.5 cm or larger). The 18-month event-free survival for patients with bulky disease who did not receive radiotherapy was 43%, as compared with 68% for patients in the RICOVER-60 trial who received radiation ($P = .002$). However, patients with bulky disease who achieved a complete remission following chemotherapy did equally well in both trials, with 18-month event-free survival rates of 86% and 84%, respectively ($P = .512$). Although functional imaging was not used in these trials, the results suggest that post-treatment PET scans might identify patients who do not require additional radiotherapy.

It is also useful to discuss the role of radiotherapy in patients who achieve partial remission following chemotherapy. Data from the DSHNHL trial, and retrospective data from Duke University in the article by Kelsey and colleagues, provide evidence that radiotherapy may improve the outcome of patients with an incomplete response or positive PET scan following primary chemotherapy. However, the survival of these patients is still worse than that of patients in complete remission after chemotherapy who did not require additional radiation. A retrospective analysis from Emory University identified 19 patients with non-Hodgkin lymphoma treated with radiotherapy because of a positive PET scan following initial chemotherapy. Twelve patients (63.2%) still relapsed, including 7 (58.3%) who relapsed in the radiation field. We recommend an attempt to biopsy residual PET-avid masses following primary chemotherapy for DLBCL. If residual disease is present, radiotherapy alone may not be sufficient. These patients may require more aggressive treatment, such as high-dose therapy in addition to radiotherapy.

Radiation therapy has an essential role for certain patients with DLBCL. It is hoped that ongoing and future trials will identify the patients who will benefit from this treatment and those for whom it is unnecessary.

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