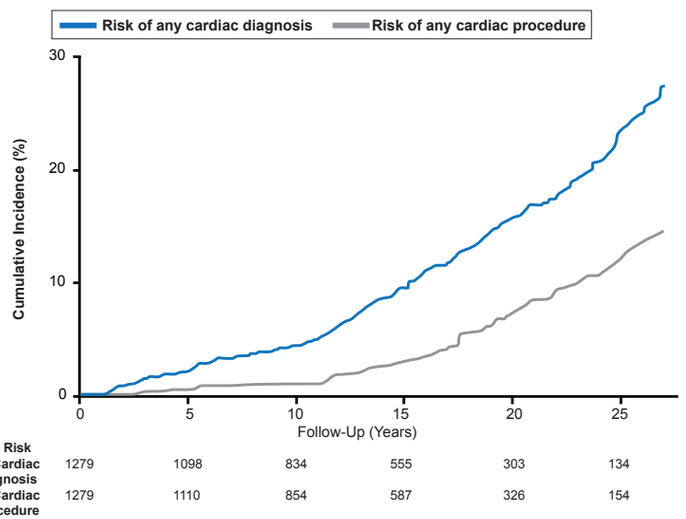
Chemotherapy, Radiotherapy, PET and Maintenance Therapy for Lymphoma

Written by **Maria Vinall**

Nancy Bartlett, MD, Washington University, St Louis, Missouri, USA, questioned the role of radiotherapy (RT) for the treatment of Hodgkin lymphoma. Currently, there is no uniform prognostic factor index to evaluate RT outcomes versus chemotherapy, while the evaluation of late effects of RT can be delayed by 10 to 30 years. Swerdlow et al. [*J Clin Oncol* 2012] showed that among young women with Hodgkin lymphoma receiving ≥40 Gy mantle radiotherapy, the 40-year follow-up cumulative risk of breast cancer was 48%. Although more likely to be diagnosed at an earlier stage, these women are at a greater risk for bilateral disease. They are more likely to die as a result of causes other than breast cancer, however [Elkin EB et al. *J Clin Oncol* 2011]. Hodgkin lymphoma patients receiving mediastinal radiotherapy are also at a greater risk of cardiac disease (Figure 1) [Galper SL et al. *Blood* 2011]. Younger age at diagnoses was associated with more risk.

Figure 1. Cumulative Incidence of Cardiac Disease in Patients Treated for Hodgkin Lymphoma With Radiotherapy



Reproduced from Galper SL et al. Clinically significant cardiac disease in patients with Hodgkin lymphoma treated with mediastinal irradiation. *Blood* January 13, 2011;117(2):412-418. With permission from the American Society of Hematology.

Peer-Reviewed Highlights From the

American Society of Clinical Oncology 2013 Annual Meeting

May 31–June 4
Chicago, Illinois, USA

Although chemotherapy plus radiation is effective in controlling stage I or II non-bulky Hodgkin lymphoma in 90% of patients, its use is associated with late treatment-related deaths. Chemotherapy alone may improve overall survival (OS) because it is associated with fewer deaths from other causes [Meyer RM et al. *N Engl J Med* 2012].

According to Dr. Bartlett, there is no safe dose of RT and, as most patients with stage I or II Hodgkin lymphoma have mediastinal nodes, it is not possible to eliminate radiation to the heart and breasts completely. However, lower doses and the use of involved field radiotherapy (IFRT) may result in fewer late effects and improved OS.

Interim positron emission tomography (PET) may have predictive value for determining who should receive RT. The Randomized Trial of Accelerated Partial Breast Irradiation trial [RAPID; NCT00282035; Radford J et al. ASH 2012 (abstr 547)] showed that patients who were PET-negative following abbreviated chemotherapy and subsequently received IFRT had a 3-year progression-free

survival (PFS) of 93.8% and OS of 97.0% versus 90.7% PFS and 99.5% OS for those who received no IFRT. Those who were PET-positive and received additional chemotherapy as well as IFRT had PFS of 85.9% and OS of 93.9%. The authors concluded that in stage I and II Hodgkin lymphoma, RT is not necessary in the 75% of patients who become PET-negative after 3 cycles of chemotherapy.

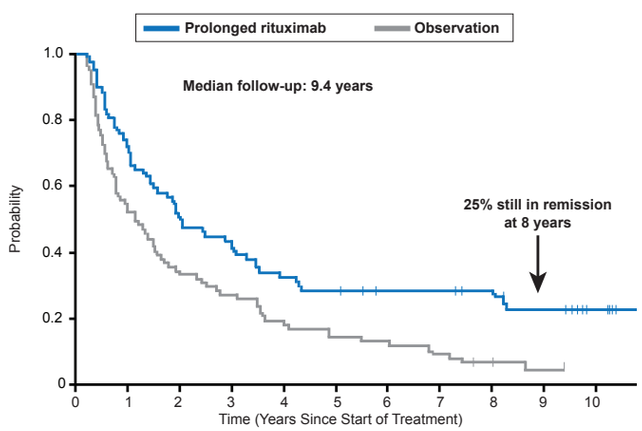
Chemotherapy alone remains the treatment of choice for non-bulky Hodgkin lymphoma because of the potential RT complications. It is hoped that new biomarkers and improved drugs will advance outcomes with chemotherapy alone and replace RT.

There are good data to suggest that using rituximab (RTX) as maintenance therapy can improve survival in patients with follicular and mantel cell lymphoma. Gilles A. Salles, MD, Hospices Civils de Lyon, Université Lyon 1, Pierre-Bénite, France, presented an update on maintenance therapy in hematological malignancies.

Long-term studies have shown that 27% of patients with follicular lymphoma exposed to RTX remain in remission after 8 years [Martinelli G et al. *J Clin Oncol* 2010].

In the Primary Rituximab and Maintenance study [PRIMA; NCT00140582], 2 years of RTX maintenance therapy significantly (p<0.0001) improved PFS in follicular lymphoma patients. Four years after randomization, 68% of patients in the RTX maintenance group were in complete or unconfirmed complete response versus 50% in the observation group (HR, 0.55; 95% CI, 0.44 to 0.68; p<0.0001). Grade 3 and 4 adverse events (mostly 2- to 4-grade infections) were recorded more often in the RTX group. There were no differences in immunoglobulin levels or quality of life between groups (Figure 2) [Salles G et al. *Lancet* 2011].

Figure 2. PFS in Follicular Lymphoma Patients on RTX



Reproduced from Salles G et al. Rituximab maintenance for 2 years in patients with high tumour burden follicular lymphoma responding to rituximab plus chemotherapy (PRIMA): a phase 3, randomised controlled trial. *Lancet* 2011;377(9759):42-51. With permission from Elsevier.

Similar results were reported in older patients with mantle-cell lymphoma [Kluin-Nelemans HC et al. *N Engl J Med* 2012]. Further follow-up is needed to assess the effect of RTX maintenance on subsequent treatment.

Fluorodeoxyglucose (FDG) PET is an appropriate measure for initial staging of a number of lymphomas and may have a limited role for routine imaging in detecting diffuse large B-cell lymphoma (DLBCL) and Hodgkin lymphoma relapse. Interim PET also has the ability to predict outcome after standard therapy for Hodgkin lymphoma patients. Andrew D. Zelenetz, MD, PhD, Memorial Sloan-Kettering Cancer Center, Weill-Cornell Medical Center, New York, New York, USA, described the use of FDG-PET for the diagnosis, restaging, and follow-up in patients with lymphoma.

For staging, PET generally shows more lesions and is superior to computed tomography (CT) for detecting lymphomas with bone involvement. CT is not effective for assessing disease in bone marrow. Only for small lymphocytic lymphoma are more lesions detected by CT scans. FDG PET imaging can also distinguish between patients with indolent and aggressive lymphoma, and although it cannot replace a biopsy, it can help guide the optimal biopsy if there is concern about transformation of indolent lymphoma [Schöder H et al. *J Clin Oncol* 2005; Noy A et al. *Ann Oncol* 2009].

If there is persistent FDG uptake after the end of therapy, there is a high risk for relapse. A negative PET scan at the end of therapy indicates good prognosis with regard to PFS and OS for Hodgkin lymphoma, DLBCL, and follicular lymphoma. As there are issues regarding positive and negative standardization of reporting and reproducibility across nuclear medicine physicians and machines, the Deauville criteria has been proposed as a way to incorporate a uniform response evaluation metric.

The use of interim PET analysis is currently an intensely studied topic. Interim analysis to detect treatment failure could change the treatment strategy (ie, either alternative treatment or closer surveillance). A comparison of the prognostic ability of early PET imaging and the International Prognostic Score (IPS) in advanced Hodgkin lymphoma demonstrated that PET is a superior prognostic tool relative to IPS and emerges as the single most important tool for planning of risk-adapted treatment in advanced Hodgkin lymphoma [Gallamini A et al. *J Clin Oncol* 2007; Zinzani PL et al. *Eur J Nucl Med Mol Imaging* 2012].

PET can identify a population of patients with Hodgkin lymphoma who have an excellent outcome after standard chemotherapy treatment but may have a limited role in detecting relapse. Long-term follow-up studies are needed to confirm these findings.