

Clinical Investigation

# Rates and Durability of Response to Salvage Radiation Therapy Among Patients With Refractory or Relapsed Aggressive Non-Hodgkin Lymphoma



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## Summary

Salvage radiation therapy has been used to cytoreduce or consolidate patients with relapsed or refractory aggressive non-Hodgkin lymphoma. Within this single-institution experience, 86% of sites treated with curative intent responded to salvage radiation therapy. However, the durability of response was moderate (5-year local control, 66%). Patients with refractory disease or nonresponse to initial chemotherapy had shorter time to local recurrence, suggesting that these patients

**Purpose:** To evaluate the response rate (RR) and time to local recurrence (TTLR) among patients who received salvage radiation therapy for relapsed or refractory aggressive non-Hodgkin lymphoma (NHL) and investigate whether RR and TTLR differed according to disease characteristics.

**Methods and Materials:** A retrospective review was performed for all patients who completed a course of salvage radiation therapy between January 2001 and May 2011 at Brigham and Women's Hospital/Dana-Farber Cancer Institute. Separate analyses were conducted for patients treated with palliative and curative intent. Predictors of RR for each subgroup were assessed using a generalized estimating equation model. For patients treated with curative intent, local control (LC) and progression-free survival were estimated with the Kaplan-Meier method; predictors for TTLR were evaluated using a Cox proportional hazards regression model.

**Results:** Salvage radiation therapy was used to treat 110 patients to 121 sites (76 curative, 45 palliative). Salvage radiation therapy was given as part of consolidation in 18% of patients treated with curative intent. Median dose was 37.8 Gy, with 58% and 36% of curative and palliative patients, respectively, receiving 39.6 Gy or higher. The RR was high (86% curative, 84% palliative). With a median follow-up of 4.8 years among living patients, 5-year LC and progression-free survival for curative patients were 66% and 34%, respectively. Refractory disease (hazard ratio 3.3;  $P = .024$ ) and

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may benefit from dose escalation or addition of radiosensitizers.

lack of response to initial chemotherapy (hazard ratio 4.3;  $P=.007$ ) but not dose ( $P=.93$ ) were associated with shorter TTLR. Despite doses of 39.6 Gy or higher, 2-year LC was only 61% for definitive patients with refractory disease or disease that did not respond to initial chemotherapy.

**Conclusions:** Relapsed or refractory aggressive NHL is responsive to salvage radiation therapy, and durable LC can be achieved in some cases. However, refractory disease is associated with a shorter TTLR, suggesting that radiation dose escalation, addition of radiosensitizers, or a combination of both may be indicated in these patients. © 2015 Elsevier Inc.

## Introduction

Definitive treatment of aggressive non-Hodgkin lymphoma (NHL) is associated with 5-year progression-free survival rates of 60% to 80% (1). In patients who relapse or have refractory disease after chemotherapy, prognosis is worse, with event-free survival ranging between 20% and 50% (2). Salvage radiation therapy may play an important role in these patients to cytoreduce and achieve minimal residual disease before high-dose therapy or as part of consolidation. Alternatively, salvage radiation therapy may provide local symptom control in the palliative setting.

Prior retrospective studies and anecdotal experience suggest that relapsed or refractory aggressive NHL tend to be radio-resistant (3), with a local failure rate of >50%. Alternative strategies have been explored to intensify radiation therapy, including accelerated hyperfractionation and concurrent chemotherapy and radiation therapy (4, 5). However, most available series were based on a relatively small number of patients treated in the pre-rituximab era. In a randomized trial comparing 30 Gy versus 40 to 45 Gy for patients with aggressive NHL, there was no difference in overall response rate or local control (LC) between the standard and lower-dose arms (6), although subgroup analysis was not performed among the small group of patients with refractory or relapsed disease (17% of cohort).

In this study, we aimed to assess the response rate and time to local recurrence (TTLR) of a modern cohort of relapsed or refractory aggressive NHL patients treated with salvage radiation therapy either with definitive or palliative intent. In addition, we sought to identify clinical factors that predict improved rates and durability of response to radiation therapy.

## Methods and Materials

### Patient cohort and eligibility

We retrospectively reviewed the records of 110 consecutive patients who completed a course of salvage radiation therapy to 121 sites for refractory or relapsed aggressive NHL between January 1, 2001, and May 31, 2011, at Brigham and Women's Hospital/Dana-Farber Cancer Institute in accordance with the Dana-Farber Cancer Institute institutional

review board. Eligible patients were adults aged  $\geq 18$  years with aggressive NHL. Both de novo and histologic transformation of indolent to aggressive NHL (eg from follicular to diffuse large B-cell lymphoma [DLBCL]) were included. Patients were excluded if they received salvage radiation therapy for treatment of primary cutaneous lymphoma or disease involving the skin or the central nervous system. For patients who received more than 1 course of salvage radiation therapy, only the first course between January 2001 and May 2011 was included in this analysis.

We extracted from medical records the following variables that could influence radiation therapy response and TTLR: age, gender, histology, transformed versus de novo disease, radiation therapy dose, once-versus twice-daily treatment, response to initial chemotherapy, and whether disease was relapsed or refractory. Refractory disease was defined as a <50% tumor response to the chemotherapy regimen given immediately before salvage radiation therapy (7). Because many patients received more than one chemotherapy regimen before salvage radiation therapy, some patients defined as having refractory disease may have initially responded to induction chemotherapy, whereas others never responded and may have even progressed on chemotherapy. Relapsed disease was new disease at any site on imaging or biopsy after an initial complete response (CR) to chemotherapy. A patient responded to chemotherapy if he or she achieved a CR or partial response (PR).

### Salvage radiation therapy treatment

Computed tomography-based simulations were performed on all patients. When available, positron emission tomography fusion was used to delineate the target volume. Three-dimensional conformal techniques were primarily used, although intensity modulated radiation therapy was occasionally used if appropriate. In some urgent cases, patients were initially treated once daily but subsequently were switched after 2 to 3 fractions to twice-daily treatment; for the purposes of our analysis these patients were categorized as receiving twice-daily treatment. In addition to the dose delivered, the biological effective dose (BED) was calculated using an  $\alpha/\beta$  ratio of 10 for each treated site.

Treatment intent was decided by the treating radiation oncologist at the time of consultation and planning. Cases

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