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## EVIDENCE-BASED ONCOLOGY

# Salvage radiotherapy increases survival in people with residual disease after chemotherapy for advance diffuse large cell lymphoma

Abstracted from: Aviles A, Neri N, Delgado S, et al. Residual disease after chemotherapy in aggressive malignant lymphoma. *Med Oncol* 2005; 22: 383–7.

## Background

Incomplete response to chemotherapy for advanced diffuse large cell lymphoma is not uncommon and residual disease can lead to relapse or disease progression. The effects of salvage radiotherapy on progression of disease or survival have not been well elucidated.

## Objective

To determine whether low-dose salvage radiotherapy improves response rate, progression-free survival and overall survival in people with a partial response to anthracycline-based chemotherapy regimen for advanced diffuse large cell lymphoma.

## Setting

Adults were recruited in a single centre between 1989 and 1997.

## Method

Single-centre randomised controlled trial.

## Participants

166 adults (59.6% male) aged between 18 and 70 years old (median 61 years) with advanced diffuse large cell lymphoma (World Health Organisation criteria) and poor prognosis (Ann Arbor: 47.0% stage III and 53.0% stage IV; International Prognostic Index:

64.5% high and 35.5% high-intermediate clinical risk), who had achieved only a partial response (residual nodal mass <5 cm) following six cycles of treatment with anthracycline-based chemotherapy (cyclophosphamide, vincristine, prednisone and either doxorubicin (CHOP: 43.4%) or epirubicin (CEOP; 56.6%). Exclusion criteria: complete response to chemotherapy; initial bulky disease (mass >10 cm); residual extra-nodal disease.

## Intervention

Participants were randomised to receive low-dose salvage radiotherapy (30 Gy in 1.5 Gy fractions over 4 weeks) or no further treatment (control). Median follow up was 135 months.

## Main outcomes

Overall survival, progression-free survival; adverse events.

## Main results

*Benefits.* Salvage radiotherapy significantly improved 10-year overall and progression-free survival compared with no further treatment (see Evidence Profile: Benefits).

*Adverse events.* Radiotherapy was reported to be well tolerated, with only mild acute toxicity and no late toxicity (no further data reported).

*Treatment-related mortality.* Not reported.

**Evidence profile: Benefits**

	Radiotherapy	Control	Absolute difference*	Significance
Progression-free survival at 10 years (%)	86	32	54	$P < 0.001$
Overall survival at 10 years (%)	89	58	31	$P < 0.001$

\* 95% CI not reported in the original publication.

**Evidence profile: Harms**

	Radiotherapy	Control	Significance
Acute toxicity	Mild (absolute figures not provided)	—	NR
Late toxicity	None	—	NR
Treatment related mortality	NR	NR	NR

NR, not reported.

**Authors' conclusions**

Salvage radiotherapy improves outcomes for people with residual disease following chemotherapy for advanced diffuse large B-cell lymphoma.

**Method notes***Random error*

Power calculation 80% power to detect a difference of 15% in complete response rate between treatment arms

*Bias* Measures to prevent bias

*Comparator bias*

Was true uncertainty about relative effects of competing treatments acknowledged? Adequate: The authors describe that no prospective studies have been carried out to determine the effects of salvage chemotherapy on conversion of partial response to complete response in diffuse large cell lymphoma

*Selection bias (are likes compared with likes?)*

Selection method Adequate  
Generation of allocation sequence Adequate

Allocation concealment Adequate: computer-based randomisation; concealment likely to have been adequate

Balanced groups Adequate: treatment groups were well balanced at baseline with respect to age, gender, prognosis and previous chemotherapy regimens

*Performance bias (assessment of the effects of possible co-interventions or contamination)*

Blinding Nature of intervention precluded blinding of participants.

*Detection bias (outcome assessment)*

Assessors blinded Unclear. However, the use of objective outcome measures reduces the likelihood of bias

*Attrition bias (assessment of the effect of loss of participants in the study)*

Withdrawals and dropouts described No: withdrawals not enumerated or described.

*Analysis*

Intention to treat analysis Yes  
Other statistical methods used Outcomes were analysed using the Cox proportional hazards model

CONSORT diagram included No

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## Commentary

Diffuse large B-cell lymphomas (DLBCLs) are one of the most common types of lymphoma, corresponding to 30–40% of all adult non-Hodgkin lymphomas.<sup>1</sup> Although in general at least half of DLBCL patients are cured with current chemotherapeutic regimens, an important number of patients may not initially respond to therapy or may eventually relapse and die from the disease.<sup>2</sup>

For the last 25 years, the standard initial treatment for DLCL has been based on CHOP combinations.<sup>3</sup> Recently, several RCTs have shown that the addition of rituximab increases complete responses and overall survival of such lymphoma patients.<sup>4–7</sup> However, a number of patients still do not achieve complete response with the initial treatment and clinicians face the dilemma of indicating further treatment. The predicament is further aggravated by the difficulty in diagnosing the nature of the residual nodal disease. Sometimes the residual mass can present itself as scar tissue requiring no further treatment or as active disease which requires intervention. Only about 20–30% of patients with residual mass are found to have residual disease upon further evaluation.<sup>8</sup> The current diagnostic methods for establishing the exact nature of residual mass is still not precise. Positron emission tomography, and computerised tomography for establishing the character of the residual mass are associated with false positive findings,<sup>9–11</sup> and surgical biopsy is an invasive procedure which can lead to considerable adverse events and potentially unnecessary stress in these patients.<sup>11</sup>

As a matter of fact, few studies<sup>12–14</sup> have been conducted in residual disease after initial chemotherapy and the guidelines, such as the US NCCN guidelines, are broad in their recommendations.<sup>1</sup> The study conducted by Aviles et al.<sup>15</sup> is the first RCT to address the use of low dose radiotherapy in such a situation. In this study, stage III or IV DLCL patients that received antracycline-based regimens (CHOP or CEOP) and had residual mass (nodal disease <5 cm) after six cycles of chemotherapy were eligible to be randomised to receive radiotherapy in the site of residual disease (total dose 30 Gy, delivered in 20 days, 4 weeks) or observation. This study included 166 patients, which were carefully followed up for up to 10 years.

The trial was well designed. The inclusion/exclusion criterion for the study was clearly stated and the allocation concealment as reported in the paper can be termed adequate. A priori sample size calculation was undertaken and the study was adequately powered to detect a 15% difference from the established response rate of 60%. The distribution of clinical or laboratory characteristics was well balanced between both treatment arms. Although drop-outs during the study were not clearly specified, the final analysis was conducted on an intention to treat basis.

The benefits of radiation therapy were significantly better in the treatment arm in terms of 10-year overall survival (89% versus 58%,  $P < 0.001$ ). Progression-free survival was 86% (11 relapses) versus 32% (57 relapses),  $P < 0.001$  and all the patients that relapsed were treated with salvage chemotherapy. Second complete responses were observed in two patients in the radiation group (2%) and 28 patients in the non-radiation arm (48%). In order to make an informed decision, clinicians need to take into account the benefits and harms of the desired treatment, therefore Aviles et al. preferably should have reported in detail the toxicity according to the treatment regimens. Nevertheless, the toxicity reported has been in accordance to the (mild) level previously reported in literature.<sup>16,17</sup>

In summary, it appears that use of radiation therapy at low dose (<30 Gy) is helpful in prolongation of progression-free survival and overall survival in DLCL patients with a residual nodal disease without adding important toxicity. However, whether the results from the trial by Aviles et al. will lead to changes in the management of disease remains to be seen, as this is the first trial to indicate the benefits from consolidation radiotherapy. The current findings should be replicated in future large scale multi-centre randomised trials.

### Quality assessment (1 = fair; 4 = excellent)

Relevance	4
Validity	3
Applicability	3
Feasibility	3
Impact	3
Knowledge context	4

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