High Response Rates and Lasting Remissions After Low-Dose Involved Field Radiotherapy in Indolent Lymphomas

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Background
The majority of patients with follicular lymphoma (FL) present with advanced Stage III or IV disease, and often have a prolonged course characterized by multiple relapses. First line therapy for advanced stage FL is generally chemotherapy; for recurrent disease, options include chemotherapy, immunotherapy, and radiation. FL is considered to be one of the most radiosensitive tumors, and previous studies have demonstrated high response rates to low-dose (4 Gy) involved field radiotherapy (LD-IFRT) in recurrent FL. This is a prospective cohort study of patients with symptomatic recurrent B-cell indolent lymphomas treated with LD-IFRT. It describes the response rates and duration of response following LD-IFRT, and represents the largest series published on the topic.

Methods
- 109 patients were assessable for the analysis, with a total of 304 sites. The histologies were as follows: 98 patients with follicular lymphoma (43 grade 1 and 55 grade 2), 9 with extranodal marginal zone lymphomas of mucosa-associated lymphoid type (MALT), and 2 with lymphoplasmacytoid lymphoma. 52% of patients had bulky disease, defined as nodes ≥ 5 cm.
- All patients received 4 Gy to either the entire lymph node area (as defined by the Rye classification) or the node with a 1.5 cm margin. 80 patients received 2 x 2 Gy, separated by an interval of 48 hours. 29 patients received 4 Gy in a single dose.
- The primary endpoint was in-field lymphoma control. Response was determined by physical examination, ultrasound of the neck nodes, and contrast-enhanced CT scans of the chest and abdomen. If patients were irradiated at more than one site and the response differed, the disease was assigned the worst category. If a patient received chemotherapy after LD-IFRT because of local failure or distant relapse, the treatment was counted as a local failure at that time point.
- Time to progression and time to local progression were calculated according to the Kaplan-Meier method. The starting point for time to progression was the first day of LD-IFRT.

Results
- The overall response rate was 92%. 61% had a complete response to the first low-dose irradiation, and 31% had a partial response. There were 8 non-responders.
- Complete response lasted up to 77 months and was ongoing at the time of analysis. Partial response lasted up to 28 months and was ongoing as well. Median follow-up was 4.5 years.
- The median time to progression (TP) was 14 months, and the median time to local progression (TLP) was 25 months. For complete responders, the median TP was 25 months and the median TLP was 42 months. For partial responders, the median TP was 9 months and the median TLP was 10 months. For non-responders, the median TP and TLP were 2 months.
- Of the 41 patients who underwent re-treatment, there was a 98% response rate. Complete response occurred in 71% of patients. The partial response rate was 27%. There were two non-responders. 107 of 109 patients achieved a response within 4 to 6 weeks after LD-IFRT.
Prognostic factors for response rates could not be distinguished. There was a difference in complete response rate between patients having \( \leq 2 \) lymphoma sites compared to patients with more sites (\( P = 0.01 \)), and between patients with tumor size \( \leq 5 \) cm and patients with larger nodes (\( P = 0.006 \)). Due to large number of comparisons, the observed \( P \) values did not allow definite conclusions. Age, sex, follicular lymphoma grade, radiotherapy regimen, and number and history of previous regimens did not predict response rates.

LD-IFRT results were compared with the response rates and response duration after each previous regimen in this group (usually chemotherapy). The probability of having no progression 1 year (about 50%), 2 years (about 33%), 3 years (about 25%), and 5 years (about 10%) after LD-IFRT was comparable to the best previous treatment.

Toxicity was virtually absent. Transient alopecia was seen in one follicular lymphoma patient with upper neck nodes, and transient hyperpigmentation was seen in one follicular lymphoma patient in an inguinal nodal field.

**Discussion**

This study provides useful data regarding the response rates and duration of response to low-dose (4 Gy) involved field radiotherapy for recurrent indolent B-cell non-Hodgkin’s lymphoma, with an overall response rate of 92%, a median time to progression of 14 months, and a median time to local progression of 25 months. Low-dose involved field radiation should be strongly considered as a highly effective palliative treatment with high response rates and rapid onset of response. Retreatment with LD-IFRT for a recurrence after a first LD-IFRT regimen provides a similarly high response rate. This regimen is a valuable asset in the management of follicular lymphoma patients and is an option for recurrent disease.