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Original article

## Radiotherapy of relapse-refractory follicular lymphoma

### Radiothérapie des lymphomes folliculaires réfractaires ou en rechute

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#### ABSTRACT

**Purpose.** – To assess the efficacy of treatment and outcomes of patients with relapsed or refractory follicular lymphoma treated with external beam irradiation.

**Patients and methods.** – Fifteen patients who received external beam radiotherapy for relapsed or refractory follicular lymphoma were studied. The median age was 68.3 years (range: 37.9–87.08 years) with four men and 11 women. Seven patients had early stage (I or II); eight advanced stage (III or IV). Median FLIPI score was 2. Two patients had high tumour bulk disease. Six patients had extranodal invasion, with five patients having bone marrow invasion.

**Results.** – The median time of follow-up after relapse or first-line treatment in case of refractory disease was 61.9 months (range: 9.1–119.7 months). Complete response after external beam radiotherapy was seen in 11 cases (73%) and partial response in two (13%), with a median dose of 30 Gy (range: 2–40 Gy) and median number of fractions of 15 (range: 2–20). Eight patients (53%) relapsed after external beam radiation therapy in a median of 20.2 months, mostly out of irradiated volumes. Most patients (66%) had a disease control after one or two courses of external beam radiation therapy. At last follow-up, 86% of patients were in remission including those with salvage chemotherapy. The toxicity profile was favourable with toxicity higher than grade 1. In univariate analysis, a Follicular Lymphoma International Prognostic Index (FLIPI) score above 2 was the only predicting factor for non-control disease.

**Conclusion.** – For relapsed and refractory follicular lymphoma, external beam radiotherapy should be considered as an effective modality when integrated in a multimodality approach. Randomised studies are warranted to validate this strategy.

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#### R É S U M É

**Objectif de l'étude.** – L'objectif était d'évaluer les résultats d'une radiothérapie externe pour un lymphome folliculaire réfractaire ou en rechute.

**Patients et méthodes.** – Les dossiers de 15 patients ont été étudiés. L'âge médian des quatre hommes et 11 femmes était de 68 ans (extrêmes : 37,9–87,08 ans). Sept patients étaient atteints d'une maladie localisée (stade I ou II) et huit d'une maladie évoluée (stade III ou IV). Le Follicular Lymphoma International Prognostic Index (FLIPI) médian était de 2. Deux lymphomes étaient *bulky*, six extranodulaires et cinq avec une infiltration de la moelle osseuse. Tous les patients ont reçu une irradiation pour leur maladie réfractaire ou en rechute.

##### Mots clés :

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**Résultats.** – Le temps médian de suivi de la maladie réfractaire ou en rechute était de 61,9 mois (extrêmes : 9,1–119,7 mois). Une réponse complète a été observée après la radiothérapie dans 11 cas (73 %), une réponse partielle dans deux (13 %), avec une dose médiane respectivement de 30 Gy et 15 Gy. Huit lymphomes ont récidivé, en médiane à 20,2 mois, mais en dehors des zones irradiées. Soixante-six pour cent des lymphomes étaient contrôlés à long terme après la radiothérapie externe. À la date de dernières nouvelles, 86 % des patients étaient en situation de rémission après la radiothérapie, avec ou sans chimiothérapie. La tolérance a été très bonne, avec une majorité de réactions de grade I. L'analyse unifactorielle a montré que le FLIPI de plus de 2 était le seul facteur prédictif de mauvais contrôle de la maladie.

**Conclusion.** – L'irradiation pour un lymphome folliculaire réfractaire ou en rechute est efficace et doit trouver sa place dans la stratégie thérapeutique multidisciplinaire. Des études prospectives sont nécessaires pour confirmer ses résultats.

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## 1. Introduction

Radiation therapy is established as a highly effective modality for localised lymphoma such as Hodgkin's lymphoma, large cell B-cell lymphoma, some T-cell lymphoma such as nasal NK/T lymphoma [1–4]. However, a declining trend of radiotherapy has been observed in the past decade [5].

For early stage follicular lymphomas, the current treatment options include radiotherapy, systemic therapy and combination of both modalities. In early stage non-bulky and low grade follicular lymphoma, radiotherapy is the preferred treatment, according to the European Society for Medical Oncology (ESMO) guidelines [6].

For follicular lymphoma, radiotherapy can be used not only as single treatment method in early stage but also as consolidation after chemotherapy in complete or incomplete responders [7].

However, few evidences exist for using radiotherapy for refractory or relapsed follicular lymphoma but is mainly based on small retrospective series. For such indications, there are currently no clear recommendations for radiation regarding its role, its timing, its exact modalities and the follow-up.

We report our experience and outcomes of patients treated by radiotherapy for relapsed or refractory follicular lymphoma in a single institution.

## 2. Patients and methods

A total of 27 patients with follicular lymphoma who were diagnosed and received radiotherapy between June 1995 and February 2014 were identified in the Curie institute database. Four patients with first-line exclusive radiotherapy or consolidative radiotherapy after chemotherapy were excluded. Six other patients were excluded because they corresponded to exclusive extranodal disease especially skin or bone localization requiring different radiation modalities. Follicular lymphoma transformation into aggressive lymphoma prior to irradiation was also an exclusion criteria. The study flow chart is detailed in Fig. 1.

All cases were pathologically confirmed by biopsy or surgical examination at diagnosis and at time of relapse. The immunohistochemical features (CD20, CD10 and Bcl2 positive) were crucial for the diagnosis.

Ann Arbor stages I and II follicular lymphomas were classified as early stages whereas stages III and IV were classified as advanced stages. The staging of the disease included the physical examination, computed tomography (CT), positron emission tomography (PET) CT and bone marrow examination by a bone marrow biopsy. Blood counts and lactate dehydrogenase (LDH) levels were also assessed. The Follicular Lymphomas International Prognostic Index (FLIPI) score was calculated on the basis of individual parameters.

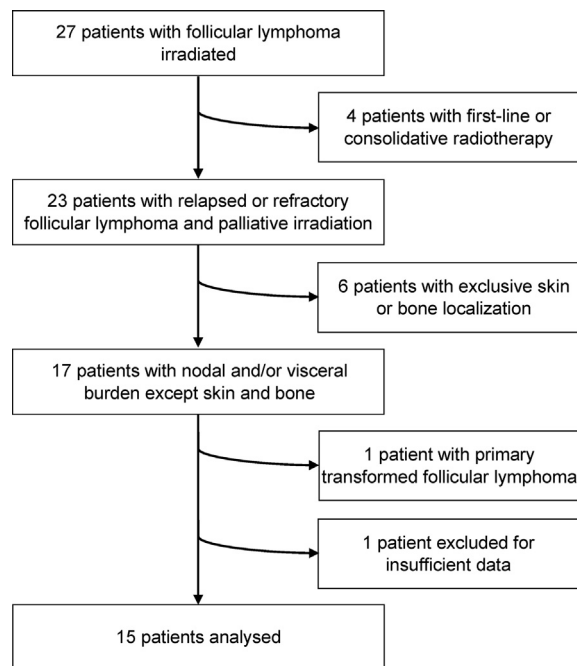


Fig. 1. Efficacy of treatment and outcomes of patients with relapsed or refractory follicular lymphoma treated with external beam irradiation: study flow chart.

Progression-free survival was defined as the interval between the end of radiation therapy and the diagnosis of recurrence.

The study was accepted by the haematological multidisciplinary team of Curie institute and Cochin hospital.

## 3. Results

### 3.1. Patient and disease characteristics

Fifteen patients were finally analysed in this study. The median age was 68.2 years (range: 38–86 years) with four men and 11 women. Seven patients had early stage (I or II) whereas eight had advanced stage (III or IV). Median FLIPI score was 2 (range: 0–4). Two patients presented with a high tumour bulk using the Groupe d'étude des lymphomes folliculaires (Gelf) classification. Six patients had extranodal invasion with 5 patients having bone marrow infiltration. Four patients had a transformation of their tumour into aggressive Diffuse B-cell lymphoma with a median time of 29.4 months (range: 0–34.5 months) after the diagnosis (transformation occurred after irradiation in all cases). One patient

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