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Scientific Abstracts
Salvage abdominal irradiation for refractory non-Hodgkin’s lymphoma

ABSTRACT
Background: Abdominal irradiation, as a part of treatment, is often ignored in the management of refractory non-Hodgkin’s lymphoma (NHL). Objective: To evaluate the efficacy and the toxicity of this approach after failure of chemotherapy.

Materials and Methods: 27 patients with intraabdominal lymphoma underwent salvage irradiation between 1982 and 2001. All patients were treated with a Cobalt-60 machine. The total dose administered to the abdomen was 18-20 Gy at the rate of 1.5-1.8 Gy per daily fraction, followed by a boost to gross disease up to 20 Gy. All patients had previously been heavily pretreated with chemotherapy. Fourteen patients, nine with follicular and five with diffuse lymphomas, had primary refractory tumors that had never achieved remission. Thirteen patients, six with follicular and seven with aggressive tumors, had refractory relapsed tumors after achieving one or more complete remissions.

Results: The response rate was 77%. The median follow-up was 53 months. The 5-year and 10-year survival rates were 25 and 17%, respectively. The in-field and out-of-field recurrence rates were 22 and 33%, respectively. Survival rates were significantly better for patients with refractory relapse compared to those with primary refractory lymphoma (P <0.01). There was no significant difference in terms of response, recurrence, or survival rates between follicular and aggressive types. Out-of-field recurrence occurred more frequently in initial stage III and IV disease. Toxic deaths occurred in three patients (11%).

Conclusion: Salvage radiotherapy for refractory abdominal NHL is a feasible alternative for both follicular and diffuse subtypes and may provide significant palliation and prolongation of survival. It is less effective in patients with primary refractory NHL than in those with refractory relapsed NHL.

KEY WORDS: Non-Hodgkin’s lymphoma, refractory, whole-abdominal irradiation

Radiotherapy alone can cure one-third to one-half of patients with indolent and aggressive non-Hodgkin’s lymphomas (NHLs) in stage I.[1] The optimal radiation dose is not defined and the extended-field is not superior to the involved-field. Radiotherapy plays only a limited role in the higher stages. Stage II and stage III follicular lymphomas, when still encompassable by the standard irradiation field, may be treated primarily by radiotherapy, with relapses in irradiated fields being quite unusual. Most studies favor combined modality treatment in localized aggressive lymphomas, with chemotherapy followed by radiotherapy instead of radiotherapy alone. Otherwise, stages III and IV follicular lymphomas and bulky stage II, stage III, and stage IV aggressive lymphomas are regarded by many investigators as generalized forms of the disease.[1,2] Accordingly, chemotherapy is the mainstay of treatment for these patients. Depending on the histology and the risk factor profile, 30 to 75% of patients can achieve complete remission with the CHOP or CVP regimens.[2-4] Patients who relapse after complete remission can still be cured by salvage chemotherapy. Patients with chemotherapy-resistant non-Hodgkin’s lymphomas have rapidly progressive diseases, and those who show evidence of disease progression during the induction phase have a particularly poor prognosis.[5–7]

It is generally assumed that recurrence indicates disseminated disease. However, local treatment may be considered for local control or to palliate symptoms when the full staging workup at progression shows a relatively limited disease. Salvage radiotherapy provides an alternative treatment strategy for patients with localized relapse in previously nonirradiated areas. Standard irradiation fields may not be large enough to enclose the bulk of the disease or all the lymph nodes of the anatomic area. The expansion to a larger field requires a technique of irradiation that takes into account, as far as possible, the anatomic conditions of the target volumes and critical organs, especially in those patients who are profoundly immunosuppressed during salvage chemotherapy.

For subdiaphragmatic abdominal disease, the standard inverted ‘Y’ field is fraught with a high failure rate, which is attributed to the exclusion of the mesenteric lymph nodes and most of the liver and intestines from the irradiated field.
Whole-abdominal irradiation up to 20-30 Gy, with two daily fractions over a 3-week period, has been reported to achieve good local control and prolonged survival in patients with refractory abdominal lymphoma of both aggressive and follicular subtypes. A safe and effective irradiation technique to treat the whole abdomen was developed at Stanford in 1973, delivering up to 44 Gy as a total central abdominal dose. In addition, abdominal irradiation using similar doses has also been widely employed in a variety of solid tumors, such as ovarian or endometrial carcinomas, with acceptable toxicity and good results in terms of local control and survival.

Based on these reports, we conducted the present retrospective study to report the pattern of failure and the long-term outcome in patients with refractory, heavily pretreated NHL managed with salvage abdominal irradiation after failure of chemotherapy in our institution.

**MATERIALS AND METHODS**

**Patients and endpoints**

Over a 19-year period, from 1982 to 2001, 31 patients with refractory subdiaphragmatic NHL were referred for radiotherapy after failure of chemotherapy. All of them received salvage whole-abdominal irradiation. Histology reports were reviewed and classified using the Working Formulation for Clinical Usage. Patients with mantle-cell lymphoma, mucosa-associated lymphoid tissue (MALT) lymphoma, immunoproliferative small intestinal disease (IPSID), and small lymphocytic class A lymphoma were excluded because of the controversial outcomes and classification in the working formulation. The remaining 27 patients were included in this study. All these patients had chemotherapy-resistant disease that contraindicated high-dose chemotherapy (HDCT) with bone marrow or stem cell rescue; in any case, this technique is not available in Lebanon. Almost all of these patients were treated before the era of chemoimmunotherapy and radioimmunotherapy.

'Refractory disease' was defined as persistent tumor masses, ascertained by CT scan, after completion of the last regimen of chemotherapy. All patients had a bulky abdominal disease, with tumor size > 5 cm, and had previously been heavily pretreated with chemotherapy.

By coincidence, 15 patients had follicular type lymphomas (classes B, C, and D) and 12 patients had aggressive type lymphomas (classes E, F, G, and H). Fourteen patients had primary refractory tumors that had never achieved remission. Thirteen patients had refractory relapsed tumors after having achieved first, second, and sometimes third and forth, complete remissions. Since this is a retrospective study, patient follow-up was done through extensive review of medical records. CT scans, clinical presentation details, and results of laboratory examinations were available, but progress notes on minor treatment complications were missing in half of the cases.

Although, the total dose delivered is similar to that used with curative intent, the goals of treatment were palliation of symptoms, maintenance of the quality of life, and improvement of progression-free and overall survivals. The parameters assessed were the pattern of failure, the pattern of toxicity, the response rates, and the survival, according to the histological type and the previous chemosensitivity status.

**Evaluation at diagnosis and before irradiation**

The initial evaluation included history and physical examination, CT scans of the whole body, complete blood cell count, bone marrow biopsy, blood urea nitrogen, serum creatinine, liver function tests, and serum lactate dehydrogenase (LDH) levels. Gastrointestinal endoscopies were done when necessary. Histological examination was done only at diagnosis for all aggressive lymphomas and primary resistant lymphomas, whereas a fresh histological examination was performed in patients with the relapsed follicular subtype. All of the above clinical, biological, and radiological evaluations were repeated at each relapse and before total-abdominal irradiation. These examinations were performed according to the internationally recognized and standard approach to lymphoma patients, without adhering to a preconceived local protocol, since this is a retrospective study. CT scanning was uniformly available throughout the study period. No lymphoma that had transformed from low-grade to high-grade was identified.

**Total abdominal irradiation**

All patients were treated with total abdominal radiation using a Cobalt-60 machine and open unblocked fields at an SSD of 80-100 cm and a daily dose of 150-180 centigray (cGy), according to tolerance. Dose was calculated at the mid plane. The total dose to the whole abdomen was 2000 cGy and was followed by reduced fields, centering on gross demonstrable residual disease and avoiding the kidneys and the liver. An additional dose of 2000 cGy was then given, taking the dose to 4000 cGy to gross disease, irrespective of the histology.

**Response and toxicity evaluation**

Response to radiotherapy was assessed 10 to 12 weeks after completion of treatment. CT scans and laboratory tests were performed at uniform times to evaluate the response in patients who had received the whole planned total dose without developing complications, and earlier in those who presented clinical evidence of progression or developed major complications during treatment. ‘Complete response’ was defined as complete resolution of the abnormalities on physical examination and radiographic imaging or the persistence of minimal imaging abnormalities, not thought to represent active disease. The surveillance plan consisted of clinical examination, blood analysis, and CT scan of the thorax, abdomen, and pelvis, performed every six months. Bone marrow biopsy was not uniformly performed at the follow-up evaluation after radiotherapy since all patients were free of bone marrow involvement at the time of irradiation,
including those who had had bone marrow involvement at diagnosis. Bone marrow biopsy was performed later however, when recurrence was suspected. Assessment was based on the World Health Organization (WHO) criteria.

Patients were monitored for acute hematological and gastrointestinal toxicities by weekly clinical examination and blood tests. Expected long-term toxicities included late renal failure, chronic radiation enteritis, pancreatitis, hepatitis, and secondary leukemia.

### Statistical analysis

For calculations of survival and progression-free survival, patients were evaluated at the time of the last follow-up. The log-rank method was used for the analysis of actuarial survival data. Fisher’s exact test and the corrected chi-square test were used to evaluate the recurrence rates. The results were studied on an intention-to-treat basis.

### RESULTS

#### Patient characteristics

Preradiotherapy patient and tumor characteristics are listed in Tables 1 and 2. A total of 27 patients were treated with salvage radiotherapy at progression after failure of chemotherapy. The median age was 56 years (range: 37-72 years); there were 15 males (55%) and 12 females (45%). At the time of initial diagnosis, 12 patients (44%) had subdiaphragmatic stage II disease, 9 patients (33%) had stage III disease, and 6 patients (22%) had stage IV disease, according to the Ann Arbor criteria. Six patients had stage II extranodal, gastrointestinal disease and 4 patients had splenic involvement. Of those with stage IV disease, 3 patients had bone marrow involvement, 3 patients had liver involvement, and one patient had ovarian involvement by aggressive lymphomas.

According to the WHO classification, the Working Formulation for Clinical Usage, there were 15 follicular, low-grade lymphomas: 4 small cleaved cell (class B) and 11 mixed small cleaved and large cell (class C), and 12 aggressive, diffuse type lymphomas: 2 small cleaved cell (class E), 8 mixed small and large cell (Class F), one large cell (Class G), and one large cell immunoblastic (Class H) [Table 1].

All 27 patients had only subdiaphragmatic stage II disease by the Ann Arbor criteria on the basis of whole-body CT scanning (positron emission tomography scanning had not yet become available). All had bulky tumor masses of > 5 cm at progression and at the commencement of the salvage abdominal irradiation. None of the patients had persistent bone marrow involvement or supradiaphragmatic disease before start of abdominal irradiation; all had refractory/resistant intraabdominal disease.

Five patients had stage II nodal follicular lymphoma at initial diagnosis. These patients might have been well served by primary radiotherapy rather than chemotherapy. However, they had received primarily chemotherapy probably because of the extensive intraabdominal disease. Two of them presented local in-field recurrence within 3 years.

Thirteen patients (48%) achieved complete initial response to first-line CHOP chemotherapy, and 14 patients (52%) had lymphomas resistant to first- and second-line chemotherapy regimens.

The median time from diagnosis to radiotherapy was 12 months (range: 8-23 months) for primary resistant lymphomas and 32 months (range: 12-73 months) for refractory lymphomas. The

### Table 1: Histologic classification

<table>
<thead>
<tr>
<th>Total</th>
<th>Follicular lymphomas (Low grade)</th>
<th>Class B: Predominantly small cleaved cell (FSCL)</th>
<th>Class C: Mixed, small cleaved and large cell (FMCL)</th>
<th>Diffuse and aggressive lymphomas (Intermediate and High Grade)</th>
<th>Class E: Small cleaved cell (DSCL)</th>
<th>Class F: Mixed, small and large cell (DMCL)</th>
<th>Class G: Large cell (DLCL)</th>
<th>Class H: Large cell, immunoblastic</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>15</td>
<td>4</td>
<td>11</td>
<td>12</td>
<td>2</td>
<td>8</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

### Table 2: Patient and tumor characteristics

<table>
<thead>
<tr>
<th>Low grade: Class E, F, and G</th>
<th>Intermediate grade: Class H</th>
<th>High grade:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Male</td>
<td>9</td>
<td>5</td>
</tr>
<tr>
<td>Mean age in years (range)</td>
<td>58 (29-70)</td>
<td>53 (40-72)</td>
</tr>
<tr>
<td>&lt;60 years</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>&gt;60 years</td>
<td>9</td>
<td>2</td>
</tr>
<tr>
<td>Disease stage at diagnosis:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>IIE</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>III</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>IV</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>(IV: Liver involvement)</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>(IV: Bone marrow involvement)</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>(IV: Ovarian localization)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Spleen involvement</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>15</td>
<td>11</td>
</tr>
</tbody>
</table>
median number of prior chemotherapy regimens received was 3 (range: 2-6).

Outcomes
After salvage radiotherapy, 77% of the patients achieved a complete response according to the criteria described earlier and 22% showed residual masses. Four patients died of intercurrent disease, free of lymphoma, at 1, 2, 4, and 5 years from radiation. Two patients are still alive, 68 months and 72 months from radiation. Most recurrences occurred within the first 3 years following radiation, with 22% occurring inside and 33% outside the radiation field. With a median observation time of 53 months (range: 3-121 months), the 5-year and 10-year disease-free survivals were 25% and 17%, respectively, for the entire group. The median survival time was 31 months. Outcomes are summarized in Tables 3 and 4 and in Figures 1 to 2. Response to radiotherapy was not correlated with previous sensitivity to chemotherapy. There was no significant difference between follicular and aggressive lymphoma in terms of response to radiotherapy, progression-free survival, or recurrence rates. Survival rates were significantly worse in patients with lymphomas that had been resistant to initial chemotherapy, compared to those with relapsed lymphomas. The P-values were 0.001 and 0.01 for the follicular and diffuse types, respectively [Tables 3 and 4; Figures 1 and 2]. Although, all the patients were refractory to salvage chemotherapy at the time of abdominal irradiation, the number of previous chemotherapy regimens used was not correlated with the response to radiotherapy. The serum LDH level was not related to the outcome or radio-resistance. There was no linear regression correlation between the time to relapse from initial chemotherapy and time to relapse from radiotherapy. The median time to disease progression was 40 months for patients with the follicular subtype and 38 months for those with the aggressive subtype. The median

| Table 3: Pattern of failure and survival |
|-------------------------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|
| Total     | Radiation resistance (%) | In-field recurrence (%) | Out-of-field recurrence (%) | Median survival (months) | 5-years PFS % | 10-years PFS % |
| Follicular type | 15 | 4 (26) | 3 (20) | 5 (33) | 30 | 22 | 14 |
| Diffuse type | 12 | 2 (16) | 3 (25) | 4 (33) | 33 | 34 | 18 |
| Whole group  | 27 | 6 (22) | 6 (22) | 9 (33) | 31 | 25 | 17 |
| Primary resistant | 14 | 4 (28) | 4 (28) | 5 (35) | 17 | 6 | 0 |
| Resistant relapse | 13 | 2 (15) | 2 (15) | 4 (30) | 47 | 34 | 31 |
| Whole group  | 27 | 6 (22) | 6 (22) | 9 (33) | 31 | 25 | 17 |

| Table 4: Outcome analysis and probabilities |
|---------------------------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|
| Radiation resistance | In-field recurrence | Out of field recurrence | Median PFS | 5-year PFS | 10-years PFS | 5-years OS | 10-years OS |
| Follicular lymphoma | 3/9 (33%) | 22% | 44% | 21 months | 10% | 0% | 10% | 0% |
| Primary refractory | 1/6 (17%) | 17% | 28% | 43 months | 36% | 33% | 45% | 40% |
| P value | NS | NS | NS | 0.05 | 0.01 | 0.001 | 0.01 | 0.001 |
| Diffuse lymphoma | 1/5 (20%) | 40% | 20% | 12 months | 0% | 0% | 0% | 0% |
| Primary refractory | 1/7 (14%) | 14% | 28% | 48 months | 30% | 30% | 50% | 44% |
| P value | NS | 0.05 | NS | 0.01 | 0.01 | 0.01 | 0.001 | 0.01 |
time to disease progression for primary resistant lymphomas was significantly reduced compared to that for lymphomas that had relapsed after initial complete response to front-line chemotherapy (23 months vs 53 months, respectively; \( P = 0.01 \)); this was independent of the histological subtype.

Although all the patients had only bulky abdominal disease at radiation, the in-field recurrence rates were similar in patients with initial stage II, III, and IV lymphomas of both histologic types. The out-of-field recurrences occurred more frequently in patients with initial stage III and IV lymphoma. The statistical analysis did not show any significant difference due to the small size of the series.

Treatment toxicity

Although the patients were not enrolled into a clinical trial, objective data on acute hematological, hepatic, and renal toxicity were available. However, we had little data on acute gastrointestinal toxicity. Based on the available data, 14 patients (51%) had shown only moderate or insignificant adverse manifestations and 5 patients (18%) had had grade IV hematological toxicity as determined by the WHO criteria. Among them, two patients died of sepsis and were consequently considered to be treatment-related deaths. One patient died of subacute intestinal obstruction related to radiation. Thus, 3 toxic deaths have marked the toxicity profile of this therapeutic approach. No secondary leukemia, secondary solid tumor, pancreatitis, or vascular abnormalities were seen. Table 5 summarizes the major toxicity-related events.

**DISCUSSION**

This study involves a particular patient population. All patients had abdominal NHL, refractory to conventional first-line and salvage chemotherapies, before the era of monoclonal antibodies and immunoradiotherapy. They were also not eligible for HDCT with hematopoietic stem cell transplantation. All of them received total-abdominal irradiation as salvage treatment. Our objective was to confirm the feasibility of this technique, to report the encouraging long-term results in follicular and diffuse subtypes, and to assess the pattern of failure.

The results from this study show that heavily pretreated patients with refractory NHL may still benefit from salvage abdominal irradiation. Complete response was readily achievable in 77% of patients treated. Significant prolongation of disease-free survival was more frequent in patients who had chemotherapy-sensitive tumors previously, as compared to those with primary resistant lymphomas (\( P < 0.01 \)). For patients with relapsed lymphomas that had responded to initial front-line chemotherapy, the 5-year survival rates were 36% in the follicular type and 30% in the diffuse type. For patients with primary refractory tumors, the 5-year survival rates were 10% in the follicular lymphomas and 0% in the diffuse lymphomas. No significant difference in terms of response and long-term outcome was seen between patients with the follicular type and those with the diffuse type of NHL. These results are in disagreement with those reported by Mahe et al.,\(^{[9]}\) probably because of a selection bias. In fact, most patients in Mahe’s follicular lymphoma group had received only one first-line chemotherapy regimen, whereas most of those in the diffuse lymphoma group had received heavier chemotherapy, with more than two successive lines. In addition, it was not clear if the relapsed follicular diseases were refractory or chemotherapy-sensitive relapses.

The occurrence of three deaths related to radiation toxicity in such a small series seems high, but it may be acceptable if one takes into account the profoundly immunosuppressed status of the patients who had been exposed to substantial doses of prior chemotherapy and also the advanced state of their disease; this is especially so, since two of these deaths were due to grade IV hematological toxicity.

Follicular lymphomas are sensitive to radiation therapy.\(^{[14,15]}\) Stage III disease may still be managed with standard radiation fields. Primary radiotherapy for stage III follicular lymphoma has yielded some impressive results according to the series published by Murttha et al. at Stanford University,\(^{[15,16]}\) De Los Santos et al. at the University of Florida,\(^{[17]}\) and Jacobs et al. at the medical college at Wisconsin,\(^{[18]}\) with 15-year disease-free survival rates of 25, 58, and 40%, respectively. In all these studies, a lower burden of disease was associated with a better outcome. On the other hand, in aggressive lymphomas, most studies favor combined modality treatment, with chemotherapy followed by radiotherapy instead of radiotherapy or chemotherapy alone in localized disease.\(^{[19]}\) Studies published on the value of radiotherapy in bulky refractory disease have yielded conflicting results. Concomitant chemoradiotherapy for refractory relapsed lymphoma is associated with a high rate of hematological toxicity but is still beneficial for local control of bulky tumor masses.\(^{[20]}\) Radiotherapy given alone has fallen out of favor as an alternative to chemotherapy in previously treated patients with NHL.

Low-dose involved-field radiotherapy may be a fast, cheap, nontoxic, and repeatable treatment in the palliative situation.\(^{[22]}\) Hyperfractionated involved-field radiation provides a good local control. Involved-field and central lymphatic-field radiation are considered to be effective but noncurative approaches for follicular lymphoma. In an attempt to achieve cures, more extended radiation fields were used. Moderate-dose total-abdominal irradiation up to 20-25 Gy,
with two daily fractions of 0.8 Gy, over 3 weeks has been tested by Mahe et al.\cite{8,9}. The study reported a high response rate of 76% and prolonged progression-free survival in refractory lymphomas, especially the follicular type, reaching 32% at 10 years. The role of fractionation in reducing the toxicity and enhancing the efficacy of whole-abdominal irradiation, using 2 daily fractions for a total daily dose of 1.6 Gy, has been suggested in several reports.\cite{8,9,22} To avoid excessive acute gastrointestinal toxicity, Calkins et al.\cite{22} used delayed split whole-abdominal irradiation with 2-6 h delay between the irradiation of each half of the abdomen.

We have used the conventional technique, like many others\cite{25-30}, who treated intraabdominal lymphomas or gynecological tumors, and the same total irradiation dose as Mahe et al.\cite{8,9}, i.e., conventional fractionation of one daily dose of 1.5-1.8 Gy, over 2-3 weeks duration, followed by a boost of 15-20 Gy to involved areas of gross disease. Our results demonstrate the feasibility of this approach and the acceptable levels of toxicity. They are in agreement with other reports, in terms of response and survival rates, and confirm the feasibility of using these conventionally fractionated doses without significant renal or liver toxicities.

Despite the fact that the cohort size is small in this series and that our study is of a retrospective design, we may conclude that this approach can achieve a high response rate in both follicular and aggressive refractory lymphomas. It provides a significant alternative for palliation and prolongation of survival, especially in view of the fact that HDCT with hematopoietic stem cell rescue requires chemotherapy sensitivity.

While abdominal irradiation references are common, our work differs in that it is directed to chemotherapy-resistant cases exclusively. We have demonstrated that this approach is highly effective in patients with NHL who have initially responded to first-line chemotherapy. It is less effective in patients with primary refractory disease. Nevertheless, it may palliate symptoms, with occasional long-term disease-free survivors; it remains a valuable therapeutic tool for these patients. Although, the toxicity profile of total-abdominal irradiation may be acceptable, transient radiation hepatitis,\cite{26,31} renal toxicity,\cite{26,28} secondary cancers,\cite{30,32} and pancreatitis\cite{33} were randomly encountered in some nonrandomized studies. Better planning of target volume could probably be achieved with 3D planning using linear accelerators.

With the emergence of the less toxic targeted radiotherapy, using radionuclides coupled to monoclonal antibodies, external-beam irradiation may lose ground, but it remains applicable to the few restraint cases.

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Source of Support: Nil, Conflict of Interest: None declared.