Thoracoscopy or CT-Guided Biopsy for Residual Intrathoracic Masses After Treatment of Lymphoma*

Dominique Gossot, MD; Philippe Girard, MD, FCCP; Eric de Kerviler, MD; Pauline Brice, MD; Jean-Didier Rain, MD; Thierry Leblanc, MD; Dominique Grunenwald, MD

Background: An intrathoracic mass persists after completion of treatment in 20% of the patients treated for Hodgkin’s disease (HD) or non-Hodgkin’s lymphoma (NHL). Gallium scan and positron emission tomography allow for diagnosis in most cases. However, in some patients, a pathologic examination of the residual mass (RM) is required. The aim of this study was to evaluate the results of a thoracoscopic approach for intrathoracic RM, as compared with image-guided biopsies.

Patients and methods: From 1996 to 1998, 29 consecutive patients treated for NHL (n = 11) or HD (n = 18) were referred either to radiology (group R; n = 8) or to surgery (group S; n = 21) for biopsy of an intrathoracic RM. There were 13 male and 16 female patients ranging in age from 15 to 56 years (mean, 32 years). The reason for a biopsy was the inability to determine the nature of the RM by means of radiologic examination or scintigraphy. Biopsy was defined as successful when (1) residual lymphoma was found in the specimen, or (2) benign tissue was found and the patient remained disease-free after a minimal follow-up period of 12 months. A biopsy was defined as a failure when a local recurrence occurred in a patient with a diagnosis of benign lesion.

Results: No significant procedure-related complications occurred in either group. The mean follow-up was 26 months (range, 13 to 72 months). In group R, residual lymphoma was found in only one patient. In group S, residual lymphoma was found in seven patients (p = 0.5). In the seven patients of group R with a diagnosis of benign mediastinal lesion, two patients had a local recurrence and one had a recurrence within the abdomen. In the 15 patients of group S in whom no residual disease was found, 1 patient had an intrathoracic recurrence (p = 0.5) while 2 patients had recurrence in a remote site.

Conclusion: Despite the limited number of patients in this series, results suggest that a thoracoscopic approach yields better data than image-guided biopsies.

Key words: Hodgkin’s disease; gallium scan; lymphoma; mediastinum; residual mass; thoracoscopy

Abbreviations: GS = gallium citrate Ga67 scan; HD = Hodgkin’s disease; NHL = non-Hodgkin’s lymphoma; PET = positron emission tomography; RM = residual mass

Persistency of an intrathoracic mass after completion of treatment of a Hodgkin’s disease (HD) or a non-Hodgkin’s lymphoma (NHL) is a common-place situation. Residual thoracic masses are present in about one third of patients after treatment for NHL or HD. Patients refractory to treatment or presenting with poor response must be detected.

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early and changed to invasive therapeutic programs such as high-dose chemotherapy and bone marrow transplantation. It is therefore of utmost importance to obtain an accurate diagnosis of the nature of an intrathoracic residual mass (RM). In these patients who receive long-term therapy and follow-up, physicians are usually reluctant to use an invasive method to achieve diagnosis. Among noninvasive methods are CT, MRI, gallium citrate Ga67 scan (GS),1–3 thallium scan,4 and positron emission tomography (PET) with fluoro-2-deoxy-D-glucose.5 Until now, GS remained the preferred examination to stage NHL or HD at completion of therapy. However, its sensitivity might not be as high as usually asserted,6 and many factors may be responsible for gallium citrate Ga67 uptake. PET scan is highly sensitive and specific for carcinomas but is still being evaluated for staging of lymphomas. Thus, some patients are still referred to the radiologist7 or the surgeon for biopsy.8 The aim of this work was to assess the role of surgical endoscopic and image-guided techniques in the diagnosis of intrathoracic RM.

Materials and Methods

From 1996 to 1998, 29 patients treated for NHL (n = 11) or HD (n = 18) have been referred to radiology (group R) or surgery (group S) for biopsy of an intrathoracic RM (Table 1). There were 13 male and 16 female patients ranging in age from 13 to 56 years (mean, 32 years). Both groups were comparable. The choice of radiology or surgery was based on localization criteria; when the mass was easily reachable under CT scan, radiology was preferred.

Nineteen patients underwent GS before biopsy; 6 patients were in group R and 13 patients were in group S. Results of GS are listed in Table 2. The reason for a biopsy was the inability to determine the nature of the RM by means of radiologic examination or scintigraphy.

Group R

Eight patients underwent a CT-guided biopsy of a mediastinal RM (group R). There were neither pulmonary nor pleural lesions in this group. A coagulation screen was performed in all patients, and informed consent was obtained prior to the procedure. In teenagers, informed consent was obtained from parents. The biopsy procedure was performed on an outpatient basis in all cases.

Table 1—Presentation of the Residual Disease*

<table>
<thead>
<tr>
<th>Presentations</th>
<th>Group R (n = 8)</th>
<th>Group S (n = 21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mediastinal mass</td>
<td>8</td>
<td>13</td>
</tr>
<tr>
<td>Mediastinal lymph node</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Lung nodule</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Mediastinal mass and lung nodule</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

*Data are presented as No.

Table 2—Final Results*

<table>
<thead>
<tr>
<th>Results</th>
<th>Group R (n = 8)</th>
<th>Group S (n = 21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Failure</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Residual lymphoma or HD</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>Thyroid rebound</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Necrosis</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Fibrosis</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Sarcoidosis</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Normal mediastinal fat</td>
<td>0</td>
<td>2</td>
</tr>
</tbody>
</table>

*Data are presented as No. Two different lesions may coexist in the same patient.

Biopsies were performed by two experienced radiologists from our staff. CT scanning was used for biopsy guidance. After disinfecting and steriley draping the patient’s skin, a local anesthesia was performed with a 1% lidocaine solution. The puncture was performed by using standard coaxial percutaneous biopsy technique in all cases using a semianatomated biopsy gun (Quick-Core biopsy needle; Cook; Bloomington, IN) that allows one to obtain a 17-mm-long core of tissue. In the largest masses, we used a sextant technique that consists of tilting the needle in several directions in order to obtain tissue samples in different areas. Limited scanning was performed to localize the lesion and to document needle progression in depth to the target. A 16-gauge biopsy needle was used in six patients, and an 18-gauge needle was used in two patients, making two to six passes (mean, 3.6 passes). Biopsies were fixed in a solution of acetic acid, ethyl alcohol, and formol. When malignant lymphoma was diagnosed on biopsy specimen, a panel of antibodies was used to determine cell lineage and histologic subtype.

Group S

Twenty-one patients underwent a thoracoscopic approach under general anesthesia according to the technique that has been previously described (group S). A split ventilation was used in all patients, and three to four ports were needed for a rigid 10-mm thoracoscope and endoscopic instruments. Two patients had a history of previous conventional surgical biopsy (one sternotomy and one thoracotomy) that led to intraoperative difficulties.

In the case of a small pulmonary lung nodule, a preoperative localization technique was used in order to facilitate and shorten the thoracoscopic resection.10 The placement of a hook wire combined with methylene blue labeling under CT-scan guidance was the preferred method for localizing the nodule.11 When a large tumor was present, a large partial biopsy was performed using scissors and endoscopic suturing. When the nodule was small, it was fully resected using a regular wedge resection with an endoscopic stapler. In the case of a mediastinal tumor, multiple biopsies were performed at different levels to minimize the hazard of overlooking residual cells.

A chest tube was placed and removed within the second postoperative day. Patients were discharged from the surgical department between the first and third postoperative day. The mean follow-up duration was 26 months (13 to 72 months). Two patients died of disease progression during follow-up. Data were compared using a χ² test with Yates correction.

Since none of the patients underwent a total removal of the RM, it was difficult to define success and/or a failure criteria due to the lack of complete pathologic proof. We chose to assert a
biopsy as successful in the two following instances: (1) residual lymphoma was found in the specimen, or (2) benign tissue was found and the patient remained disease free after a minimal follow-up period of 12 months. Similar criteria are usually chosen when dealing with this issue. A biopsy was defined as a failure when a local recurrence occurred in a patient with a diagnosis of benign lesion.

RESULTS

In group R (n = 8), residual lymphoma was found in only one patient. Fibrosis was found in three patients; thymic hyperplasia was found in two patients. Other diagnoses are listed in Table 2. The only complication in this group was one minor pneumothorax that did not require chest drainage and healed spontaneously.

In group S (n = 21), residual lymphoma was found in seven patients; fibrosis in six patients, and thymic hyperplasia in two patients (p = 0.5). Unexpected diseases (tuberculosis [n = 2] and sarcoidosis [n = 1]) were found in three patients. Other rare diagnoses are listed in Table 2. In group S, two patients underwent biopsy of both a pulmonary nodule and a mediastinal mass. In one of these patients, residual HD was found in both RMs. In the second patient, fibrosis was found in the mediastinum and tuberculosis was found in the lung nodule. Another patient had a loculated mediastinal lesion (Fig 1). Fibrosis was found in the upper part of the lesion and residual HD in the lower part. There was no morbidity in this group. The mean stay in surgery was 2.2 days (1 to 4 days).

Outcome

In the seven patients of group R with a diagnosis of benign mediastinal lesion, two patients had a local recurrence and one had recurrence within the abdomen. In the 14 patients of group S in whom no residual disease was found, there were two recurrences in a remote site and one intrathoracic recurrence (p = 0.5; Table 3). In this patient, the surgical examination had been difficult and remained incomplete because of tight adhesions related to a previous sternotomy.

Correlation With GS

In group R, four of the six GS results were positive. Residual disease was found only in one of the four positive GS findings. Two of the three patients with a positive GS and negative CT-guided biopsy results had recurrence. The third patient did not have recurrence but was treated on the basis of the positive GS result.

In group S, 13 patients underwent a preoperative GS. Six of these results were positive. In only one patient, fibrosis was found and he recurred early. In the five other patients with positive GS results,
residual lymphoma was found. On the other hand, in one of the six patients with negative GS results, persistent HD was found. One patient with nonconclusives GS result had only necrotic tissue (Table 4). The correlation with GS was better in group S than in group R.

**DISCUSSION**

An intrathoracic RM is present in >20% of patients after treatment of an HD or a NHL.1 Eighteen percent of these patients experience a relapse at the level of the RM.13 Theoretically, only a complete surgical resection of the RM could determine that the patient is disease free. A secondlook surgery has been advocated as the method of choice by some authors.14,15 This attitude is questionable for the following reasons: (1) complete removal of tumoral and fibrotic tissues requires large incisions in patients who may have undergone previous surgery, (2) the morbidity is high, and (3) <20% of mediastinal RMs lead to relapse.16

Thus, the use of noninvasive methods such as CT, GS, or PET scan seems preferable. However, there is no consensus about the method of choice. CT alone does not allow one to discriminate between residual tumor and fibrosis or necrosis. According to most recent studies, CT has a poor sensitivity with respect to the diagnosis of residual disease. In a retrospective review of HD and NHL, Stumpe et al12 have found the specificity of CT to be only 41% for HD and 67% for NHL. MRI has been shown17 to be slightly more reliable with respect to the diagnosis of fibrosis.

GS is much more reliable than CT and MRI since gallium uptake is proportional to the amount of residual cells.2 In a recent study,18 some of us demonstrated that GS has a high specificity (91%) and a positive predictive value of 81% in 53 patients with RM after treatment of HD. Other authors19 have found similar results for aggressive diffuse NHL. However, for follicular NHL, results appear to be less reliable.6 The specificity of GS is not optimal because of numerous causes of false-positive findings, such as tuberculosis, sarcoidosis, bronchitis, or thymic hyperplasia.19 The latter is a commonplace cause of mediastinal enlargement after chemotherapy. It is known as “rebound” thymic hyperplasia.20 It may occur up to 14 months after completion of chemotherapy and is found in >11% of the patients. Although thymic enlargement usually appears as an homogeneous mass of the anterior mediastinum (Fig 1, 2), doubt may remain in some patients. Furthermore, most thymic rebounds are associated with gallium citrate Ga67 uptake.21 In addition, GS must not be performed close to the end of chemotherapy to avoid false-negative findings. Partially necrotic or small-sized tumors may also lead to false-negative findings in GS.

PET seems to reach higher specificity. In a series of 44 RMs with positive CT results, Zinzani et al 21 found 100% relapse among the 13 patients with positive PET findings and only one relapse (4%) among the 24 patients with negative PET findings. Stumpe et al12 have found CT and PET to have similar sensitivities but PET is significantly more specific than CT. Its specificity for RM is 96% in patients with HD and 100% in patients with NHL. However, although the predictive positive value of PET is 100%,22 it seems that it mainly predicts early progression but cannot exclude the presence of minimal residual disease.22 Indeed, in the series of Jerusalem et al,22 clinical relapses were observed more frequently in patients with than without RM.

<table>
<thead>
<tr>
<th>Table 3—Outcomes of Patients Without Residual Lymphoma Found at Biopsy*</th>
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<tbody>
<tr>
<td>Outcomes</td>
</tr>
<tr>
<td>Remission</td>
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<tr>
<td>Recurrence within the biopsy site</td>
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<td>Recurrence outside the biopsy site</td>
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*Data are presented as No.

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<th>Table 4—Correlation Between GS and Final Pathologic Result*</th>
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<tr>
<td>Result of Preoperative GS</td>
</tr>
<tr>
<td>Positive</td>
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<tr>
<td>Negative</td>
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<td>Indeterminate</td>
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*Data are presented as No.
These data and the limited follow-up do not allow to draw definite conclusion about the accuracy of PET. To our knowledge, no published data are available concerning the ability of PET to distinguish mediastinal recurrence from benign thymic hyperplasia.

Thus, there are still circumstances where doubt remains and where a pathologic proof is required. Due to the minimal invasiveness, CT-guided biopsies are often considered as the method of choice when no peripheral palpable lymph node can be biopsied. The accuracy of CT-guided biopsies for the diagnosis of lymphoma ranges from 80 to 90% in many series, especially when several samples can be obtained using a coaxial technique. In the series of Pappa et al., the size of the samples were sufficient for phenotyping in all cases. The CT-guided approach has become our method of choice for initial diagnosis of NHL and HD. However, our

**FIGURE 2.** Thymic rebound with positive GS result in a 20-year-old woman with large-cell NHL located in the pelvis. Left, a: GS. Center, b: CT scan before chemotherapy. Top right, c: CT scan at the end of chemotherapy. Bottom right, d: CT scan 4 months later.

**FIGURE 3.** Left, a: loculated mediastinal RM after completion of chemotherapy in a 13-year-old patient with HD. Thoracoscopic biopsy revealed fibrosis in the anterior aspect of the lesion (top right, b) and residual HD in the posterior aspect (bottom right, c). A CT-guided procedure would have more likely sampled the anterior aspect of the mass.
data underline its limitations when dealing with RM. In RM, performing multiple biopsies is essential since residual disease usually coexists with fibrotic and/or necrotic tissue or thymic hyperplasia (Fig 3).\(^6\) The fact than two of the seven CT-guided biopsy patients with negative results did have recurrences within the chest indicates that residual cells were most likely missed despite the use of large cutting needles and a sextant sampling technique.

On the other hand, in the surgical group, only 1 of 14 patients with negative biopsy results had a local relapse. Furthermore, in this patient, a previous history of sternotomy made the thoracoscopic examination difficult and incomplete.

In conclusion, despite the increasing use of GS and PET scan, there are still cases where certainty is wanted, ie, where a biopsy is required. Although our results are not significant because of the limited number of patients, our data show that CT-guided biopsies do not determine definitely the nature of a RM after treatment of HD or NHL. Only surgery allows for multiple biopsies in different sites (as demonstrated in this series, benign and malignant lesions may coexist), thus avoiding the risk of missing remaining malignant tissue. In these patients submitted to invasive therapeutic programs, open conventional surgery should be avoided for the following reasons: (1) satisfactory specimens can be obtained by endoscopic surgical techniques, and (2) open surgery makes an eventual secondary thoracoscopy more difficult and less profitable.

**REFERENCES**


