Avoiding Reoperation for Indeterminate Thyroid Nodules Identified as Malignant After Surgery

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Needle biopsies of thyroid nodules now permit identification of most carcinomas and selection of patients for treatment, including surgery. However, in approximately 15% of cases, the needle biopsy specimen indicates that the lesion is cellular and indeterminate for distinction of a benign lesion from a low-grade, well-differentiated thyroid carcinoma. The terms suspicious and cellular with cytologic atypia have also been used to designate the needle biopsy findings of thyroid nodules identified as indeterminate in this report. Surgery is usually advisable for the indeterminate category of thyroid nodules because the frequency of carcinoma has been reported to be from 20% to 60%. Even at operation, the study of frozen sections frequently does not provide a definitive diagnosis for this category of patients. In some situations, permanent sections examined after surgery do disclose evidence of a carcinoma, often a low-grade, well-differentiated follicular carcinoma determined on the basis of capsular or blood vessel invasion and cytologic features. In other cases, a low-grade papillary (usually a follicular variant) thyroid carcinoma is identified. A decision regarding reoperation to remove additional thyroid tissue to permit treatment with radioactive iodine must then be made, especially for carcinomas larger than 2 cm in diameter.

In an effort to obviate the risks, expense, and technical difficulties of reoperation, our initial operation in patients with indeterminate thyroid nodules has included not only removal of the lobe containing the questionable nodule but at least a contralateral subtotal lobectomy. Removal of this additional thyroid tissue enhances the efficacy of postoperative radioactive iodine therapy for carcinoma. Thus, the patient is not subjected to controversy and the potential risks of reoperation if radioactive iodine is clinically indicated. In addition to contralateral subtotal thyroid lobectomy, it has been our practice to sample lymph nodes in the ipsilateral midjugular group, as well as to remove lymph nodes adjacent to the thyroid lobe and anterior superior mediastinum to permit an assessment of the presence of metastases. This aids operative as well as postoperative decisions, especially for the later use of radioactive iodine therapy. The rationale for this approach relates to the frequency of carcinoma in patients with indeterminate thyroid nodules and the need for administration of radioactive iodine for some of these patients versus the complications associated with an extended operation.

We reviewed cases of patients treated surgically during a 10-year period for thyroid nodules for which the diagnosis of carcinoma was uncertain. Particular attention was given to those nodules considered to be indeterminate for carcinoma by fine-needle aspiration biopsy. Emphasis was given to the following: (1) the frequency of carcinoma in indeterminate thyroid nodules; (2) the timing of the diagnosis (before or after surgery) for those patients found to have a thyroid carcinoma; (3) the frequency of use of radioactive iodine for patients in whom the diagnosis of thyroid carcinoma was established after surgery; (4) the efficacy of the extended operation in

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permitting treatment with radioactive iodine; and (5) the incidence of complications related to the extended operation.

PATIENTS AND METHODS

During the 10-year period from 1980 through 1989, 69 patients underwent surgery for thyroid nodules for which the diagnosis was uncertain at the time of operation. A diagnostic breakdown of the patients is shown in Table 1. This report focuses on 37 patients with indeterminate thyroid nodules, which were those found by fine-needle aspiration biopsy to be cellular with cytologic features not permitting distinction from benign lesion, such as nodular hyperplasia, from a low-grade carcinoma. Patients with nodules considered to be benign by fine-needle aspiration biopsy but for which surgery was performed were operated on for several reasons, including a large nodule, a history of external radiation therapy to the neck area, and continued enlargement despite thyroid hormone suppression. Two patients in the latter group were considered to have a very-low-grade follicular carcinoma on the basis of fact of capsular invasion on postoperative study of permanent sections. For 18 patients, the material obtained by needle biopsy, which was usually repeated, was considered inadequate for cytologic diagnosis, but surgery was advised on the basis of other factors.

The standard operation for these patients with an uncertain diagnosis was an ipsilateral lobectomy and contralateral subtotal thyroidectomy, with removal of lymph nodes adjacent to the involved thyroid lobes, the contralateral superior mediastinal lymph nodes, and one or several lymph nodes in the ipsilateral midjugular group. By subtotal contralateral lobectomy, we mean removal of at least one half to two thirds of the lobe to permit ablation of remaining thyroid tissue by radioactive iodine, if indicated (Figure). The term subtotal lobectomy is used in this report to indicate an ipsilateral total lobectomy and contralateral subtotal lobectomy leaving a thyroid remnant weighing 4 g or less. By preservation of this thyroid remnant, hypoparathyroidism and injury to the laryngeal nerves are avoided. The location of the recurrent laryngeal nerve on the side of the remnant was usually identified to better ensure preservation.

All but one of these patients with thyroid carcinoma had received no previous external radiation therapy to the neck; the exception was a patient who refused to undergo a preoperative needle biopsy. The study group evidenced no unusual demographic characteristics.

RESULTS

We concentrated our attention on the 37 patients for whom fine-needle aspiration biopsy indicated the presence of a cellular lesion that was indeterminate as carcinoma. In 11 (30%) of these cases, the thyroid nodules were found to be malignant (Table 1). In addition, an incidental occult microscopic papillary carcinoma was found in extranodal thyroid tissue in two patients, with a lymph node adjacent to the thyroid gland containing a microscopic metastasis in one of the patients.

The histologic varieties of thyroid carcinoma present in the 11 patients in whom indeterminate nodules were found to be malignant are listed in Table 2. Excluding the incidental occult carcinomas, the diagnosis of carcinoma was made only by study of permanent sections after surgery for eight of the 11 patients found to have malignant thyroid nodules. The four patients treated after surgery with radioactive iodine had a multifocal papillary variant of follicular thyroid carcinoma with regional lymph node metastases (two patients) or a large follicular thyroid carcinoma with blood vessel and capsular invasion (two patients).

For three of these four patients treated after surgery with radioactive iodine, the diagnosis of thyroid carcinoma was established after postoperative studies of permanent sections. For one patient, the diagnosis of a follicular thyroid carcinoma was made by study of frozen sections taken at the time of operation. Following administration of single doses of radioactive iodine in these four patients, all uptake in the neck was eliminated, with no evidence of uptake elsewhere in the body. The dose of iodine 131 varied from 50 to 100 mCi and was estimated on the basis of requirements for ablation of the thyroid remnant as well as for demonstrated micrometastases in cervical or mediastinal lymph nodes.

The majority of carcinomas in thyroid nodules considered indeterminate by fine-needle aspiration biopsy were very-low-grade, well-encapsulated follicular carcinomas or low-grade Hurthle cell carcinomas. The diagnosis of malignancy was made in these patients primarily on the basis of capsular, not vascular, invasion.

All patients received thyroid hormone replacement therapy following subtotal thyroidectomy. The serum thyroid-stimulating hormone (TSH) levels were monitored to ensure adequate thyroid hormone replacement.

None of the patients developed postoperative complications of permanent hypoparathyroidism or recurrent laryngeal nerve damage and none required reoperation. None has shown evidence of recurrence of thyroid carcinoma. During this period, five other patients were seen in our institution who required reoperation because of a suspicion of residual thyroid carcinoma and the advisability of treatment with radioactive iodine following a previous lobectomy or partial lobectomy.

Cervical lymph node biopsy specimens disclosed no metastasis in all but four patients in this group; these four patients were given postoperative radioactive iodine therapy. In these patients, the lymph nodes containing metastases were in the anterior superior mediastinum or adjacent to the thyroid gland. None of the lymph nodes removed from the midjugular group contained metastases in this series. The decision to administer radioactive iodine after surgery was based on several factors, including the presence of capsular invasion by a higher-grade follicular carcinoma larger than 3 cm in diameter in a patient older than 50 years and the presence of metastases to regional lymph nodes.

Large-needle biopsies were performed on six patients in this series and simply supported the fine-needle aspiration biopsy results and a decision for surgery. In other cases, the use of large-needle biopsy provided a definitive diagnosis when fine-needle aspiration biopsy did not.

COMMENT

A frequent question in managing thyroid carcinoma has long been what to do if the diagnosis is established on the basis of the study of permanent sections following a lobectomy. If only a lobectomy is performed for thyroid carcinoma, confusion can arise after surgery regarding the need to reoperate to remove more thyroid tissue to facilitate the use of radioactive iodine therapy. This issue has been highlighted by evidence from long-term studies that, in at least some patients with papillary thyroid carcinoma, the postoperative administration of radioactive iodine can be of therapeutic benefit. Furthermore, patients with well-encapsulated follicular thyroid carcinomas that are more than 3 cm in diameter have a significant risk of metastases, justifying a thyroidectomy sufficient to facilitate the use of radioactive iodine therapy.

Endocrinologists vary in their enthusiasm for radioactive iodine therapy in the definitive management of well-differentiated thyroid carcinoma. Evidence suggests that patients with papillary thyroid carcinomas larger than 1.5 cm in diameter, especially when associated with regional lymph node metastases, deserve consideration for more than a thyroid lobectomy. Some surgeons continue to advise patients with thyroid nodules that are indeterminate by needle biopsy that two operations may be needed because the initial operation is to consist only of a lobectomy and, if carcinoma is identified, a second operation may be needed.

Reoperation following thyroid surgery may entail increased operative risk of complications. Even if these risks are small in reoperations performed only to remove a contralateral thyroid lobe that is not significantly abnormal anatomically.
Table 1.—Occurrence of Carcinoma in Thyroid Nodules With Uncertain Preoperative Diagnosis

<table>
<thead>
<tr>
<th>Category</th>
<th>Total No. of Patients</th>
<th>Diagnosis of Carcinoma in Nodule</th>
<th>Incidental (Occult) Microscopic Carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preoperative fine-needle aspiration biopsy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cellular, indeterminate</td>
<td>37</td>
<td>11</td>
<td>2</td>
</tr>
<tr>
<td>Inadequate</td>
<td>13</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Benign, operation for other reasons</td>
<td>15</td>
<td>2*</td>
<td>0</td>
</tr>
<tr>
<td>Patient refused needle biopsy, operation on basis of clinical findings</td>
<td>4</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>69</td>
<td>15</td>
<td>3</td>
</tr>
</tbody>
</table>

*Diagnosis of very-low-grade follicular carcinoma based on foci of microscopic capsular invasion.

Table 2.—Characterization of Carcinoma in 37 Thyroid Nodules That Were Indeterminate by Needle Biopsy

<table>
<thead>
<tr>
<th>Variety of Carcinoma</th>
<th>Total No. of Patients</th>
<th>Source of Diagnosis</th>
<th>No. of Patients Treated With Iodine 131</th>
</tr>
</thead>
<tbody>
<tr>
<td>Papillary</td>
<td>3</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Follicular</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Very-low-grade follicular, well encapsulated</td>
<td>4</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Low-grade Hurthle cell</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Occult, incidental</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>13</td>
<td>3</td>
<td>10</td>
</tr>
</tbody>
</table>

*Metastasis to regional lymph node present.

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Photograph of thyroid gland illustrating subtotal thyroidectomy (ie, right lobectomy and contralateral subtotal lobectomy) for a nodule in the right lobe that was indeterminate by needle biopsy.

Indecisiveness about the need for reoperation when the diagnosis of thyroid carcinoma is established only after a lobectomy has been performed.

This study and others have found that carcinoma occurring in thyroid nodules considered to be indeterminate by needle biopsy is low grade, and lobectomy is frequently adequate treatment. We acknowledge that many patients with well-differentiated thyroid carcinoma have an excellent prognosis after lobectomy. However, in this series, of eight patients with thyroid carcinoma recognized only after surgery, three had the follicular variant of papillary carcinoma, and two of these three were treated with radioactive iodine. Another three of the eight patients were treated with radioactive iodine because of metastases to central or anterior superior mediastinal lymph nodes or because of a large, low-grade follicular thyroid carcinoma.

Thus, at least in some of the low-grade, well-differentiated thyroid carcinomas, the extent of the carcinoma was considered sufficient to justify the use of radioactive iodine therapy. Others have reported that, except for very-low-risk, well-differentiated thyroid carcinomas, subtotal thyroidectomy combined with the selective use of radioactive iodine improves the outlook. Therefore, for the significant minority of patients (perhaps 20%) who have a risk of recurrence and subsequent morbidity, an extended operation for all indeterminate thyroid nodules is considered to be justified and does not add measurably to the operative risk.

The amount of thyroid tissue that can be satisfactorily ablated by radioactive iodine in an effort to destroy any residual thyroid carcinoma, particularly micrometastases, throughout the body is not well defined. For maximal therapeutic benefit from radioactive iodine, elimination of all thyroid tissue has been desired. We prefer that less than 5 g of thyroid tissue be present when ablation with radioactive iodine is to be accomplished. For the patients in this study, a minimum of 50 mCi of iodine 131 was administered for ablation of the thyroid remnant, with a larger dose administered on the basis of known micrometastases to regional lymph nodes. Uptake of a tracer dose of radioactive iodine can also be used to determine the therapeutic dose.

Rather than risk subtle hypothyroidism at a later date and to possibly reduce the recurrence of benign nodules in residu-
al thyroid tissue, it has been our policy to advocate the administration of thyroid hormone following subtotal thyroidectomy for indeterminate nodules. There is always the risk, however, of patient noncompliance in taking thyroid hormone when needed. All but one patient in this study group were instructed to take thyroid hormone after surgery. Of those patients whose serum TSH levels were determined before thyroid hormone intake was initiated, a significant number were found to have an elevated or high normal serum TSH level. The serum TSH level has been used to monitor the adequacy of thyroid hormone dosage. It has been our observation that for some patients the postoperative serum TSH level is elevated or high normal even following a unilateral thyroid lobectomy alone. The cost of taking thyroid hormone for the group of patients who prove not to have thyroid carcinoma does not appear to be a disadvantage when one considers the overall savings achieved by avoiding reoperation for those patients who do have carcinoma as well as the savings achieved by reducing the potential for recurrence of benign thyroid nodules many years later.

Subtotal thyroidectomy for indeterminate thyroid nodules is justified for reasons other than avoiding reoperation to facilitate the therapeutic administration of radioactive iodine in treating thyroid carcinoma that is ultimately recognized. The opportunity to study extranodular thyroid tissue from both lobes of the thyroid gland for evidence of multicentric thyroid carcinoma or intrathyroidal metastases provides additional information to use in deciding whether to administer radioactive iodine after surgery.

Furthermore, during surgery the surgeon will detect in some patients gross evidence of small nodules in the contralateral thyroid lobe not appreciated before surgery, but which justify removal. Although ultrasonography can detect thyroid nodules, the routine use of this study is not cost-effective in our opinion because needle-aspiration biopsy is more reliable and cheaper in detecting cystic features of a nodule, and significant thyroid nodules can be detected by the surgeon during surgery.

Subtotal thyroidectomy for indeterminate thyroid nodules may obviate the later occurrence of nodules in the contralateral lobe that then require evaluation and possible reoperation. The incidence of benign nodules developing in remaining thyroid tissue after lobectomy for benign nodules has been reported to be at least 15% after 10 years. We have observed that nodular hyperplasia is frequently diffuse throughout the thyroid gland or may coexist with adenomas. Thus, late recurrence of clinically evident benign thyroid nodules can be expected in such settings. Also, the precise distinction between benign nodular hyperplasia and cellular adenoma is not absolute by fine-needle aspiration biopsy.

Total thyroidectomy has been advocated as the preferred operation for benign thyroid nodules. This appears reasonable if the surgeon is confident that extending the operation to this degree for a benign lesion does not increase morbidity. In at least some patients, an attempt to remove all thyroid tissue can be expected to increase the risk of permanent hypoparathyroidism. Residual thyroid tissue following subtotal thyroidectomy is effectively eliminated, if necessary, by the administration of radioactive iodine without the risks of an absolute total thyroidectomy.

The broad spectrum of differentiated thyroid carcinoma is emphasized in this study, which demonstrates the occurrence of incidental occult thyroid carcinoma associated with a dominant thyroid nodule that is benign. Such incidental carcinomas may be present in other smaller and less evident nodules in the thyroid or, as occurs more often, as microscopic foci in extranodular thyroid tissue. This usually is not significant in considering additional therapy. However, in one of our patients, a microscopic metastasis was found in a lymph node adjacent to the thyroid gland near the location of the occult incidental thyroid carcinoma.

Biopsies of regional lymph nodes in the management of thyroid nodules indeterminate by needle biopsy can provide additional valuable information in determining treatment. If metastasis to a regional lymph node is found during surgery, the existence of a primary thyroid carcinoma can be assumed. Removal of regional lymph nodes centrally in the neck and anterior superior mediastinum can provide helpful information in determining the advisability of administering therapeutic radioactive iodine.

It has also been our policy to perform biopsies of ipsilateral midjugular lymph nodes. If metastatic thyroid carcinoma is detected by a biopsy of lateral cervical lymph nodes at the time of operation, we perform a functional or modified radical lymph node dissection. However, in this series of patients with indeterminate thyroid nodules, none of the lateral lymph nodes was found to contain metastatic carcinoma. This may reflect the lower grade of carcinoma when ultimately recognized in thyroid nodules indeterminate by needle biopsy. Since an evaluation of lymph nodes at the midjugular location does provide additional information in determining the advisability of additional treatment with radioactive iodine, we have continued the practice.

Hürthle cell nodules comprise a significant component of indeterminate thyroid nodules. These are notoriously difficult for pathologists to identify as malignant without studying permanent sections after operative removal. Although more than a thyroid lobectomy may not be needed for small, low-grade Hürthle cell carcinomas, it appears reasonable to perform a subtotal thyroidectomy for such lesions when they are large or multiple inasmuch as such lesions appear to be capable of metastasis. In a few patients, low-grade Hürthle cell carcinomas of the thyroid gland are multicentric. Although the known lack of response of Hürthle cell carcinoma to radioactive iodine makes subtotal thyroidectomy unnecessary on this basis, evidence of bilateral nodules in the presence of indeterminate Hürthle cell nodules does justify this operative procedure.

Previous external radiation therapy to the neck further indicates the need for treatment of more than a thyroid lobectomy for thyroid nodules indeterminate by needle biopsy. The standard operation advocated for this situation is a near total thyroidectomy. However, only one of the patients in our series had received external radiation therapy to the neck, and the thyroid nodule in this patient was benign.

This report also documents the recognition of incidental parathyroid adenomas in patients undergoing surgery for thyroid nodules. One of the two patients in this series found to have an incidental parathyroid adenoma had previously received external radiation therapy to the neck region. On occasion, patients have multiple palpable thyroid nodules, often bilateral, that may have varied pathologic characteristics. We prefer to perform needle biopsies of each of these nodules insofar as it is feasible. A history of a multinodular thyroid gland of many years' duration does not rule out the presence of carcinoma.

Although a study of frozen sections for indeterminate thyroid nodules may not provide a more precise diagnosis at operation, the pathologist may be able to indicates a degree of suspicion of malignancy. However, such impressions may prove to be misleading and may not agree with the final diagnosis; the surgeon's judgment remains critical. In our opinion, a subtotal thyroidectomy and appropriate cervical lymph node biopsies constitute reasonable treatment in these cases.

As is evident in the present series, appropriate dosages of

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radioactive iodine administered after surgery are capable of destroying at least 3 to 4 g of residual thyroid tissue. We also expect radioactive iodine to be capable of eliminating microscopic metastases, and we use it routinely in cases of proven extrathyroidal metastasis.

References


Invited Commentary

This article addresses the important clinical question about the surgical treatment of patients with indeterminate or suspicious thyroid nodules by aspiration biopsy and cytologic examination. The authors suggest that when one cannot determine by cytologic or frozen section examination whether a suspicious thyroid nodule is benign or malignant, a total lobectomy on the side of the suspicious nodule and a subtotal or near total lobectomy on the contralateral side should be performed. The authors used such an approach in 37 patients with indeterminate thyroid nodules. Eight (22%) of the nodules were subsequently proved to be malignant, and three patients received postoperative radioactive iodine therapy. None required reoperation.

One must certainly listen to the advice of these experienced surgeons; it is difficult to argue with success. Percutaneous needle biopsy has been shown to be cost-effective and is quite accurate in diagnosing patients with papillary, medullary, and undifferentiated thyroid cancer. In fact, when an experienced cytologist is available, the results of cytologic studies are more accurate than those obtained by frozen section examination. Cytologists, however, cannot distinguish between follicular adenomas and follicular adenocarcinomas or between Hürthle cell adenomas and Hürthle cell carcinomas. They sometimes also have difficulty diagnosing patients who have follicular variants of papillary carcinoma, and it is these patients with indeterminate nodules whom this report addresses.

I treat patients with indeterminate thyroid nodules differently than do Block et al. In virtually all the studies summarized by Charbit et al (Ann Intern Med. 1984;101:25-28), about 20% of thyroid nodules are indeterminate or suspicious, and about 26% of these are malignant. I use the term suspicious rather than indeterminate because some cytologists use the term indeterminate when an inadequate specimen is obtained. Patients with insufficient tissue to make a diagnosis should undergo a repeated percutaneous biopsy. Most suspicious nodules are follicular neoplasms and I recommend an iodine 123 scan for these patients. In euthyroid patients in whom the nodule is "hot," as determined by iodine 123 scanning, thyroidectomy is not required since these nodules are rarely malignant. When the nodule is "cold," I recommend thyroidectomy.

Prior to thyroidectomy I tell patients that I will probably perform a thyroid lobectomy for benign nodules and for suspicious nodules when it cannot be determined whether the lesion is malignant. If a nodule is malignant, I perform a total or near total thyroidectomy. I use frozen section analysis when suspicious lymph nodes are found or when tumor has an irregular margin or appears grossly to be malignant. In about 10% of patients with indeterminate or suspicious thyroid nodules, carcinoma is diagnosed only later by permanent section. I usually reoperate on these patients to complete the total thyroidectomy and discuss this with them prior to the initial operation.

The reason I recommend this approach rather than that of the authors is that most of these lesions are benign and thus only about 10% of patients require reoperation. When only a lobectomy is performed, the patients with follicular adenomas do not require thyroid hormone treatment. When a total thyroidectomy has been performed, one can use iodine 131 to treat any metastases seen with scanning, whereas when a near total thyroidectomy has been performed, one must first ablate the thyroid remnant and then administer another dose to ablate any micrometastases. One might suggest that reoperation is associated with a higher incidence of complications, but this should not be the case when patients only require a lobectomy because the recurrent laryngeal nerve and parathyroid glands are in virgin territory.

Although patients with minimally invasive follicular carcinomas and encapsulated papillary thyroid carcinomas that are less than 1.5 cm are adequately treated by lobectomy alone, it is difficult to argue against total thyroidectomy for larger or more invasive thyroid carcinomas when this operation can be performed safely. In a recent report by DeGroot et al (J Clin Endocrinol Metab. 1996;71:414-424), more aggressive thyroid surgery (total or near total thyroidectomy) followed by treatment with radioactive iodine resulted in the fewest recurrences and the best survival rate.

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