Feasibility of Sentinel Lymph Node Detection in Nodular Thyroid Disease

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ABSTRACT

Background and purpose: Sentinel lymph node biopsy has been proven to be successful and accurate in predicting the nodal status in melanoma and breast cancer. Occult lymph node metastases are common in well differentiated thyroid cancer (WDTC). Although the prognostic significance of these occult lymph node metastases remains controversial, identifying these patients may help direct therapy. The purpose of the study was to assess the technical feasibility and the safety of the sentinel lymph node biopsy in uni-nodular thyroid disease.

Methods: Patients of previously untreated benign solitary thyroid nodule, diagnosed preoperatively by fine needle aspiration cytology without any palpable cervical lymph node were prospectively studied. The nodule was injected with isosulfan blue vital dye. Blue stained lymphatics were traced. Then, hemithyroidectomy was performed.

Results: A total of 30 patients underwent sentinel lymph node biopsy; lymphatics were observed in 23 patients and sentinel lymph nodes were found in 18. In 5 patients, blue stained lymphatics were traced to the outside of the central compartment but no sentinel lymph node was identified. Sentinel lymph nodes were located in the central compartment in 14 cases, in the lateral compartment in 3 cases and in one patient 2 sentinel lymph nodes were found in both the central and the lateral compartments. Overall detection of sentinel lymph nodes was possible in 60% of cases. There were no intra or postoperative complications.

Conclusions: The role of sentinel lymph node biopsy has yet to be determined in the thyroid setting. Certainly the technique can be performed safely, but its accuracy needs further refinement and investigation on larger series of patients before it can be recommended in the routine management of thyroid neoplasia.

Key Words: Sentinel node - Biopsy - Solitary thyroid nodule.

INTRODUCTION

The sentinel lymph node (SLN) is defined as the first lymph node draining a regional lymphatic basin. Lymphatic mapping and sentinel lymph node biopsy (SLNBx) using both vital dyes and radioisotopes have been proven to be accurate in predicting the nodal status in melanoma and breast cancer [1,2]. Sentinel lymph node biopsy has been developed as an alternative to elective lymph node dissection in patients with clinically node-negative disease. The identification and removal of the SLN has allowed detection of microscopic metastatic disease, thereby allowing selective lymph node dissection in these patients and avoiding unnecessary nodal dissection and its associated morbidity. Only recently, SLNBx techniques have been applied to other tumor types including squamous cell carcinoma of the head and neck [3], Merkel cell tumors [4], and thyroid cancer [5-6]. Kelemen et al. [5], pioneered sentinel lymphadenectomy in thyroid tumors. Their study included a heterogeneous group of patients of both benign and malignant cases. This technique, if feasible and safe, could be used to select patients for selective lymph node dissections, postoperative radioiodine ablation therapy or both. The aim of this study was to assess the technical feasibility of sentinel lymph node biopsy with isosulfan blue vital dye in patients presenting with uni-nodular thyroid disease.

PATIENTS AND METHODS

Inclusion criteria: In the period from January 2002 to December 2003, a total of 30 patients were enrolled in this study. Patients with a solitary thyroid nodule not suspicious for ma-
lignancy by fine-needle aspiration cytology, with no palpable lymph nodes (LN), no history of head and neck surgery, and no known allergy to dye met the inclusion criteria. As we were conducting a technical feasibility study for a procedure and not a clinical trial, only patients with solitary thyroid nodule not suspicious for malignancy were included. Informed consent was obtained from each patient.

**Surgical procedure:** At the time of surgery, a collar incision was performed in all patients. After sub-platysmal flap elevation, the midline fascia was opened and the strap muscle was gently separated from the thyroid gland. When the tumor was exposed adequately, approximately 0.5 to 1cc Isosulfan Blue (1%) solution (manufactured by: Ben Venue Labs, Inc., Bedford, OH 44146 USA) was injected intra-tumoral using a tuberculin syringe. Care was taken not to stain any of the surrounding structures with the vital blue dye. To avoid spillage, the stain was injected slowly, applying little pressure and blotting the injection site with a wad of cotton when the needle was withdrawn.

Within a couple of minutes, blue stained lymphatic channels could be visualized, starting from the thyroid primary lesion which became apparent and led to the identification of the blue stained LN. The sentinel lymph node was then resected. Hemithyroidectomy proceeded with suture of the thyroid vessel stumps, identifying and safeguarding the recurrent laryngeal nerve and parathyroid glands. Postoperatively, patients were monitored for evidence of recurrent laryngeal nerve palsy and bleeding.

**RESULTS**

During the period extending from January 2002 to December 2003, a total of 30 patients (25 females and 5 males) with the diagnosis of benign solitary thyroid nodule underwent attempted SLNBx. Their median age was 31 years, ranging from 18 to 54 years. The pathologic diagnosis of the thyroid nodules for patients who underwent SLNBx and lymphatic mapping is shown in Table (1).

In 7 of these patients (23.3%) no lymphatic channels could be seen; and in 23 patients (77.7%) blue stained lymphatic channels were apparent at operation (Fig. 1). Of the 23 patients with successful tests, SLNs were identified in 18; 5 patients had lymphatic channels that tracked through the central compartment (paratracheal and tracheo-esophageal area) and ipsilateral supraclavicular area and the lower third of the jugulocarotid chain (lateral compartment), but no SLN was identified. In 3 cases, SLN were confined to the lateral compartment and in 14 cases SLN were removed from the central compartment. In one patient, two SLNs were found: One inside the central and the other in the lateral compartments. All patients in whom SLN (n=18) was identified had one SLN, except in two cases where two SLNs were identified (Fig. 2) There was no mortality or morbidity directly related to SLN-Bx.

**DISCUSSION**

Sentinel lymph node biopsy is now firmly established as a valuable technique in the management of melanoma and breast cancer, while its utility in thyroid disease remains to be determined. Introduced by Morton et al. in 1992 [1], it provided an accurate alternative to the formal lymph node dissection previously required to obtain prognostic information about nodal status, and to treat patients with melanoma. It is thus, understandable that there is enthusiasm to extend the technique to the management of other types of cancer with a propensity to regional lymph node metastases, such as thyroid cancer especially well differentiated types (WDTC). The utility of SLNBx in thyroid neoplasia may have some theoretical advantages. If SLNBx might accurately detect those patients with occult nodal disease, a selective approach to metastases (with either nodal dissection and/or radioiodine ablative therapy) could be individualized for each patient [7].

<table>
<thead>
<tr>
<th>Pathological diagnosis</th>
<th>Number of patients N (%)</th>
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<tr>
<td>Colloid nodule</td>
<td>16 (53)</td>
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<tr>
<td>Follicular adenoma</td>
<td>9 (30)</td>
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<tr>
<td>Hurthle cell adenoma</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Nodular thyroiditis</td>
<td>3 (10)</td>
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<tr>
<td>Total</td>
<td>30 (100)</td>
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Surgical exploration and palpation have been demonstrated to inaccurately predict nodal spread of disease in WDTC. Noguchi et al., performed lymph node dissection in 57 patients with papillary thyroid carcinoma (PTC). Among the patients with clinically negative nodal disease, 82% had metastatic spread on histologic examination of the nodes [8]. Similar results were reported by Hamming and colleagues, with 70% of clinically node negative patients, having metastatic nodal disease after prophylactic modified neck dissection [9]. Finding a reliable diagnostic method on which to base decisions to ensure an adequate lymphadenectomy is the goal of many endocrine surgeons dealing with WDTC. Much effort has been spent on this problem and the SLN has been recently introduced as a mean for establishing the pathological status of LNs.

A variety of methodologies have been utilized when carrying out SLNBx for thyroid cancer. SLNBx techniques can broadly be classified as vital dye techniques, radiotracer techniques, and a combination of both techniques. Kelemen et al. [5] were the first to demonstrate that SLNBx with isosulfan blue dye staining is feasible in thyroid neoplasia. Their study included 17 patients in whom 15 SLNs were identified, and in two cases, the lymphatic spread extended retro-sternally and so, no SLN was retrieved.

In a similar study, by Dixon et al., where SLNBx was carried out on 40 patients with nodular thyroid lesions using vital blue dye (15 malignant and 25 benign), lymphatic channels were seen in only 31 patients (78%) and SLNs were found in 26 patients, and 5 patients had lymphatic channels that tracked through the central compartment, but no SLN was identified [10]. Fukui et al. [12] carried out SLNBx on 22 patients with PTC, in their study, SLNs were identified in 21 of 22 patients (95%). In the current study, the overall success rate in identifying the SLN was 60% (18/30). This rate is somewhat similar to that of Dixon et al., 65% (26/40) [10], but lower than that reported in other series; Kelemen et al. [8] 88% (15/17), Pelizzo et al. [11], 76% (22/29) and Fukui et al. [12] 95% (21/22).

In the present study, SLN was identified in the central compartment in 77.8% (14/18) of cases; whereas, 3 SLNs were only identified at the lateral compartment (16.7%), bypassing the central compartment. This was in contrast to the results of Kelemen and his co-authors [5] in which SLN were always identified in the central compartment (15/17). Two of their cases had a second SLN outside the central compartment in the lateral neck. In another study, Pelizzo et al. [11] carried out SLNBx on 29 N0 patients with preoperative cytological diagnosis of PTC using patent blue vital dye. The location of the
SLN was in the central compartment in 19/22 (86%) and in the lateral compartment in 3 patients (14%). Although the central compartment is usually representative of the first regional drainage basin, skipped lesions have been reported. Noguchi et al. [8] demonstrated that 7% of thyroid metastases appear in the lateral compartment only, bypassing the central lymph nodes. Also Dixon et al. [10] found that 12.5% (5/40) of the patients in whom it appeared that the SLN was outside the central compartment. This was similar to our finding of 10% (3/30) incidence of identification of SLN in the lateral compartment without involvement of the central compartment. This was in contrast to Tsugawa and coworkers [13], who performed SLNBx on 11 patients with PTC. In their study, SLN staining occurred in all cases, which was paratracheal in 5 patients, jugulocarotid in 4 (36.4%) and both paratracheal and jugulocarotid in 2. It was also, reported that 23.8% (5/21) of the patients with PTC had SLNs in the lateral compartment by Fukui et al. [12]. Therefore, SLNBx may well have a place, if only to guide the surgeon as to the extent of dissection that needs to be undertaken at the time of thyroidectomy. The use of intra-nodular injections of Patent Blue dye to identify the SLN is still relatively new. The method initially proved rather difficult to implement. There are several disadvantages of this technique, firstly is spillage of the dye into the thyroid compartment, which interferes not only with the recognition of the parathyroid glands and the recurrent laryngeal nerve, but also with the identification of the SLN. We learned to overcome this drawback by injecting the dye very slowly, and immediately blotting the site of injection. The second disadvantage that might occur is non visualization of the lymphatics. We encountered this draw back in 7 out of 30 cases in the current study (23.7%). This was previously observed by other investigators, in 30% by Dixon et al. [10], and in 24.1% (7/29) by Pelizzo et al. [11]. Several factors play a role for failure of lymphatic visualization; firstly disruption of the lymphatics during initial dissection prior to injecting the vital dye [10]. Secondly, tumor-blocked lymphatic channels have been identified as a potential cause for failure to identify the SLN [14]. Thirdly, the search for the SLN may be fruitless as it may be concealed in a retrosternal or retro-esophageal site [11].

A third disadvantage of SLNBx exists. Blue dye uptake by a parathyroid gland was recorded in two series [10,15] and led to mistakenly removing the gland as a sentinel lymph node. This affinity of the parathyroid glands for dye has been previously exploited for intra-operative gland identification [16]. Staining of the parathyroid gland with dye must therefore, be considered a major drawback of this technique and necessitates the need to identify the parathyroid glands prior to injection.

Lymphoscintigraphy and intra-operative gamma probe guidance has been utilized as a technique to localize the SLN in WDTC. Gallowitsch et al. [17] described a PTC case in which Tc-labeled colloidal albumin injected intra-tumor was successful in identifying the SLN. In the largest study using a radiotracer technique, SLNBx was carried out on 9 patients with thyroid masses [18]. The SLN was identified in 4 of 6 WDTC patients (66%), in the latter series. This was in agreement with the findings of two other studies reporting a sensitivity of 50% [6] and 66% [19] for lymphoscintigraphy. Its advantage is that injection of the radiolabel material is done preoperatively, thereby eliminating disruption of the lymphatic channels during the initial dissection. Radioscintigraphy would also diagnose those patients in whom the SLN lies outside the central compartment. One of the disadvantages of lymphoscintigraphy is that SLNs may be missed if they lie very close to the injection site and most probably hidden behind the thyroid in the paratracheal space; this can be easily detected with gamma probe after removal of the thyroid. Another disadvantage is spillage of the colloid into the surrounding tissue, which can be detrimental because it will impede any further evaluation. In addition, this technique is too expensive.

Combination of both techniques, dye and radio colloid together was described in a single report in which SLNBx was carried out on 6 patients with PTC [6]. The SLN was identified in all cases and all nodes correctly predicted the disease status of the patient's neck. When considered separately, the vital dye technique identified 50% of the SLNs and the radiotracer technique identified 83% of the SLNs. Thus, in this pilot study these two techniques complimented each other.
The sensitivity of SLNB in detecting occult disease with vital blue dye alone needs to be considered. In the study by Dixon et al. [10], a total of nine patients with PTC had metastatic nodal disease detected on LN dissection or postoperative scanning; the SLNBx detected only 6 patients. In a recent update of the original series by Kelemen et al. [5], Haigh et al. [15] reported that occult nodal disease was detected in only 9 of their 16 patients with PTC. Combining the results of these two series, SLNBx detected occult disease in 15/25 (60%) cases with PTC. Since the incidence of occult nodal disease in this condition was reported to be as high as 90% [9,20], the sensitivity of the biopsy technique in detecting micrometastases is questionable.

On considering carrying out SLNBx on WDTC patients in a disease with a high prevalence of nodal metastases that are of questionable prognostic value, the clinical justification for carrying out a procedure aimed at nodal staging is questionable. Although a number of studies [13,30] have demonstrated that SLNBx may be an accurate technique for obtaining information about cervical lymph node involvement in patients undergoing thyroidectomy; unfortunately, that in itself is not sufficient to justify the introduction of SLNBx into clinical practice in this area. The advantages of SLNBx in patients with melanoma and breast cancer are self evident. Axillary and groin dissections are potentially morbid procedures, requiring a substantial skin incision and are associated with risks such as lymphoedema. Information about lymph node status is a significant prognostic factor determining survival and guiding further management. Neither of these criteria applies to WDTC. The WDTC drains, in most cases, to the paratracheal nodes or to nearby jugular nodes. Those nodes can be readily removed at the time of thyroidectomy through the same incision, without the need to extend the scar, or to unnecessarily increase the risk of complications.

More importantly, cervical lymph node involvement has never been demonstrated to be a prognostic factor in relation to survival of patients with WDTC, other than in a selected group with advanced disease [21]. None of the commonly utilized thyroid cancer patients risk assessment systems: AMES (Lahey Clinic) [22], AGES/MACIS (Mayo Clinic) [23,24], GAMES (Memorial Sloan-Kettering) [25,26] demonstrated that neck nodal metastases correlated with patient survival. Also, the questionable biological significance of nodal metastases was reflected in the American Joint Committee on Cancer (AJCC) staging system for WDTC. In this staging system, nodal disease status plays no role in the staging of patients younger than 45 years of age [27]. Thus, if clearance of local draining lymph nodes can be undertaken without the morbidity associated with axillary or inguinal dissection, and knowledge of lymph node status does not affect survival anyway, why SLNBx for thyroid cancer?. The answer may lie in changing attitudes towards the place of selective neck dissection in patients with WDTC [28]. Gosnell et al. [29] stated that central neck dissection was an underutilized procedure and should be the standard of care at initial operation for PTC. Such a practice may well reduce local recurrence rates, even if survival is not affected. If performed, then it is best directed to those nodes most likely to be involved. However, the phenomenon of initial nodal spread outside the central compartment have been repeatedly demonstrated [8,30], so central neck dissection may miss the involved LN. The presence of cervical lymph node metastases has been associated with an increased incidence of local regional recurrence [20], yet in large retrospective studies the presence of lymph node metastases is not associated with a decrease in survival [31]. This has led some authors to recommend compartment-oriented dissections of lymph nodes in WDTC to decrease the recurrence rate and possibly improve survival in selected patients [20,32]. The SLNBx may help to identify those who harbor occult lymph node metastases outside the central compartment to select patients for more extensive nodal dissection. In conclusion SLNBx is safe and feasible in thyroid neoplasia, however further studies are necessary to improve the diagnostic accuracy prior to routine clinical practice.

**REFERENCES**
