Techniques

Radio-guided Surgery for Non-\(^{131}\)I-avid Thyroid Cancer

Domenico Rubello, \(^1\) Maria Rosa Pelizzo, \(^2\) Dario Casara, \(^3\) Andrea Piotto, \(^2\) Antonio Toniato, \(^2\) Lorraine Fig, \(^4\) and Milton Gross \(^4\)

Objective: In this paper we report in a larger series the use of radio-probe-guided surgery (RGS) in nonradioiodine-avid, well-differentiated thyroid cancer (DTC). Design: Thirty-seven patients with locoregional recurrent, nonradioiodine avid DTC were studied with \(^{99m}\)Tc-sestamibi directed RGS using a handheld gamma probe as an intraoperative detector. Outcome: Twenty-three women and 14 men were followed after RGS for 35.4 ± 12.5 months (range 9–57). There were 33 papillary (one “tall” cell variant), 2 follicular, and 2 Hürthle cell cancers. In 7 patients, thyroid cancer recurred in the neck while cervical lymph node metastases were found in 31 patients (one patient had papillary cancer in both the thyroid bed and cervical lymph nodes). Sixty-six discrete nodules ranging from 6 to 45 mm (mean tumor diameter, 18.4 ± 8.5 mm) were identified by both high-resolution ultrasound and \(^{99m}\)Tc-sestamibi probe-guided RGS. After RGS, Tg (thyroglobulin) fell in 33 of 37 patients and mean target/nontarget sestamibi uptake ratios decreased in all 37 patients (\(p < 0.0001\)). Conclusion: These data confirm our earlier observations that a \(^{99m}\)Tc-sestamibi intraoperative gamma probe can be used to identify and guide resection of recurrent tumor and involved lymph nodes in locoregional metastases of nonradioiodine-avid thyroid cancer.

Introduction

The loss of radioiodine-concentrating ability by differentiated thyroid cancer (DTC) is seen in as many as 30% of cases, which increases to approximately 40% in patients over 65 years old (1–5). In addition, loss of radioiodine avidity has been seen after radioiodine therapy and as a result of progressive tumor dedifferentiation (6,7). Elevated cellular metabolic activity, thyroglobulin (Tg) secretion, and the distribution of potential sites of metastases to cervical and mediastinal lymph nodes are preserved; however, this functional change adversely affects prognosis and limits the approach to therapy in patients with suspected metastatic disease (8–10). Anatomic imaging with high-resolution ultrasound has proven useful in the identification of small lymph nodes, but it alone cannot discern the presence of metastases (11). Scintigraphy with radiopharmaceuticals with avidity for thyroid cancer has been demonstrated to be useful in this regard. Technetium-99m (\(^{99m}\)Tc) labeled methoxyisobutylisonitrile (\(^{99m}\)Tc-MIBI), \(^{99m}\)Tc-tetrafosmin, \(^{201}\)Thallium, \(^{131}\)I-fluorodeoxyglucose, and others have been used to depict nonradioiodine-avid metastases of differentiated thyroid cancer with high sensitivity and accuracy (11–19). When combined with high-resolution ultrasound, \(^{99m}\)Tc-MIBI scintigraphy can be used to diagnostic advantage in patients with locoregional metastases of nonradioiodine-avid thyroid cancer (20,21). Further, surgical intervention can be facilitated with the ability to positively identify involved lymph nodes with an intraoperative gamma probe technique. In this report, we expand our previous experience in the use of \(^{99m}\)Tc-MIBI radio-guided surgery for locoregional recurrence of nonradioiodine avid, differentiated thyroid cancer (22).

Materials and Methods

Thirty-seven patients with locoregional recurrent, nonradioiodine-avid, well-differentiated thyroid cancer were studied with \(^{99m}\)Tc-MIBI directed radio-guided surgery (RGS) using a handheld gamma probe as an intraoperative detector. Selection criteria for RGS were previously described and included: (1) prior treatment for DTC by total thyroidectomy and \(^{131}\)iodine therapy, (2) negative radioiodine-131 scan with increasing serum Tg levels at follow-up, (3) locoregional recurrence on both \(^{99m}\)Tc-MIBI and high-resolution ultrasound

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of the neck, and (4) discernable accumulation of $^{99m}$Tc-MIBI uptake in tumor foci without distant metastases (22).

Technetium-$^{99m}$ MIBI scans were performed as described previously (20–22). A $550–740$ MBq dose of $^{99m}$Tc-MIBI was injected intravenously, and whole-body and spot views of the neck and chest were acquired for 20 to 30 min and at 2 h after injection. A large field-of-view gamma camera (Orbiter 7500 or E-CAM, Siemens, Hoffman Estates, IL, USA) was equipped with a parallel-hole, low-energy, high-resolution collimator. Neck ultrasound was performed at the same time with a small-port, high-resolution 10-MHz transducer (Technos, Esaote, Italy).

Serum Tg was measured by immunoradiometric assay (Nycomed, Milan, Italy) in patients both on and off L-thyroxine. Patients with a Tg level of < 2 ng/mL were considered athyrotic (21–24). Serum anti-Tg antibody (TgAb) levels were measured by a radioimmunoassay method (Biodata, Milan, Italy) (21,22).

An 11 mm handheld, commercially available gamma probe (Scintiprobe 100, Pol.hi.tech, Carsoli-Aquila, Italy) was used. The intraoperative procedure for RGS has been previously described (22) and consisted of the following:

1. In the operating suite, 10 min before starting the procedure, a low dose of $^{99m}$Tc-sestamibi 1 mCi (37 MBq) was injected in a peripheral vein, followed by a flushing dose of saline (30 mL).
2. Using the earlier obtained scans of the neck as a guide, the neck was surveyed using the gamma probe to identify foci of $^{99m}$Tc-sestamibi accumulation.
3. Through a wide neck incision the gamma probe was again used to scan the operative field for foci of $^{99m}$Tc-sestamibi accumulation.
4. Radioactivity was measured using the gamma probe over foci of $^{99m}$Tc-sestamibi accumulation (T), over nontumor areas for background activity (B), directly over resected tumor tissue, and over the tumor bed to assess the success of the procedure. Tumor (T)/bed (B) and tumor bed (TB)/B ratios were calculated.
5. The operating surgeon was queried as to the usefulness of RGS in each patient using a 4-point scale: 1, very useful; 2, useful; 3, moderately useful; 4, not useful.

Verbal and written, institutionally approved informed consent was obtained from each patient. In the case of minors, permission was obtained from parents. Pregnant operating room personnel, including the operating surgeon, to the low dose (1 mCi) of administered $^{99m}$Tc-sestamibi was ~ $1 \mu$Ci/h. The operating surgeon assessed RGS as very useful in 8 patients in whom metastatic foci were embedded in fibrotic tissues or located behind blood vessels, useful in 17 patients, moderately useful in 10 patients, and not useful in 2 patients.

Results

Thirty-seven consecutive patients with recurrent locoregional, nonradioiodine-avid well-differentiated thyroid cancer underwent RGS with $^{99m}$Tc-sestamibi and a handheld gamma probe. Eight of the 37 patients in this series were previously reported in the literature (22). Table 1 reviews the clinical, laboratory, imaging, and pathology findings in this group. There were 23 women and 14 men with an average age of 45.6 years (range 17–65 years) followed for a mean time of 34.5 ± 12.5 months (range 9–57 months). All patients underwent total thyroidectomy and radioiodine therapy and were maintained on L-thyroxine at a dose titrated to achieve suppressed thyroid-stimulating hormone (TSH) levels. Radioiodine doses ranged from 100 mCi (370 MBq) to 300 mCi (1110 MBq) (Table 1). Nineteen patients received a single dose (minimum dose 150 mCi [555 MBq]; maximum dose 300 mCi [1110 MBq]); 15 patients received two doses (cumulative dose between 250 mCi [925 MBq] and 400 mCi [1480 MBq]), and 3 patients received three doses (cumulative dose of 300 mCi [1110 MBq], 500 mCi [1850 MBq], and 800 mCi [2960 MBq], respectively). There were 33 papillary cancers (one tall cell variant), 2 follicular cancers, and 2 Hürthle cell carcinomas. In 7 patients, thyroid cancer recurred in the neck while cervical lymph node metastases were found in 31 patients (one patient had papillary cancer in the thyroid bed and cervical lymph node metastases).

Preoperative mean target/nontarget MIBI uptake ratio was 2.52 ± 0.89 (range 1.0–5.4) and fell postoperatively in the operative field in all 37 patients ($p < 0.0001$) (Fig. 1). Thyroglobulin levels were elevated in 33 patients, with 4 patients expressing anti-Tg antibody preoperatively. Postoperatively Tg fell in all 33 patients (23 had postoperative Tg levels < 2.0 ng/mL) and was < 1 ng/mL in 2 of the 4 patients with the preoperative presence of anti-Tg antibodies, which became negative postoperatively (Fig. 2). In 2 patients (see Table 1, patients 4 and 34) with markedly elevated preoperative Tg levels of 980 ng/mL and 1833 ng/mL, initial postoperative declines of Tg (275 ng/mL and 720 ng/mL, respectively) were temporary, with marked increases at follow-up intervals of 6 and 8 months to 1320 ng/mL and 1125 ng/mL, respectively, with the development of lung metastases. Neither the size nor the number of tumor foci correlated with preoperative Tg levels.

Sixty-six discrete nodules were identified by both high-resolution ultrasound and $^{99m}$Tc-sestamibi probe RGS (Fig. 3) and were resected. Mean tumor nodule diameter was 18.4 ± 8.5 mm (range 6–45 mm). In 23 patients, a solitary focus of thyroid cancer was located in the thyroid bed (6 patients) or in a cervical lymph node (17 patients); in 7 patients, two foci were located in the thyroid bed (2 patients) and in cervical lymph nodes (5 patients); in 6 patients, three cervical lymph nodes were identified, and in 2 patients, four and six cervical lymph nodes containing thyroid cancer, respectively, were identified (Table 1). There were no complications (postoperative hypoparathyroidism or recurrent laryngeal nerve palsy) after RGS. Estimated radiation exposure to operating room personnel, including the operating surgeon, to the low dose (1 mCi) of administered $^{99m}$Tc-sestamibi was ~ 1 μSv/h. The operating surgeon assessed RGS as very useful in 8 patients in whom metastatic foci were embedded in fibrotic tissues or located behind blood vessels, useful in 17 patients, moderately useful in 10 patients, and not useful in 2 patients.

Discussion

Radioiodine-negative thyroid cancer presents a challenge in diagnosis and localization. Loss of radioiodine avidity by
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<td>16</td>
<td>3.6</td>
<td>1.0</td>
<td>1833</td>
<td>720</td>
<td>9</td>
</tr>
<tr>
<td>34</td>
<td>M</td>
<td>46</td>
<td>Papillary</td>
<td>Lung mets</td>
<td>1125</td>
<td>11</td>
<td>3.2</td>
<td>0.9</td>
<td>1125</td>
<td>9</td>
<td>16</td>
<td>LWD</td>
</tr>
</tbody>
</table>

Status (LDF, LWD) established by measuring serum Tg both under L-thyroxine and after TSH stimulation withdrawal in 21 patients and recombinant human TSH in 14 patients. Ttx (total thyroidectomy); $^{131}$I therapy; LN, lymph nodes; T/B, tumor to background ratio measured intraoperatively by gamma probe; TB/B, tumor bed to background ratio measured intraoperatively by gamma probe after lesion extirpation; Tg, thyroglobulin; LDF, living disease-free (Tg levels < 1.0 ng/mL); LWD, living with disease.
DTC is seen in older patients and more-aggressive and less-differentiated cell types (5). Thyroglobulin levels are elevated despite the loss of the ability to accumulate radioiodine (21). Accurate localization of recurrent thyroid cancer is important, especially in patients whose tumors have lost the ability to accumulate radioiodine since effective therapy becomes dependent on a surgical approach (21). Ultrasound alone or in combination with 99mTc-sestamibi has been shown to be sensitive in localizing recurrent thyroid cancer (21,22,25,26). The incorporation of intraoperative probe-guided surgery is based on the success of this technique in the treatment of parathyroid adenomas (27–29).

Radiopharmaceuticals available for imaging non-radioiodine-avid thyroid cancer include 201Thallium, 99mTc-tetrafosmin, 99mTc-sestamibi, 111In-pentetreotide, and 18F-fluorodeoxyglucose (30). The mechanisms responsible for 99mTc-MIBI and 99mTc-tetrafosmin uptake by thyroid cancer are probably due to cellular mitochondrial content, but other factors such as cellular desmoplasia, membrane potentials, and active transport may also play a role (31–33). In a comparison study by Nishyama and colleagues, 201Thallium and 99mTc-tetrafosmin demonstrated equal sensitivity in the detection of locoregional metastases of well-differentiated thyroid cancer (12). 99mTc-sestamibi was used by Alam and coworkers to localize locoregional metastases of well-differentiated thyroid cancer with sensitivity and positive predictive and negative predictive values of 94.4, 96.3, and 97.7%, respectively (13).

Pentetreotide is a somatostain analog that has been shown to localize thyroid neoplasms to include medullary thyroid cancer, but it has not been applied to the identification of locally recurrent disease in the neck. Fluorodeoxyglucose, a glucose analog, has been used to localize a wide variety of neoplasms using positron emission tomography and has been specifically useful in localizing radioiodine negative thyroid cancers (34,35). The recent availability of handheld probes designed to detect positron emissions is now being applied in the localization of metastatic disease and may allow studies of this type in thyroid cancer.

In a preliminary report we presented 8 patients with recurrent, 131I-negative, well-differentiated thyroid cancer in which locoregional metastases were identified at surgery with probe-directed, low-dose 99mTc-sestamibi (22). The present study expands and confirms our earlier experience, now with 37 patients, all of whom had their recurrent thyroid cancer successfully localized and extirpated using this technique. Thyroglobulin levels fell postoperatively in all patients: based on a postoperative Tg level of <2 ng/mL (6 weeks after thyroid hormone withdrawal or after recombinant TSH administration, with follow-up intervals...
and ultrasound are readily available, inexpensive, and within the scope of the diagnostic capabilities of virtually all laboratories. Furthermore, the addition of intraoperative probe guidance is not technically demanding.

This work builds upon our experience and the reports of others in the localization and probe-guided extirpation of thyroid cancer and parathyroid adenomas using 99mTc-sestamibi and demonstrates the applicability of this approach in the treatment of locoregional recurrence of radioiodine-negative thyroid cancer.

References


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FIG. 3. 99mTc-sestamibi scan of a patient with recurrent thyroid cancer in a right cervical lymph node (arrow).

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