18F-fluorodeoxyglucose and 131I Radioguided Surgical Management of Thyroid Cancer
Carrie L. Francis, Chuck Nalley, Chris Fan, Donald Bodenner and Brendan C. Stack, Jr
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What is This?
Abstract

Objective. To describe a technique that assists in the surgical management of recurrent local regional well-differentiated thyroid cancer (WDTC).

Study Design. Case series with chart review.

Setting. Two academic health centers from 2001 to 2009.

Subjects and Methods. Patients operated upon by the senior surgeon (BCS) for recurrent WDTC.

Results. Thirteen patients with recurrent WDTC were operated upon with radioguided surgical (RGS) technique to identify recurrence for excision. Eight patients had iodine avid disease and were candidates for RGS with 131I. The remaining 5 patients had cancer with a proven loss of iodine avidity and were, therefore, operated upon with a fluorodeoxyglucose (FDG) RGS technique.

Conclusion. RGS is a feasible approach to identify recurrent disease in an operated field and ensure its successful excision. Although focal disease may be identified with this technique, this is not a tool for limited excisions (“berry picking”).

Keywords
thyroid cancer, radioguided surgery, iodine, FDG, fluorodeoxyglucose, PET, positron emission tomography

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Thyroid cancer is the most common endocrine malignancy in the United States, accounts for approximately 33,000 new cases annually, and is on the rise. Well-differentiated thyroid carcinoma (WDTC) boasts 10-year survival rates over 90%. Despite low mortality, locoregional recurrence (LRR) occurs in 6% to 30% of patients and can be associated with a significant drop in the 10-year survival rates to 50%. Nodal recurrence has a poor prognosis; studies have indicated 30% will have regional disease unable to be eradicated and 15% mortality. Therefore, an aggressive approach to initial management and strict follow-up are the accepted methods to render most patients disease free. 131I scintigraphy (131I WBS), ultrasonography (US), and serum thyroglobulin (Tg) are well-defined tools for surveillance after postsurgical radioactive iodine (RAI) ablation. US is a very sensitive tool and can accurately identify up to 95% of recurrences, particularly in conjunction with fine-needle aspiration (FNA). Tg is only produced by thyroid tissue and provides a sensitive and specific marker for persistent or recurrent disease. US examination and serum Tg levels are usually obtained at 6 months, 12 months, and then annually, if disease free. When serum Tg is elevated and/or US imaging is suspicious, FNA with or without 131I WBS is usually obtained. 131I WBS evaluates the functional activity and the distribution of thyroid tissue and can be used in radioguided surgery (RGS) for thyroid cancer. WBS, however, may be negative in 20% of cases where there is elevated Tg. Under those circumstances, 18F-fluorodeoxyglucose positron emission tomography (18F-FDG PET) combined with computed tomography (CT) can be obtained to detect recurrence. Many
studies have supported the benefit of 18F-FDG PET/CT as a useful diagnostic tool.13,15 131I and 18F-FDG PET are complementary exams for detecting thyroid cancer; when one is positive, the other is negative. The development of nodal recurrence or residual macroscopic thyroid tissue is considered a surgical disease, and thus detection and localization of disease are of paramount importance in comprehensive surgical management.13

Once recurrence has been determined, intraoperative localization becomes important. Although thyroid surgery has a low morbidity, operating in a previously operated, scarred, and fibrotic wound raises the risk of nerve or parathyroid injury significantly.13 131I RGS has been shown to increase therapeutic control in previously detected and undetected tumors.11,16 In 131I WBS-negative patients, there is an emerging interest in the 18FDG radioisotope being used intraoperatively.17,18 Authors have suggested that 18F-FDG RGS can be of benefit in the overall management and survival of thyroid cancer patients with LRR.17

Despite the increasing application of 18F-FDG RGS by other disciplines, there are few studies describing the 18F-FDG RGS experience in head and neck surgery. Our cases series describes the senior author’s experience with an intraoperative 18F-FDG handheld gamma probe in 5 of 13 patients with WDTC and RGS. The aim of this series is to describe our technique and the potential clinical importance of this modality that can lower Tg, which is a measure of WDTC control.

Methods

Patients

Thirteen patients (10 women and 3 men; age range, 24-72 years; mean 44 years) with pathologically proven WDTC were evaluated retrospectively from Penn State Hershey Medical Center (Hershey, Pennsylvania) and the University of Arkansas for Medical Sciences (UAMS; Little Rock, Arkansas). All patients had prior surgical management of their WDTC followed by 131I RAI ablation. Twelve patients had the diagnosis of papillary thyroid carcinoma and 1 patient Hurthle cell carcinoma. Twelve of 13 patients were Tg positive. All patients were treated with postoperative thyroid hormone suppression. Our clinical practice is to follow patients with ultrasonography. Patients judged to be at risk for recurrence by ultrasound and confirmed by ultrasound-guided fine-needle biopsy were referred for nuclear medicine imaging. All patients were examined using scintigraphy and/or 18F-FDG PET/CT and then referred for RGS. Patients were separated into 2 groups: 131I avid (8 of 13) and 18F-FDG avid (5 of 13). All 18F-FDG avid patients had localizing PET/CT scans, had negative WBS, or were considered 131I failures after an ablation. Institutional review board (IRB) approval at both institutions was obtained for this study.

Radioguided Surgical Technique

Patients with ultrasound findings, elevated thyroglobulin, positive cytology, and localizing findings on nuclear medicine imaging were treated with radioguided surgery. Patients were given their indicated isotope on the day of surgery preoperatively. In FDG cases, the patients were kept in an isolated holding area for at least 2 hours prior to being transported to the operating room for surgery to reduce exposure to hospital staff. These patients were brought to the operating room with institution of radioactivity precautions as implemented by the radiation safety officer of their respective hospital.19 Radioactivity from FDG-injected patients was closely monitored at UAMS because of its high energy level, and this has been reported elsewhere.17,20 The patients all received general anesthesia.

Previous incisions were used or extended for exposure as was indicated based on the anatomy of the recurrent disease. Upon approaching the area of suspected recurrence as determined by a review of preoperative nuclear medicine and/or anatomic imaging, the RGC device was used to scan the area to focus the dissection and excision of the “hot spot.” For 131I cases, a standard, commercially available gamma probe was used (Carewise, Morgan Hill, California, or Neoprobe, Dublin, Ohio) with its spectral window set for the 131I isotope. For FDG cases, either a study device (IRB approved) or a specially designed and shielded gamma probe was used (both from Radiation Monitoring Devices, Watertown, Massachusetts). Both of these devices were comparable in sensitivity to detection of disease. All radiation data used for interpretation were in counts per second. No timed counting intervals were used in our intraoperative assessment.

Focused dissection revealed the target of interest. This may have been residual tissue or disease in the thyroid bed or nodes in the central or lateral necks. This was determined to be at least 2 times the background level and was excised. Target confirmation was an ex vivo measurement that was greater than 20% of the background activity (taken from the right shoulder). Specimens were labeled as radioactive, placed in formalin, and sent to pathology for processing later after time for adequate radioactive decay. No radioactive targets were left in field that were not physiologic (salivary glands) at the end of the procedure. The procedures were done as outpatients or after a 23-hour observation stay.

Results

Patient characteristics and data are recorded in Table 1. Twelve patients had a diagnosis of papillary carcinoma, and 1 patient had a diagnosis of Hurthle cell carcinoma. Prior to RGS, all patients were treated surgically followed by RAI. Eleven patients had prior reported total thyroidectomy. One patient underwent hemithyroidectomy because his other thyroid lobe had been removed during a total laryngectomy over 2 decades earlier. Another patient had diagnostic hemithyroidectomy, but because of his poor medical status at the time, he never underwent completion surgery.

Prior to 131I or 18F-FDG PET/CT imaging, suspicion for recurrence was detected by a combination of modalities, including elevated Tg and US findings. Eight of 13 patients were 131I positive on thyroid scan and uptake. Five of 13 patients were 131I negative or 18F-FDG PET/Tg positive. Prior to thyroid scan and uptake, stimulated Tg was obtained in all patients except 3. Two patients were missing Tg data, and the
third patient’s recurrent papillary thyroid carcinoma was incidentally found during another procedure, and definitive treatment with RGS in a heavily operated neck was performed without obtaining a preoperative stimulated Tg because of the known presence of residual thyroid gland.

Four preoperative Tg levels were unavailable. Four of 9 were above 10 ng/mL. Two had strongly positive 131I WBS. Two patients had suspicious US findings plus FNA proven recurrence. The final patient had conventional surgery 6 months prior without resolution of Tg level and a strongly positive 18F-FDG PET/CT. Patient J had detectable Tg after surgery but was noted to have distant lung metastasis at the time.

Surgical characteristics, findings, and follow-up are outlined for the 131I group in Table 2. All but one of the patients underwent completion thyroidectomy by the senior author. Four patients underwent central neck dissection; 3 underwent unilateral selective neck dissection on the side of the primary tumor. Lymph nodes were included in the surgical specimen in 6 patients. Patient E was diagnosed with a follicular adenoma. Patient M had negative pathology on bilateral and central neck dissection. Preoperatively, patient M had intense uptake in the thyroid bed on WBS; no FNA was obtained. These 2 cases would therefore be considered false positives for Tg surveillance.
All patients were treated postoperatively with RAI ablation. Five of 8 posttreatment scans were negative. Of the 3 patients (H, B, and J) who had positive postablation thyroid scans after 131I RGS, 2 scans (patients B and J) were positive for distant lung metastasis. Patient B was treated for distant metastasis; repeat 131I WBS was negative and serum Tg undetectable. Patient J was also treated; repeat 131I WBS showed uptake in a supraclavicular node. This node was negative on FNA, yet serum Tg was detectable. On recent US examination, patient J was noted to have US findings of recurrence. FNA, yet serum Tg was detectable. On recent US examination, patient J was noted to have US findings of recurrence.

Patient A developed LRR after 131I RGS. Since that time, the patient developed a second LRR in November 2008 with an elevated Tg of 2.7 on hormone withdrawal. 131I was negative, and PET was not obtained. After recombinant human thyrotropin stimulation, a US of the neck showed a lower midneck mass with suspicious characteristics, Tg was 0.7, and FNA was positive. Postoperative Tg was undetectable in 7 patients, including patient H, who had a positive 131I WBS. Only patient A developed an LRR after initial treatment.

Surgical characteristics, findings, and follow-up are outlined in Table 3. Three of the 5 patients unresponsive to 131I showed negative uptake on WBS. The other 2 patients were identified as noniodine avid secondary to recurrence after 131I ablative treatment. Four patients were managed with 18F-FDG PET/CT detection and 18F-FDG RGS. In 1 patient, 99mTc-sestamibi was used for detection and RGS. Two patients had completion thyroidectomy. Two patients underwent central neck dissection. Four patients had unilateral selective neck dissection. Eighteen lymph nodes were obtained in the surgical specimens, and 9 were positive. 18F-FDG PET/CT images showed foci that were consistent with the surgical specimens. Two patients were treated with external beam radiation postoperatively. Two patients are followed with US surveillance. Patient L underwent another RAI ablation. Posttreatment WBS showed mild activity in the left upper mediastinum and left lower cervical neck. Subsequent US examinations have been negative. Only 4 patients had postoperative 18F-FDG PET/CT scans. One of 4 patients had positive posttreatment 18F-FDG PET/CT scans. Patient F had elevated Tg and showed distant lung metastasis that were treated. Average length of follow-up was 39 months. Follow-up Tg was undetectable in 3 of 5 patients. To date, no one has developed recurrence.

No permanent complications were noted, and all patients did well with their surgery. Patient I had temporary vocal cord paresis that resolved over 6 months. Patient A developed temporary hypocalcemia that resolved 3 to 4 weeks after surgery. To date, all patients (both groups) are alive. Four are alive with disease; 9 are alive without disease.

### Discussion

Studies have suggested that up to 95% of lesions with the functional ability to concentrate iodine for hormone synthesis have low glucose metabolism, whereas those without this ability have a high glucose metabolism and thus high 18F-FDG avidity.21 In the follow-up of WDTC, when recurrent disease is suspected, Tg is elevated, and 131I WBS is negative, 18F-FDG PET/CT detection can be crucial to diagnosis and management. FDG PET/CT has 61%, 98%, and 86% sensitivity, specificity, and accuracy, respectively, for metastatic thyroid cancer.22 The ability to intraoperatively localize and remove preexisting and additional undetected disease in the setting of scar and fibrosis may contribute to overall cure and survival.

The standard methods for thyroid cancer follow-up include US, 131I or 123I WBS, and serial Tg measurements.5,6 Scintigraphy using 99mTc-sestamibi has been reported with success in patients suspected of recurrence and negative WBS.23-27 18F-FDG PET/CT, however, is still considered a more sensitive assessment tool.27-29 99mTc-sestamibi RGS has been reported by researchers in the past but not commonly employed because 18F-FDG is more specific.23 99mTc-sestamibi RGS was used to identify and guide resection of LRR in patient C. The combination of CT and 18F-FDG PET has been found to increase the diagnostic accuracy by providing anatomic localization.30,31

### Table 3. 18F-FDG PET Surgery Characteristics, Findings, and Follow-up

<table>
<thead>
<tr>
<th>Patient</th>
<th>Arm</th>
<th>Surgery</th>
<th>Pathology</th>
<th>Postoperative Treatment</th>
<th>Postoperative scan</th>
<th>Follow-up Tg</th>
<th>Distant Metastasis</th>
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<td>C</td>
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<td>CT (+) Left SND (1/1) Left RP (1/1)</td>
<td>XRT</td>
<td>NEG</td>
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<td>CND</td>
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<td>US</td>
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<td>Lungs</td>
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<tr>
<td>I</td>
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<td>CND (2/5)</td>
<td>US</td>
<td>NEG</td>
<td>11.5</td>
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<tr>
<td>K</td>
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<td>Right SND</td>
<td>(1/1)</td>
<td>XRT</td>
<td>NEG</td>
<td>&lt;0.2 (12/2007) 1.5 (8/2007)</td>
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</tr>
<tr>
<td>L</td>
<td>18F-FDG PET</td>
<td>Right SND</td>
<td>(3/3)</td>
<td>RAI with uptake and ablation</td>
<td>US NEG</td>
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<td>Mediastinum</td>
</tr>
</tbody>
</table>

Abbreviations: CND, central neck dissection; CT, completion thyroidectomy; 18F-FDG PET, 18F-fluorodeoxyglucose positron emission tomography; NEG, negative; POS, positive; RAI, radioactive iodine; RP, retropharyngeal; SND, selective neck dissection; Tg, thyroglobulin; US, ultrasound surveillance; XRT, radiotherapy.
US is the mainstay of cancer surveillance and significant in the detection of recurrent thyroid cancer. US may be the most sensitive tool available and will detect recurrences (95%) without the presence of risk factors such as rising Tg levels or positive WBS. Also, the ability to perform FNA at the time of US is cost-effective and sensitive.

Tg values should be undetectable following successful thyroidectomy and thyroid ablation. This makes Tg a sensitive and specific marker of recurrence if levels become elevated. Even in the presence of a negative WBS, elevated Tg can be an accurate predictor of recurrence. Thyroglobulin greater than 10 to 20 ng/mL is consistent with metastasis despite having negative imaging.

$^{131}$I WBS evaluates the functional activity and distribution of the thyroid tissue. Studies suggest that retaining the ability to concentrate $^{131}$I has prognostic importance. Recurrence signifies an aggressive histology and possible tumor dedifferentiation. In the case of WDTC, loss of the ability to concentrate and use $^{131}$I may have a negative effect on overall survival rates. Although negative $^{131}$I whole-body scintigraphy has become a clinical dilemma, $^{18}$F-FDG PET has emerged as a possible diagnostic solution and therapeutic tool in this patient population.

A diagnostic $^{18}$F-FDG PET can positively identify pathologic disease in more than 3 times the number of cases identified by $^{131}$I WBS. Most of these recurrences have been shown to recur in the neck, leaving surgical intervention as the best option for cure. In our case series, 9 of 13 patients (69.9%) developed recurrence in the central or lateral neck. Four of 13 were positive for cancer in the residual thyroid bed. Because $^{18}$F-FDG PET is able to identify metastatic disease with increased sensitivity than $^{131}$I, we have attempted to demonstrate the intraoperative use of $^{18}$F-FDG PET radioguided surgery in attaining disease control when $^{131}$I WBS is negative.

$^{131}$I RGS is not a new approach to revision thyroid surgery. Likewise, $^{18}$F-FDG PET radioguided surgery has been used intraoperatively to detect the small tumors of many different malignancies, including colorectal cancer, melanoma, and metastatic head and neck cancer. A European study evaluating the feasibility of $^{18}$F-FDG PET radioguided surgery found a positive correlation between $^{18}$F-FDG PET imaging and detection of histologically confirmed WDTC in all of their patients, as well as a “surgical cure” in most of the population. The $^{18}$F-FDG radioisotope is potentially advantageous in that it produces higher energy gamma rays than conventional radioisotopes, allowing detection with a handheld gamma probe. The high energy irradiation is also a liability due to high background levels.

Risks associated with the radioguided approach include patient and health care worker radiation exposure. More procedures using radionuclides will increase the amounts of exposure to this group of patients. If this technique were to proliferate, exposure of operating room personnel to radiation would also increase in an environment that is not accustomed to routinely handling these workplace hazards. Our pilot study addressing this issue indicates that a surgeon could be exposed to up to 188 hours annually before reaching recommended maximum doses.

If LRR develops at our institution, we determine whether the patient is $^{131}$I avid or nonavid. In our practice, only the $^{131}$I non-avid patients are offered $^{18}$F-FDG RGS. This study suggests that $^{18}$F-FDG PET imaging was feasible with intraoperative gamma probe localization and histologic confirmation. Using the $^{18}$F-FDG PET gamma probe did not identify new areas of pathologic disease but only confirmed the sites suggested by preoperative $^{18}$F-FDG PET imaging. This can be helpful to the surgeon operating in a scarred and fibrotic surgical bed. RGS may help to ensure that the uptake target that is prompting the revision surgery is successfully located and completely excised. In addition, studies have shown that undetected tumors have been identified on pathology with $^{131}$I RGS, suggesting that en bloc dissections rather than “berry-picking” procedures are recommended. Although no $^{18}$F-FDG RGS studies have mentioned this specifically, the idea seems transferrable.

This is a small retrospective study with many variables. Some information is missing from the medical record. The postoperative treatment scans and follow-up Tg are not uniform. Two patients received postoperative radiotherapy. $^{18}$F-FDG avidity is thought of as an indicator of tumor de-differentiation and a poor prognostic sign, which may explain the more aggressive postoperative treatment of these 2 patients. Patient L underwent RAI treatment after $^{18}$F-FDG RGS. RAI, however, may still be indicated to drive iodine into microscopic disease even if affinity for iodine is low from a previous negative WBS scan.

Future questions in the application of $^{18}$F-FDG radioguided surgery may lie in the number of positive lymph nodes undetected by $^{18}$F-FDG PET/CT but found on pathology of en bloc dissection. Other advancements in $^{18}$F-FDG RGS technology lie in the combination of radioguided localization with real-time anatomic registration and tracking similar to that currently used with CT-guided endoscopic sinus surgery.

**Conclusion**

Our series describes both $^{131}$I avid $^{131}$I nonavid populations. The use of $^{18}$F-FDG PET radioguided surgery lowered Tg to undetectable levels in 2 of 5 patients. $^{131}$I RGS lowered Tg to undetectable levels in 6 of 7 patients (1 was missing). RGS is a feasible approach and a low-risk technique to identify recurrent disease in an operated field and perhaps increase its successful excision. Although focal disease may be identified with this technique, this is not a tool for limited excisions (“berry picking”). Further investigation with prospective enrollment and uniform long-term follow-up is needed.

**Author Contributions**

Carrie L. Francis, writing, data analysis; Chuck Nalley, data analysis, writing; Chris Fan, endocrinologist, editing; Donald Bodenner, endocrinologist, editing; Brendan C. Stack Jr, concept, surgeon, data analysis, editing.

**Disclosures**

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