

## Case Report

# Radioguided Occult Lesion Localization in Surgery for Recurrent Thyroid Cancer and Review of Literature

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## Abstract

### Reason

Reoperative thyroid surgery can be difficult technically and associated with higher complication risk. Recurrences may be obscured by fibrosis related to prior treatment or masking of relative anatomy. Radioguided occult lesion localization (ROLL) using technetium-99m labeled macroaggregated albumin (Tc99m-MAA) has merit for intraoperative gamma probe assisted localization of recurrent disease in the scarred operative bed. Little is known about the applicability of ROLL to head and neck surgery including thyroid surgery.

### Case Presentation

A total of eight lesions in six patients were injected with Tc99m-MAA under ultrasound guidance at our institution. The lesions were preoperatively identified either with high-frequency ultrasound or MRI. The patients selected all had biopsy confirmed recurrent thyroid cancer (5 with papillary and one with medullary histology, 5-19 mm in size). Identification was successful in all eight injections (100%). There were no adverse events to Tc99-MAA injection.

### Conclusion

Preoperative radioguided occult lesion localization with Tc99m-MAA offers potential as an adjunct for localization of thyroid disease in the recurrent setting that may improve ease of operation and safety as surgeons and radiologists improve their experience. These cases demonstrate the merits of Tc99m-MAA for precise preoperative localization.

**Key Words:** Intraoperative Localization; Radioguided Occult Lesion Localization; Recurrent Thyroid Cancer; Radioguided Surgery

**Abbreviations:** mCi - MilliCurie; RAI - Radioactive Iodine; RLN - Recurrent Laryngeal Nerve; ROLL - Radioguided Occult Lesion Localization; SAN - Spinal Accessory Nerve; Tc99m-MAA - Technetium-99m Labeled Macroaggregated Albumin; Tg - Thyroglobulin; US - Ultrasound; PTC- Papillary Thyroid Cancer; rPTC- Recurrent Papillary Thyroid Cancer

## Introduction

Papillary thyroid cancer is one of the most common cancers in the United States with an incidence of 14.9 cases per 100,000 people [1]. While prognosis is generally good, papillary thyroid cancer may recur both in cervical lymph nodes and/or locally within the surgical bed with a recurrence rate of 10 to 45% [2]. Whether it is residual disease or a true locoregional recurrence, resection is the recommended treatment. Redo thyroid surgery is fraught with difficulty and is associated with significant morbidity in comparison to primary thyroid surgery. Patients are at higher risk of injury to surrounding structures including the recurrent laryngeal (RLN), spinal accessory (SAN), phrenic nerves, parathyroid glands, or thoracic duct [3].

Surveillance for residual or recurrent thyroid carcinoma has improved with close monitoring of thyroglobulin (Tg) levels and high-frequency ultrasonography such that recurrent differentiated thyroid carcinoma is frequently detected as small, non-palpable lesions. These lesions may be difficult to locate in the operating room especially in reoperative cases where tumor may be embedded in dense scar tissue. In addition,

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undirected dissection may lead to injury of surrounding structures. Delayed surgery for small recurrences with a “watch and wait” approach is often emotionally tolling and unacceptable to many patients despite questionable impact on overall survival.

Multiple techniques have been developed for intraoperative identification of recurrence including preoperative ultrasound-guided blue dye or charcoal injection [4-9], intraoperative ultrasound-guided navigation, and radio-guided surgery. This report will discuss our experience with radioguided occult lesion localization (ROLL) in surgery for recurrent thyroid cancer using Technetium-99m labeled macroaggregated albumin (Tc99m-MAA). ROLL was first described in other areas of oncologic surgical practice in 1998 [10]. Tc99m-MAA was adopted as a localizing agent at our institution due to the low patient and operator associated radiation dose, its large particle size, which prevents diffusion out of the target lesion, and its lack of color which prevents field staining and obscuring of anatomy. This technique was used for eight injections within six patients as discussed below and summarized in Table 1.

## Methods

### Patient Selection

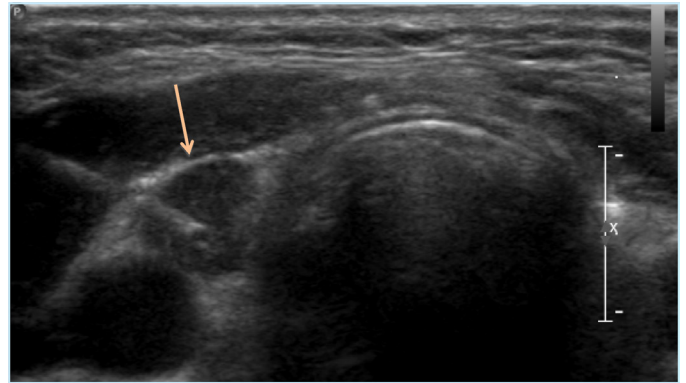
Patients were referred by endocrinologists after biopsy proven recurrence and selected for ROLL by surgeon after careful study and perceived difficulty in localization. Selection criteria for ROLL included small lesion size, difficult surgical access due to crowded anatomy, multiple prior resections with scarred neck and concern for recurrent nerve injury or devascularization of parathyroids, or previously failed exploration prior to referral.

### Surgical Technique

After a patient was selected, the patient was brought to radiology preoperatively for Tc99m-MAA injection. Tc99m-MAA was injected at a dose of 0.5 mCi (milliCurie) in 0.2 ml into each lesion under ultrasound guidance the morning of surgery (Figure 1). The preoperative counts after injection ranged from 1.7K-30K counts/s [The preoperative counts decreased over time as our technique improved]. The patient was then taken to the operating room for gamma probe directed localization and resection of the target lesions. After explantation, the gamma probe was used to assess specimen and background counts.

### Case 1

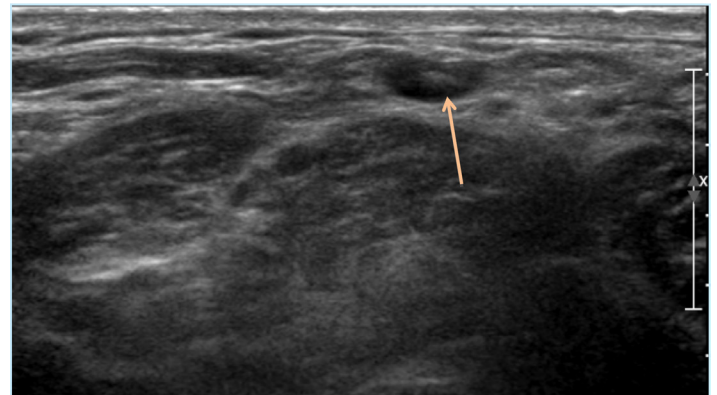
A 47 year-old female patient presented with recurrent papillary thyroid cancer (rPTC) having undergone five previous operations including a total thyroidectomy for a left sided primary tumor as well as treatment with radioactive iodine (RAI). Physical exam did not reveal any palpable lymphadenopathy. Work-up revealed two left-sided nodules with recurrent papillary thyroid cancer at levels IV and VI. A targeted surgery was performed with successful removal of the two lesions.



**Figure 1.** Injection of Tc99m-MAA into a right thyroid bed recurrent papillary thyroid carcinoma under ultrasound guidance.

### Case 2

A 56 year-old male patient was referred to us with persistent disease in the left neck after total thyroidectomy and central node dissection 5 months prior followed by RAI for a left-sided papillary thyroid cancer (PTC). A low-lying left level IV lymph node measuring 6 mm was identified on imaging and biopsied positive for metastatic PTC (Figure2). There was concern for missing the low-lying small node intraoperatively. A left modified radical neck dissection, including levels IIA, III, and IV, was performed. A total of 53 nodes were removed of which 3 were positive,

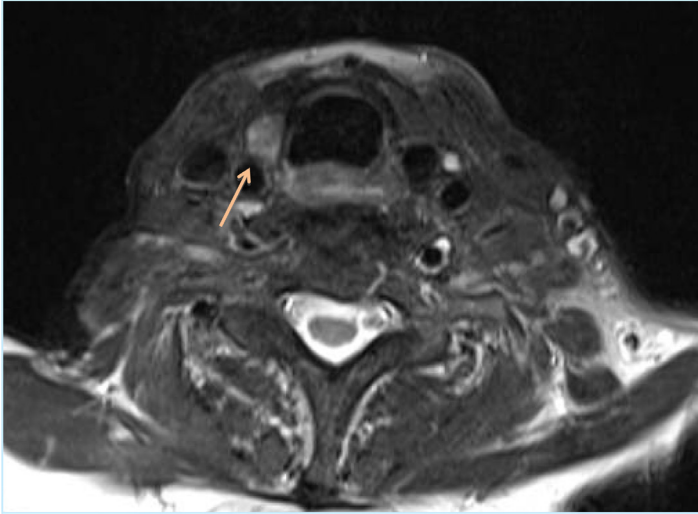


including the hot, radiolabeled low level IV node.

**Figure 2.** Level IV Lymph Node, biopsy-proven metastasis, as seen on high-resolution ultrasound.

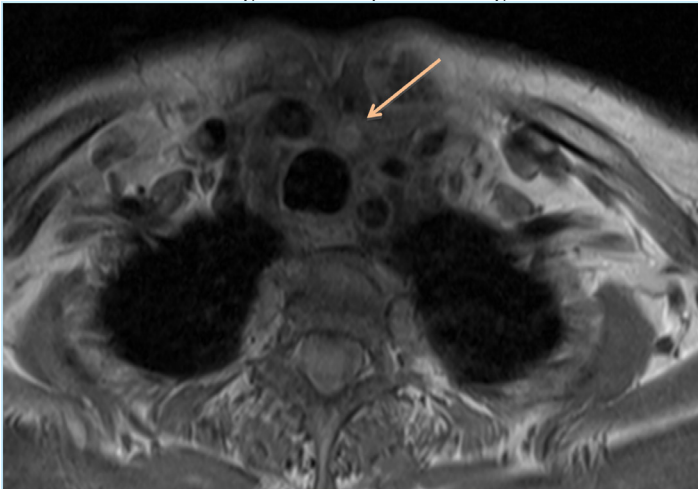
### Case 3

A 71 year-old female diagnosed with PTC 9 years prior now returned with biopsy proven recurrence in right and left paratracheal nodes (Figures3 and 4). Her previous surgeries included a total thyroidectomy with limited central neck dissection and later selective neck dissection including levels II-V. She received multiple rounds of RAI for a total dose of 450 mCi. The patient was selected for ROLL given concern for recurrent laryngeal nerve and parathyroid injury. The surgery was directed at the two areas of recurrence with successful removal of both radiolabeled lesions which



were shortly confirmed on pathology.

**Figure 3.** Recurrent papillary thyroid cancer in the right thyroid bed detected on MRI, T2-weighted turbo spin echo images.



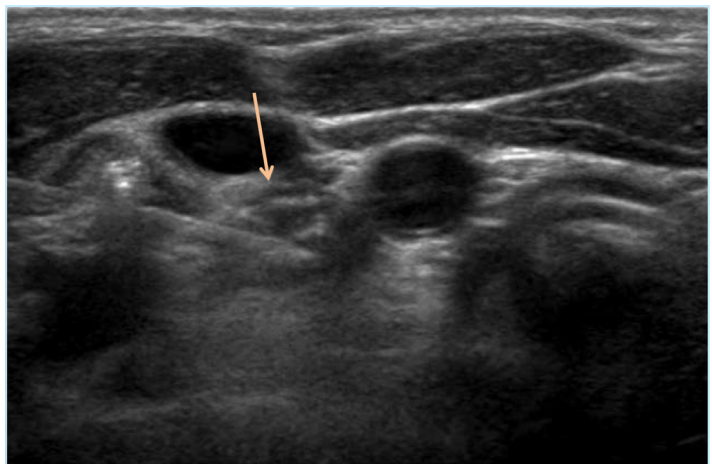
**Figure 4.** Recurrent papillary thyroid cancer in the left paratracheal nodule detected on MRI, T2-weighted turbo spin echo images.

#### Case 4

A 29 year-old female with PTC underwent total thyroidectomy, central and right lateral neck dissection and RAI 8 years prior. She was referred to us with two new PET-positive sub-centimeter right neck nodes in levels IV and VI (Figure 5). Preoperative biopsy confirmed rPTC in the level IV node but was inconclusive in the level VI node located at the take-off of the subclavian artery. Figure 6 shows injection of the inconveniently located level VI node. The surgery was particularly difficult given the previous operation and the location of the level VI node in the supraclavicular fossa. A revision right neck dissection of levels II-VI was performed including the radiolabeled level VI node. Pathology confirmed 3/56 positive nodes.



**Figure 5.** PET-CT showing a mildly PET-positive level VI lymph node found to be positive for metastatic papillary cancer.



**Figure 6.** Tc-MAA injection into a right low level IV node close to the internal jugular vein and carotid artery.

#### Case 5

A 60 year-old female underwent a total thyroidectomy with limited central compartment node dissection and postoperative RAI for a multifocal PTC at an outside facility four years prior. Imaging found a 1.3 x 1.1 cm recurrence in the left paratracheal region. Biopsy confirmed rPTC for which she had an unsuccessful attempt at localization and resection by an outside surgeon. We employed ROLL in another surgical attempt and identified a 1.9 cm radiolabeled lesion within dense scar in close proximity to the left recurrent laryngeal nerve. Pathology was confirmed.

#### Case 6

A 29 year-old female with MEN-2 and medullary thyroid cancer underwent a total thyroidectomy, bilateral neck dissection, partial sternotomy and mediastinal dissection 2.5 year prior for a T4aN1bM0 tumor, with 36/155 positive lymph nodes. She was treated with cabozantinib for a bony metastases 0.5 years after her initial surgery with complete resolution but ultimately had another biopsy proven recurrent lesion in her supraclavicular fossa. A decision was made for surgery with ROLL given

tumor location, scarred tissue and difficult habitus. Guided dissection revealed three of four positive lymph nodes, the largest measuring 1.2 cm.

## Results

ROLL was successful in identifying all eight lesions injected with Tc99m-MAA. Lesion size ranged from 6-19 mm, and background counts were all below <300 counts/s after explantation (table 1). There were no intraoperative or postoperative complications associated with surgery. Follow-up ranged from 12.1 months to 26.2 months. All patients are free of locoregional recurrences, and one patient is alive with stable metastatic disease from medullary thyroid carcinoma.

**Table 1.** Summary of Cases using Tc99m-MAA ROLL. NED – no evidence of disease; AWD – alive with disease, NR – not recorded

Case	Age	Sex	Lesions and Location	Pre-excision Counts	Post-excision Counts	Disease Status/ Follow-up (months)
1	47	F	Left inferior 8mm level IV node; Left 5mm thyroid bed nodule	30K, 30K	<250	NED/38.8
2	56	M	Left inferior 6mm level IV node	30K range	<300	NED/20.3
3	71	F	L inferior 8 mm level VI; Right 10mm level VI nodes	13K, 9K	<300	NED/26.2
4	29	F	Right inferior level IV scar tissue	NR	<300	NED/12.5
5	60	F	Left paratracheal 19 mm node	9.1K	0	NED/11.7
6	29	F	Right supraclavicular 12 mm node (Medullary thyroid cancer)	1.7K	0	AWD/8.3

## Discussion

In a previously untouched neck compartment where there is clinical evidence for disease, we strongly advocate compartmental dissection in a comprehensive fashion in order to minimize the risk of recurrence and challenges that this situation may entail. The goal of surgery with locoregional recurrences in the previously dissected neck is to remove all recurrent disease as well as completion of any compartments not previously dissected encompassing the area of recurrence. Locoregional recurrence in differentiated thyroid cancer may be associated with a decrease in survival and quality of life [11,12]. Although there is ongoing debate regarding the survival benefit of management of regional disease both in the primary and recurrent setting, uncontrolled recurrent disease may lead to RLN paralysis, paralysis of SAN or other cranial nerves, or invasion into the esophagus, trachea, or larynx leading to significant morbidity and even mortality. For these reasons, current ATA guidelines suggest resection of recurrent thyroid cancer sparing uninvolved structures before there is progression of disease [13]. Recurrences are often detected by either high-

resolution US or elevated serology (thyroglobulin, calcitonin, CEA) well before they become palpable. Such recurrences can be difficult to localize intra-operatively even when performing a compartmental dissection. Redo operations are made difficult by scarring and distortion of anatomy. The goal of redo operations is to remove any recurrent disease within an involved compartment; therefore, it is vital to identify all disease. While preoperative and intraoperative US may provide mapping of concerning lesions, the anatomy may be hard to correlate and navigate surgically once the skin incision has been made.

Several techniques have been described for improved intraoperative localization of small foci of recurrence such as charcoal or blue dye injection under US guidance [4-9]. These methods appear to be effective for localization; however, radioguided occult lesion localization (ROLL) offers a few benefits over charcoal or blue dye injection. ROLL uses

Tc99m-MAA, which is an ideal localizing agent due to the large particle size of macro-aggregated albumin and low patient and operator dose exposure associated with Tc99m. The large size theoretically prevents local diffusion of the agent and contamination of the operative field, which can potentially occur with blue-dye injection. In addition, use of a gamma probe that detects the radioactive signal permits for a directed dissection aimed at the area of recurrence in a reoperative, scarred field. While generally well tolerated, blue dye may also be associated with allergic reaction, anaphylaxis, and tissue necrosis [8].

Several small studies have evaluated the effectiveness of ROLL in patients with well-differentiated thyroid cancer. Igan et al. [14] report their series of 8 patients who underwent preoperative US mapping of recurrent lesions, which ranged in size from 3-38 mm. A total of 23 suspicious lesions were injected with Tc99m-MAA with counts ranging from 3,358-10,093 counts/s. The post-explantation counts ranged from 310-425 counts/s. All preoperatively identified lesions were correctly excised as determined by 6-week postoperative US and serology levels, which returned to normal



in all patients without evidence of metastatic disease. Giles et al. [15] performed a randomized trial of 20 consecutive patients (11 patients underwent ROLL and 9 patients underwent intraoperative US) between January 2011 and 2012 undergoing reoperation for non-palpable rPTC. Preoperative and operative variables were similar between the groups. ROLL compared favorably to intraoperative ultrasound at operative localization of recurrent thyroid cancer, with rates of 100% and 89%, respectively. One patient in the intraoperative US group had incomplete resection of suspected lesions. With the exception of this one patient, thyroglobulin levels dropped after surgery. There were no complications in either group. Over time, baseline counts decreased to 0 suggesting that with expertise gained over time, ROLL can be precisely executed.

Given the limited data on ROLL in thyroid cancer, we sought to confirm these studies in our own patients with recurrent thyroid cancer. Our study adds to the growing body of literature in support of ROLL in this patient population. From our experience and from review of these studies, it appears that ROLL allows for easy and safe identification of thyroid recurrences intraoperatively.

We were able to accurately identify targeted lymph nodes in difficult areas during reoperative surgery. All lesions were removed with a confirmed drop in gamma counts and pathologic confirmation of recurrent carcinoma excision. We also show the application of ROLL in medullary thyroid cancer, which to our knowledge, has not previously been reported. This targeting technique may be applicable in re-operative surgery for any cancer histology throughout the body.

## Conclusion

Reoperative thyroid surgery can be safely completed with a low risk of morbidity. ROLL is safe and well tolerated. In addition, it does an excellent job of intraoperative localization of predetermined thyroid cancer recurrences even with difficult anatomy. It may serve as an adjunct to reoperative surgery to ensure adequate minimally invasive localization of tumors.

## Declarations

Ethical Approval and Consent to participate - City of Hope institutional IRB was obtained for this study.

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