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What is This?
Neural Monitored Revision Thyroid Cancer Surgery: Surgical Safety and Thyroglobulin Response

Eimear Phelan, MD¹, Dipti Kamani, MD¹, Jennifer Shin, MD¹, and Gregory W. Randolph, MD¹,²

Abstract
Objective. To evaluate the postoperative complications and to evaluate and stratify thyroglobulin (Tg) response associated with revision surgery for thyroid malignancy.

Study Design. Case series with chart review.

Settings. Academic, tertiary care center.

Subjects and Methods. All patients with regionally recurrent thyroid carcinoma and who underwent revision thyroid surgery by the senior author (GWR) during a 5-year period were identified. All patients had pre- and postoperative laryngeal examination and underwent surgery with standardized neural monitoring. Postoperative complications and thyroglobulin (Tg) response were recorded.

Results. One hundred seventeen cases meeting the criteria for revision surgery for recurrent thyroid cancer were identified. Among this group, 30% presented for their third or higher revision procedure. Preoperative permanent vocal cord palsy was present in 14% (n = 16), and 19% (n = 22) had preoperative permanent hypocalcaemia. There were no new cases of either temporary or permanent vocal cord palsy in our study group. Approximately 5% developed temporary and 3% permanent hypocalcaemia requiring medical treatment. The mean basal Tg following revision surgery was 5.6 ng/ml (range, 0.2-32.7), which represented a mean postoperative significant decline in Tg of approximately 90%. In nearly 40%, basal Tg was undetectable postoperatively. Tg response was stratified based on the number of revision surgeries, Tg decline was observed in 90% of all cases, 92% after first revision surgery, 85% after second, 34% after third, and 70% after fifth revision surgeries.

Conclusion. Revision thyroid cancer surgery can be performed with low rates of complications and significant impact on Tg levels even after multiple revision surgeries.

Keywords
revision thyroid surgery, IONM, neural monitoring, hypocalcemia, recurrent laryngeal nerve injury, hypoparathyroidism, complications of revision surgery, thyroid cancer recurrence, papillary thyroid carcinoma, thyroglobulin Tg response

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Introduction
Patients with papillary thyroid cancer (PTC) with early stage I disease have a risk of recurrence of up to 10%, and in stage II and III disease, recurrence rates of 20% and 30% have been reported, respectively.¹³

Reoperative thyroid bed surgery has been reported to significantly increase the incidence of operative complications as compared to primary thyroidectomy.⁴⁵ Surgical treatment issues for recurrent nodal disease for PTC and medullary cancers (MTC) are similar and so for the purposes of study of revision surgical safety, patients with PTC and MTC were included and for the study of thyroglobulin (Tg) response, only PTC patients were studied.

We undertook this analysis to test the following null hypotheses in patients presenting with recurrent thyroid malignancy:

Hypothesis 1: Revision thyroid surgery is not associated with low rates of vocal fold paresis and hypocalcemia.

Hypothesis 2: Revision thyroid surgery is not associated with significant change in thyroglobulin levels.

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Methods

Internal review board approval was obtained from Massachusetts Eye and Ear Infirmary human subjects committee. A retrospective case series with chart review evaluated consecutive patients undergoing revision surgery for recurrent thyroid malignancy from 2004 to 2009. Criteria for inclusion were: (1) previous thyroidectomy for thyroid malignancy, (2) presentation with recurrent thyroid malignancy (criteria described in the following), and (3) management with revision thyroid surgery after multidisciplinary evaluation by endocrinology and otolaryngology. Patients were included regardless of previous radioactive iodine treatment, central neck dissection, lateral neck dissection, or external beam radiation. All of these patients had pre- and postoperative laryngeal examination. Intraoperative nerve monitoring (IONM) was applied using a standardized IONM setup.6

Data analysis was performed using Stata 12.0 (StataCorp LP, College Station, Texas). A paired \( t \)-test was utilized for matched pairs analysis with preoperative and postoperative data. Values logged by the center’s laboratory as <0.2 for thyroglobulin were treated as 0 values.

Preoperative Criteria for Revision Thyroid Nodal Surgery

Patients in our unit are followed by a multidisciplinary team of endocrinology and otolaryngology. The mainstay of thyroid cancer follow-up currently is serial high-resolution cervical ultrasound (US), coupled with intermittent suppressed stimulated Tg measurements without routine radioactive iodine scanning. In the setting of a Tg-positive, ultrasound-positive abnormality, axial computed tomography (CT) scanning with contrast is obtained to further define and localize cervical nodal disease.7 Specific radiographic criteria for our unit have been previously described.7 Surgical candidacy is generally established for FNA-positive central neck nodes that are 8 mm or larger and FNA-positive lateral neck nodes that are 10 mm or larger after multidisciplinary discussion with the patient.

Surgical Technique/Approach to Revision Surgery

Our approach to revision neck surgery has been described in detail.8,9 For revision central neck surgery, the back door lateral approach is employed, which allows full identification of carotid sheath structures, including vagus nerve, while accessing the central neck (Figure 1). Recurrent laryngeal nerve (RLN) monitoring is utilized to provide a neural map as to the location prior to dissection and visualization of the RLN.

Results

Presenting Characteristics Prior to Revision Thyroid Surgery

Between 2004 and 2009, 117 patients (41 males, 76 females) underwent revision thyroid surgery with mean age being 46.2 years (range, 12-80.2) and mean follow-up being 2.5 years (range, 0.05-6.5). In patients where initial disease stage was available: 72.8% (n = 78) were classified as stage I, 1.9% as stage II, 13.1% as stage III, and 12.1% as stage IV. The majority of patients (55.5%, n = 65/117) had a total thyroidectomy and a neck dissection (central and or lateral neck dissection) performed as their initial surgery. The mean age at primary surgery was 38.6 years (range, 8-71.5). The mean number of revision surgeries was 1.5 (range, 1-7) with a mean age at first revision surgery of 45.8 years (range, 12-79.9). The average time between the first surgery and last revision surgery was 7.3 years (range, 0.1-44.1). In 70% of cases, our revision surgery represented the patient’s second major thyroid cancer operation. In 21%, our revision surgery represented the third major thyroid cancer operation. In 5.1%, our surgery represented the fourth major thyroid cancer operation. In 0.8%, our revision surgery represented a fifth or greater revision surgery.

Many cases presented with complications from prior surgeries. At the time they presented for their revision procedure, 14% (n = 16) had preoperative permanent vocal cord palsy and 19% (n = 22) had permanent hypocalcemia.

Complications of Revision Thyroid Surgery

There were no new cases of either temporary or permanent vocal cord palsy in our series. Approximately 5% (n = 5/95) developed temporary hypocalcaemia (<6 months) and 3% (n = 3/95) developed a permanent hypocalcaemia (>6 months) requiring medical treatment. Other postoperative complications included 2 postoperative hematomas requiring drainage, 2 chyle leaks managed conservatively, and 1 postoperative neck seroma (Table 1).

Operative Findings of Revision Thyroid Surgery

The mean estimated blood loss during revision surgery was 40 ml (range, 15-100).
Of the cases involving lateral neck nodes, the total number of lymph nodes dissected was 1451 nodes with a mean of 16.5 (range, 0-51) dissected nodes per case. Among those, a mean of 2.7 nodes were positive (range, 0-16) per case. Among these positive nodes 9% (n = 8) had extra nodal extension.

Of the cases involving central neck dissection, the total number of lymph nodes dissected was 300 nodes with a mean of 4 (range, 0-16) lymph nodes dissected per unilateral paratracheal dissection. The mean number of positive nodes per case was 2.3 (range, 0-10). Thirteen percent (n = 10) of central neck nodes cases had extra nodal extension.

The majority of revision surgery cases had some form of postoperative treatment: 64% (n = 75) had I131, 6.8% (n = 8) had external beam radiotherapy, and 0.9% (n = 1) had chemotherapy (clinical trial).

Recurrence after Revision Thyroid Surgery
The rate of isolated cervical node recurrence after our revision surgery was 7.6% over 2.4 years of follow-up. There were no deaths due to recurrent thyroid cancer in the limited follow-up period. A total of 16.2% (n = 19) recurred (locoregional and distant) at the time of last follow-up.

Thyroglobulin Response
Fifty-eight cases had both preoperative and postoperative Tg basal levels for Tg response analysis. Eight cases were excluded from this analysis due to Tg antibodies and 1 due to known preoperative distant metastasis. The mean basal (ie, nonstimulated) Tg prior to final revision surgery was 53.5 ng/ml. The mean Tg post revision surgery was 5.6 ng/ml, which represented a mean postoperative decline in Tg of 90% overall, which represented a significant difference in Tg level preoperatively compared to postoperatively (P = .0106, paired t-test). In 41.2% (n = 24) of cases, the Tg level was undetectable after revision surgery (Figure 2).

An additional analysis was performed to determine whether an increased number of revisions impacted the observed postoperative Tg decline. Forty-two cases had a first revision surgery with a mean preoperative Tg of 65 ng/ml (range, 0.2-600.0) and postoperative Tg of 5.3 ng/ml (range, 0.2-32.7), which represents a statistically significant decline of 92% (P = .0233, paired t-test). Among these, 36% (n = 15) had undetectable Tg postoperatively. Eleven cases had a second revision surgery with a mean preoperative Tg of 37 ng/ml (range, 1.5-197.0) and postoperative Tg of 5.5 ng/ml (range, 0.2-30.0), which represents a mean Tg decline of 85%. Among this subset, 55% (n = 6) had a postoperative undetectable Tg. Five cases had a third revision surgery with a mean preoperative Tg of 16 ng/ml (range, 3.93-49.3) and postoperative Tg of 10.6 ng/ml (range, 0.2-27.2), which represents a mean Tg drop of 34%. Among these, 60% (n = 3) had a postoperative undetectable Tg. One case had a fifth revision surgery with a preoperative Tg of 2.0 ng/ml and postoperative Tg of 0.6 ng/ml, which represents a Tg decrease of 70%. There was no significant difference in thyroglobulin level preoperatively versus postoperatively when the second (P = .2140, paired t-test) and third (P = .6058, paired t-test) revisions are considered as a separate group, but the sample sizes are small (n = 11, n = 5, respectively) in these subsets (Figures 2, 3).

Table 1. Complications of revision thyroid cancer surgery.

<table>
<thead>
<tr>
<th>Complication</th>
<th>Percentage (Proportion)</th>
</tr>
</thead>
<tbody>
<tr>
<td>New onset vocal cord weakness (temporary or permanent)</td>
<td>0% (0/117)</td>
</tr>
<tr>
<td>New onset postoperative hypocalcemia</td>
<td></td>
</tr>
<tr>
<td>Temporary</td>
<td>5% (5/95)</td>
</tr>
<tr>
<td>Permanent</td>
<td>3% (3/95)</td>
</tr>
<tr>
<td>Postoperative hematoma</td>
<td>1.6% (2/117)</td>
</tr>
<tr>
<td>Postoperative seroma</td>
<td>0.8% (1/117)</td>
</tr>
<tr>
<td>Chyle leak</td>
<td>1.6% (2/117)</td>
</tr>
</tbody>
</table>

Figure 2. Percentage decline in mean thyroglobulin (Tg) and percentage undetectable Tg post revision surgery stratified based on number of revision. *P value, paired t-test for percentage postoperative Tg decline for overall and rev1 were significant with $P = .0106$, $P = .0233$, respectively.

Abbreviations: Overall, all revision surgeries together; rev1, first revision surgery; rev2, second revision surgery; rev3, third revision surgery; rev5, fifth revision surgery.
Calcitonin Response
There were a small number of cases (n = 6) in our study who had a primary diagnosis of medullary thyroid cancer in which pre- and postoperative calcitonin levels were available. One case was excluded due to the presence of known preoperative distant metastasis. The mean preoperative calcitonin level was 503.7 pg/ml (range, 5.5-2162.0), with a mean postoperative calcitonin level of 198.4 pg/ml (range, 5.0-651.0). This represented a mean decline of 61% in calcitonin. There was no significant difference in calcitonin level preoperatively as compared to postoperatively (P = .3043, paired t-test), but the sample size in this subset is small (n = 5).

Discussion
While the group of patients presenting for recurrent thyroid cancer surgery predominantly belonged to stage I (>70%) at initial surgery, at presentation for revision surgery they were a morbid group: 14% had preoperative vocal cord paralysis and nearly 20% had permanent hypoparathyroidism. Of note, over 50% had prior nodal surgery as part of the initial thyroid surgery. In our group, 30% presented for their third or higher revision thyroid cancer surgery.

Revision Surgery Complications
The incidence of permanent recurrent laryngeal nerve paralysis for reoperative thyroid surgery is variable but generally higher than for primary surgery. Beahrs and Vandertoll found that 8% of those undergoing a second surgery and 22% of those undergoing a third surgery for benign disease suffered a permanent RLN paralysis; when surgery was for malignant disease, the rate rose to 12% and 36%, respectively.

Complication 1: RLN Paralysis—Temporary/Permanent. In our series, we did not have any temporary or permanent RLN paralysis. It is our impression that this was achieved because of neural mapping using RLN stimulation and vagal stimulation through lateral neck approach (Figure 1).

Complication 2: Hypocalcemia—Temporary/Permanent. In our study, 5 patients (5%) developed temporary (<6 months) and 3 patients (3%) developed permanent (>6 months) hypocalcaemia requiring medical treatment, which is comparable to the literature. The incidence of permanent hypoparathyroidism following reoperative thyroid cancer surgery ranges from 0% to 9%. Kim et al reported, in 20 reoperative patients, 3 cases of transient and 1 of permanent hypoparathyroidism. Clayman et al found 5% (3 patients) developed permanent hypoparathyroidism after revision surgery.19 In a study of 14 revision patients by Palme et al, temporary and permanent hypocalcemia was reported in 2 patients each. Farrag et al in 33 reoperative thyroid bed surgery patients reported 2 cases of transient and none of permanent hypocalcemia.14 Shah et al in 82 patients found 20% (n = 17/82) had temporary and 7% (n = 6/82) had permanent hypoparathyroidism. Hughes et al in 61 revision patients had 6 cases of temporary hypocalcaemia.15

Revision Surgery Tg Response
In our study, the revision surgery group had a 90% decline in mean Tg after the revision surgery. Subsets undergoing first or second revision surgery had good Tg responses with a 92% and 85% drop, respectively.

Overall, 41.2% (n = 24) of cases had undetectable Tg level after revision surgery. Among first revision surgery 36%, second revision surgery 53%, and third revision 60% had postoperative undetectable Tg. Our study is the first study to stratify Tg response based on number of revisions. Even after multiple revisions Tg decline occurs, but these data are limited.

In a 33 patients series by Farrag et al, Tg levels were “significantly decreased or undetectable” in most patients when compared to pre-revision thyroid bed surgery. Normalization of the serum Tg occurred in 50% (10/20 patients) who received sodium iodide I131 ablation and in 71% (5/7 patients) who did not. Hughes et al reported that in 61 patients, 57% patients had undetectable basal Tg and 21% (13/61) patients had undetectable stimulated Tg during the follow-up period. Clayman et al reported at last follow-up, 66% (130/196) of patients had no detectable Tg. A recent review concluded that secondary nodal surgery was associated rates of biochemical cure ranging from 27% to 81% depending upon strictness of definition and patient selection.
With regard to the long-term outcome in patients with recurrent papillary cancer, Clayman et al described with median of 7.25 years after surgery, 90% (167/185) of the patients were without evidence of central disease, and 10% (n = 18) had developed central compartment recurrences within a median interval of 24.3 months. These data are similar to ours with a 7.6% recurrence rate in our series with a mean follow-up of 28 months.

**Nonsurgical Treatments for Recurrent Thyroid Cancer**

Nonsurgical treatments for nodal metastasis include percutaneous ethanol injection (PEI), radiofrequency ablation (RFA), and percutaneous ultrasound guided laser ablation. Monchik et al reported a 67% decline in 6 patients treated with PEI with 1 case of temporary hoarseness. Heilo et al reported that in 30 out of 38 patients Tg became undetectable. Papini et al reported percutaneous ultrasound-guided laser ablation resulted in a decrease in mean basal Tg from 8.0 to 2.0 ng/ml at 12-month follow-up (P < .02 vs baseline) with 60% having undetectable Tg levels.

**Limitations**

This series suggests that in the setting of surgical experience with neural monitoring, rates of complications are low in patients requiring multiple revision nodal surgery. We cannot, however, determine whether the low rate of complications is strictly due to neural monitoring. Nonetheless, it is our strong impression that neural monitoring is tremendously helpful in the offering of safe and effective revision thyroid cancer surgery. We appreciate that our rates of surgical complications may not be applicable to all surgical settings and that our mean follow-up of only 2.5 years is short. Despite the treatment algorithm that exists in our multidisciplinary unit, we also recognize that some patients with small volume recurrence may follow an indolent course and may be treated with nonsurgical options mentioned previously or observation.

**Conclusion**

Recurrent disease in our patients occurred primarily in patients who initially presented with stage I disease. In contrast, those presenting for recurrent thyroid cancer surgery constitute a morbid group: 14% of our patients presenting for revision surgery had preoperative vocal cord paralysis; nearly 20% had preoperative hypoparathyroidism; over 50% had prior nodal surgery. In our group of revision thyroid cancer patients, 30% presented for third or higher revision thyroid cancer surgery. Overall, Tg declined significantly, by 90%, and became unmeasurable in just over 40% of our patients. Tg elevation may not be expected to occur in atypical high-risk variants of differentiated thyroid cancers. This study demonstrates re-operative thyroid cancer surgery in experienced hands with neural monitoring can be performed safely with acceptable complication rates of 3% hypoparathyroidism with 0% temporary or permanent paralysis of the RLN.

**Author Contributions**

Eimear Phelan, design, data acquisition, data analysis and interpretation, drafting the article, final approval of the version to be published; Dipti Kamani, design, data acquisition, data analysis and interpretation, revising article critically for important intellectual content, final approval of the version to be published; Jennifer Shin, data interpretation, revising article critically for important intellectual content, final approval of the version to be published; Gregory W. Randolph, conception and design, data analysis and interpretation, revising article critically for important intellectual content, final approval of the version to be published.

**Disclosures**

**Competing interests:** Jennifer Shin, Springer Publishing—book royalties from Evidence-Based Otolaryngology; Plural Publishing—book royalties from Otolaryngology Prep and Practice.

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