Evidence-Based Workflows for Thyroid and Parathyroid Surgery

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ABSTRACT
A need exists to reduce care variations by standardizing the practice of thyroid and parathyroid surgery. During the course of a year, a task force developed algorithms representing decision points and workflows based on American Thyroid Association guidelines and three internal studies of surgical practices in the Northern and Southern California Regions of Kaiser Permanente conducted in collaboration with Health Information Technology Transformation & Analytics (HITTA).

INTRODUCTION
In keeping with a movement toward specialty redesign based on standardization and subspecialization, workflows were developed between March 2015 and March 2016 to guide evidence-based best practices and reduce disparities in care. The evidence base for thyroid and parathyroid workup and surgical procedures includes American Thyroid Association (ATA) guidelines1 and three studies2,3 of surgical practices in Kaiser Permanente (KP) Northern California and KP Southern California conducted in collaboration with Health Information Technology Transformation & Analytics (HITTA).

The first study used a robust set of variables and propensity score methods to match 2362 patients undergoing hemithyroidectomy, total thyroidectomy, or parathyroidectomy as outpatients (discharge within 8 hours of completion) to 2362 patients undergoing the same procedures as inpatients.2 Outcomes assessed were 30-day rates of complications, Emergency Department visits, all-cause hospital readmissions, and mortality. No statistically significant differences between inpatients and outpatients were found for complication rates or postdischarge utilization, and we concluded that outpatient surgery should be used for all patients for whom it is appropriate.2

The second study used similarly robust variables and propensity score methods to match 3135 patients who underwent hemithyroidectomy and total thyroidectomy, or parathyroidectomy performed by a high-volume surgeon (> 40 cases per year) to 3135 patients with the same procedure performed by a low-volume surgeon (≤ 20 cases per year).3 Rates of all-cause 30-day complications, mortality, readmission, and Emergency Department visits; proportion of outpatient procedures; incision-to-close (“cut-to-close”) time; and length of stay were assessed. For hemithyroidectomies, high-volume surgeons had fewer readmitted patients, more outpatient procedures, shorter lengths of stay, and shorter cut-to-close times. For total thyroidectomies, high-volume surgeons had lower rates of all surgery-related complications and of the individual complications of hypocalcemia and surgical site infections, more outpatient procedures, and shorter lengths of stay and cut-to-close times. We concluded that high-volume surgeons improve patient safety and have the potential to contribute to organizational efficiency that may be underutilized in some settings.

The third study used decision-tree analysis to identify patient-level characteristics associated with 30-day complications after thyroid and parathyroid surgery.4 Among patients undergoing thyroidectomies, the most important predictor of risk was thyroid cancer. For patients with thyroid cancer, additional risk predictors included coronary artery disease and central neck dissection. For patients without thyroid cancer, additional risk predictors included coronary artery disease, dyspnea, complete thyroidectomy, and lobe size. Among patients undergoing parathyroidectomies, the most important risk predictor was coronary artery disease, followed by cerebrovascular disease and chronic kidney disease.5

Summaries of the evidence-based workflows are presented here.

THYROID NODULE: WORKUP
Figure 1 diagrams the workup of the patient with thyroid nodules. Thyroid nodules are evaluated to rule out cancer and rarely to address local symptoms. Palpable thyroid nodules are uncommon. Nonpalpable nodules are identified frequently on imaging studies. Thyroid nodule evaluation requires a dedicated ultrasound examination of the thyroid and adjacent lymph nodes. Whereas most nodules are benign, clinically significant thyroid cancer is seen in a small minority of patients, and surgical treatment may be necessary. Nearly all thyroid cancers are differentiated (papillary, follicular, or mixed).
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Figure 1. Thyroid nodule: Workup (full-size, color version available at: www.thepermanentejournal.org/files/Summer2016/16035-1.pdf).

- Consider observation alone depending on patient characteristics, comorbidities, and imaging features.
- Bethesda System for Reporting Thyroid Cytopathology categories: I = nondiagnostic or unsatisfactory; II = benign; III = atypia of unknown significance; IV = follicular neoplasm or suspicious; V = suspicious for malignancy; VI = malignant.
- AUS = atypia of unknown significance; CT = computed tomography; FNA = fine-needle aspiration; I = iodine; MRI = magnetic resonance imaging; Tg = thyroglobulin; T4 = thyroxine; TSH = thyroid-stimulating hormone; US = ultrasound; X^2 = twice.

Pathology | Nuclear medicine and medical imaging
---|---
Surgery consult | Endocrinology

< 0.4

Normal or elevated

No radionuclide scan

Serum TSH (no Tg level) obtained within 6 months of scan

Repeat TSH level and T4

Radionuclide scan I-123

< 0.4

Normal or elevated

Observe

Benign

Option to consider repeat FNA in 6-12 months for low-risk nodules

Consider repeat US or FNA in 6-12 months for high-risk nodules

If repeat FNA is also benign, then no further US is necessary

If repeat FNA is benign, do follow-up US in 2-3 years

Routine TSH suppression NOT recommended
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- If repeat FNA yields AUS X 2 or first FNA demonstrates follicular neoplasm, then consider molecular testing.

- Indeterminate or malignant:
  - US evaluation of central and lateral neck with FNA of any suspicious nodes ≥ 8-10 mm in smallest diameter.
  - Order preoperative serum calcium test.

- If there are abnormal nodes at the periphery or limits of the sonogram, extensive nodal disease, or the primary tumor is very large or invasive:
  - Cross-sectional imaging with CT with contrast or MRI.
  - Order levothyroxine if anticipate postoperative TSH supplementation needs.
  - Surgery consult.

- Tracking metric.

- If no repeat FNA performed, US in 2-3 years.

- > 1-cm nodule suspicious.

- ≥ 1.5-cm nodule.

- Endocrine does node assessment and US-guided FNA.

- Multiple nodules > 1 cm - 1.5 cm require evaluation in same fashion or FNA of dominant and/or suspicious nodules.
Serum thyroid-stimulating hormone (TSH, thyrotropin) levels should be measured as part of the initial evaluation of a thyroid nodule. If serum TSH level is suppressed, further workup for hyperthyroidism is warranted by confirming suppressed TSH level and checking the serum thyroxine (T₄) level. If the TSH level remains suppressed, the patient should undergo a radiiodine thyroid uptake and scan. The workup and management of hyperthyroidism is beyond the scope of this summary.

Observation is recommended for nodules that are predominantly cystic or spongiform, for nodules smaller than 1.5 cm and in the absence of sonographic high-risk features, and for nodules smaller than 1 cm and suspicious but with no high-risk factors.

Diagnostic fine-needle aspiration (FNA) is recommended for cytologic evaluation of nodules greater than 1 cm with a high-suspicion sonographic pattern. FNA is recommended for most nodules 1.5 cm or larger. In addition to size criteria, high-risk factors, including family history or other clinical features, may influence the decision to perform an FNA of a smaller thyroid nodule.

Ultrasound-guided FNA is the procedure of choice in the evaluation of thyroid nodules. In the case of an incidentally noted thyroid nodule in a patient with clinically significant morbidities or a limitation in functional status, pursuing a diagnostic workup of the nodule may not be relevant. The most common practice is to acquire two to three cytologic aspirates from each nodule. If multiple nodules are found, the clinician should evaluate each on the basis of size criteria and sonographic findings.

Medical therapy with levothyroxine is not indicated for the management of benign thyroid nodules.

For indeterminate cytologic findings, such as the Bethesda System for Reporting Thyroid Cytopathology³ categories “atypia of undetermined significance or follicular lesion of undetermined significance” or “follicular neoplasm or suspicious for a follicular neoplasm,” molecular testing may be considered. Results of molecular testing may suggest the need for either observation or total thyroidectomy. In the absence of molecular testing, diagnostic lobectomy remains the recommended initial surgical procedure because malignancy may be present in up to 15% of these cases.

If abnormal results of cytologic evaluation are found and surgery is advised, it is important to have a detailed evaluation of cervical lymph nodes to assist in surgical planning. If it has not been done already, the clinician should refer the patient for diagnostic imaging for a nodal compartment neck sonogram to be available at the time of surgical consultation. Sonographically abnormal lymph nodes warrant added diagnostic workup by the endocrinologist or interventional radiologist, who will perform nodal FNA for cytologic analysis or thyroglobulin washout or both.

Primary hyperparathyroidism is uncommon but represents an important potential comorbidity for patients undergoing thyroid surgery. We recommend there be evidence of a serum calcium level at least one year in advance of surgery to screen for hypercalcemia.

A single benign FNA cytologic result does not guarantee nodule benignity. The false-negative rate is 1% to 3%. Repeated FNA or ultrasound monitoring at 6 to 12 months is recommended for low-risk nodules. If the repeated FNA is negative, no further sonography is recommended. For high-risk nodules, repeated sonography and/or FNA in 6 to 12 months is recommended. If the repeated FNA is also benign, repeated sonography is recommended in 2 or 3 years.

The endocrinologist should discuss the indication for and extent of thyroid surgery with the patient. All patients with a diagnosis of thyroid cancer or a suspected thyroid cancer should be referred for surgery. It is advisable to refer patients to a high-volume surgeon with expertise in thyroid and parathyroid surgery.

**THYROID NODULE: PERIOPERATIVE MANAGEMENT**

Figure 2 displays the evidence-based recommendations for perioperative management of thyroid nodules. Our KP study demonstrated increased efficiency and decreased complications when management included a consultation with a high-volume thyroid surgeon (defined as having completed more than 40 cases per calendar year as the primary surgeon).³ Further analysis will inform our goal of directing care to higher-volume surgeons who perform at least 20 cases of thyroid and parathyroid surgeries per year. Surgical risks and potential postoperative complications should be carefully reviewed with the patient using a standardized procedurespecific consent form. Patients with clinically significant substernal extension should be referred to a center with thoracic surgery backup.

Preoperative documentation of the patient’s voice is recommended. Documentation can be accomplished by using a patient-reported outcome tool, such as the Voice Handicap Index, or by examination. Direct laryngeal evaluation should be performed in patients with previous neck or thoracic surgery, abnormal voice, or known thyroid cancer. Intraoperative monitoring of the recurrent laryngeal nerve is optional, but identification and preservation of the nerves is recommended. Steps also should be taken to preserve the external branch of the superior laryngeal nerve.

The parathyroid glands should be preserved. Perioperative antibiotics are not routinely recommended unless the case is longer than anticipated or includes possible entrance into the upper aerodigestive tract or a sternotomy. Drains also are not recommended unless there is a large residual space, lateral neck dissection, or sternotomy.

Diagnostic lobectomy is typically appropriate for indeterminate lesions, atypia of undetermined significance lesions, or suspicious for malignancy lesions smaller than 4 cm. Well-differentiated thyroid cancer that presents in a low-risk patient as a nodule between 1 cm and 4 cm without extracapsular spread may be treated with thyroid lobectomy alone. Patients with nodules exceeding 4 cm or with contralateral nodules should be considered for total thyroidectomy. However, the treatment team may recommend, or the patient may consider, total thyroidectomy to avoid reoperation and/or to enable radioactive iodine (RAI) ablation therapy. Thyroidectomy without prophylactic central neck dissection may be appropriate for
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Small T1 or T2 noninvasive, clinically node-negative papillary thyroid carcinomas (cN0) and for most follicular cancers.

Patients with T3, T4, or any TN(+) or M(+) disease should undergo a near-total or total thyroidectomy, with therapeutic central compartment (Level VI) neck dissection in the presence of clinically involved nodes. Prophylactic central neck dissection (ipsilateral or bilateral) should be considered in patients with advanced primary well-differentiated tumors with clinically involved lateral neck lymph nodes or clinically uninvolved central neck lymph nodes (cN0) if the information will be used to plan further steps in therapy. Therapeutic lymph node dissection of the lateral neck compartment should be performed for patients with biopsy-proven metastatic lateral cervical lymphadenopathy.

Postoperative management of patients who undergo complete thyroidectomy includes levothyroxine supplementation with a recommended standard dose of 1.5 µg/kg and adjustment to 1.0 µg/kg to 1.4 µg/kg for older patients or those with comorbidities, such as cardiac disease.

Hypocalcemia management may be achieved with empirical therapy or by obtaining intraoperative parathyroid hormone (PTH) levels, which can be drawn at the time the incision is closed. If the intraoperative PTH level exceeds 20 pg/mL, no supplementation is recommended. For an intraoperative PTH level of 10 pg/mL to 20 pg/mL, we recommend prescribing calcium supplementation at discharge; if the level is less than 10 pg/mL, the clinician should recommend calcium supplements and prescribe calcitriol. If the intraoperative PTH level is less than 6 pg/mL or the patient is at high risk of postsurgical hypocalcemia and is receiving empirical therapy or is symptomatic, one should consider checking a serum calcium level by the third postsurgical day.

If abnormal voice quality is noted by the surgeon or by the patient, the clinician should conduct a laryngeal evaluation with early referral to speech therapy if dysphonia is present or suspected.

The endocrinologist is responsible for requesting postoperative thyroid hormone replacement therapy and obtaining TSH and thyroglobulin measurements six to eight weeks after surgery.

**THYROID CANCER: POSTOPERATIVE INITIAL THERAPY**

The goal is to standardize initial postoperative treatment on the basis of postoperative ATA risk group determination and the patient’s early response to treatment (Figure 3). Using these individualized dynamic risk assessment tools, TSH treatment goals and early decisions about RAI therapy can be made.

The clinician should obtain TSH, thyroglobulin, and thyroglobulin antibody (TgAb) levels six to eight weeks after surgery. Appropriate treatment planning is guided by correct cancer staging. Staging should be updated as additional clinical information becomes available.

Using both the MACIS (metastasis, age at presentation, completeness of excision, invasion, size) scoring system (Figure 4) and the ATA guidelines will help clarify the patient’s risk. Although MACIS may be a better predictor of future survival/mortality, ATA risk stratification may be more predictive of local recurrence. When using the MACIS calculator (available on the Internet at www.thyroid.org/thyroid-cancer-staging-calculator or on KP HealthConnect in Northern California), one should assume no distant metastases to calculate the score unless distinct metastases are known. The endocrinologist should note the stage, MACIS score, ATA risk group, initial and current TSH goal, appropriate tumor marker, use of RAI, and posttreatment whole-body scan results as well as planned or last postoperative thyroid ultrasonography.

### MODIFIED 2009 ATA RISK STRATIFICATION (2015)

**LOW RISK**

- No local or distant metastases
- Clinically N0 or N1 micrometastases (< 5 involved nodes with lesions < 2 mm)
- All macroscopic tumor resected
- No local invasion (no extrathyroidal extension)
- No vascular invasion
- If Iodine-131 given, no uptake except in the thyroid bed
- No aggressive history
- Intrathyroidal encapsulated follicular variant papillary thyroid cancer
- Intrathyroidal well-differentiated follicular with only capsular invasion
- Intrathyroidal well-differentiated follicular with ≤ 4 foci of vascular invasion
- Intrathyroidal papillary microcarcinoma, unifocal or multifocal, including V600 BRAF mutated (if known)

**INTERMEDIATE RISK**

- Microscopic invasion of tumor into the perithyroidal soft tissues
- Clinical N1 or > 5 pathologic N1 with all involved lymph nodes < 3 cm in largest dimension
- Radioactive iodine avid metastatic foci in the neck on the first posttreatment whole body radioactive iodine scan
- Aggressive histology (eg, Tall cell, hobnail variant, columnar cell carcinoma)
- Papillary thyroid cancer with > 4 foci of vascular invasion
- Intrathyroidal, papillary thyroid cancer, primary tumor 1 cm - 4 cm, V600E BRAF mutated (if known)
- Multifocal papillary microcarcinoma with extrathyroidal extension and V600E BRAF mutated (if known)

**HIGH RISK**

- Macroscopic invasion of tumor into the perithyroidal soft tissues (gross extrathyroidal extension)
- Incomplete tumor resection
- Distant metastases
- Pathologic N1 with any metastatic LN ≥ 3 cm in largest dimension
- Postoperative serum thyroglobulin suggestive of distant metastases
- Follicular thyroid cancer with extensive vascular invasion (> 4 foci of vascular invasion)
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Figure 2. Thyroid nodule: Perioperative management (full-size, color version available at: www.thepermanentejournal.org/files/Summer2016/16035-2.pdf).

AUS = atypia of unknown significance; FN = follicular neoplasm; ioPTH = intraoperative parathyroid hormone (pg/mL); RLN = recurrent laryngeal nerve; $T_4 =$ thyroxine; TAV = telephone appointment “visit”; Tg = thyroglobulin; TID = three times a day; TSH = thyroid-stimulating hormone; $X^2 =$ twice.
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**Endocrinologist orders levothyroxine preoperatively**
Patients should all be sent home on T, pending final pathology UNLESS gross residual disease

**Endocrinologist orders postoperative TSH and Tg**

**Consider lobectomy versus total thyroidectomy based on patient preference**

**Completion or total thyroidectomy**

**Total thyroid and central with or without lateral compartment dissection**

**Empiric therapy may be considered if ioPTH not obtained or available:**
- Low risk: calcium 500-600 mg TID
- Intermediate risk: calcium 1000-1200 mg TID
- High risk: calcium AND calcitriol 0.25-0.5 μg daily

**Consider drawing ioPTH X 2 at 5-10 minute intervals after removal of thyroid gland**
- ioPTH > 20: no supplementation or low-dose calcium
- ioPTH 10-20: give calcium at discharge
- ioPTH <10: give calcium and calcitriol at discharge

**Surgery does TAV at 6-8 weeks for postoperative voice check**

**Consider endocrinology input if having difficulty with immediate postoperative hypocalcemia management or if ongoing beyond 4 weeks**

**It postoperative ioPTH < 6, high-risk patient on empiric therapy, or patient symptomatic, consider serum calcium check on postoperative day 2 or 3**

**WELL-DIFFERENTIATED THYROID CANCER**

**BENIGN**

**Pathology**

**Nuclear medicine and medical imaging**

**Surgery consult**

**Endocrinology**

If ordering a postoperative calcium test for symptomatic patients, use the diagnosis “postoperative” or “history of parathyroidectomy or thyroidectomy”

Do not use “hypocalcemia” without previous laboratory-validated diagnosis.
Figure 3. Thyroid cancer: Postoperative initial therapy (full-size, color version available at: www.thepermanentejournal.org/files/Summer2016/16035-3.pdf).

a Calculate MACIS (metastasis, age at presentation, completeness of excision, invasion, size) score as if there are no distant metastases, unless known. If Tg level is out of proportion to presumed burden of disease and MACIS score is borderline for therapy, proceed with radioactive iodine therapy.


ATA = American Thyroid Association; I = iodine; MACIS = metastasis, age at presentation, completeness of excision, invasion, size; RAI = radioactive iodine; rhTSH = recombinant human TSH; Tg = thyroglobulin; TgAb = thyroglobulin antibody; TSH = thyroid-stimulating hormone, mIU/L; THW = thyroid hormone withdrawal; USC = University of Southern California Endocrine Laboratories.
A postoperative thyroglobulin level below 10 ng/mL suggests a low likelihood of clinically significant persistent disease. However, a thyroglobulin level exceeding 10 ng/mL does not always indicate clinically significant residual disease, and confirmation by a posttherapy scan is recommended. Initial thyroglobulin testing should be done using an assay sensitive for thyroglobulin antibodies, given that the presence of antibodies can reduce the validity of thyroglobulin measurements.

On the basis of ATA risk group and response to therapy, patients with low-risk disease should be assessed for possible thyroid remnant ablation therapy with RAI. RAI remnant ablation is an early option for patients who do not appear to be heading for an excellent response to therapy. For most cases of remnant ablation, stimulation with recombinant human TSH is recommended. Unifocal micropapillary disease is usually treated only when the postoperative thyroglobulin level is higher than expected.

Some patients with intermediate-risk disease and almost all patients with high-risk disease benefit from RAI treatment. Thyroglobulin and TgAb levels six to eight weeks after surgery aid in deciding which intermediate-risk patients might benefit from RAI. For the treatment of high-risk patients with known or suspected metastatic disease, thyroid hormone withdrawal therapy is recommended, often with pretherapy diagnostic scanning.

High-risk patients should be treated with recombinant human TSH stimulation only if thyroid hormone withdrawal is medically contraindicated. Typical RAI doses are 125 mCi for local disease, including lateral neck nodes, 150 mCi for pulmonary metastases, and 200 mCi for skeletal or other metastases.

Dosimetry can help avoid overtreatment in the case of comorbid renal failure or widespread pulmonary metastases. If dosimetry in renal failure is not possible, the patient’s dialysis schedule can guide empirical reduction of iodine(I)-131. If dialysis occurs the day after treatment, the clinician should give 40% of the dose calculated as if the patient had normal renal function. If dialysis will occur 2 days later, 22% of the calculated dose should be given.

The likelihood of sufficient iodine clearance after a contrast computed tomography (CT) study at 4 months is approximately 95%. Patients may be treated after thyroid hormone withdrawal or after recombinant human TSH stimulation depending on risk stratification.

**THYROID CANCER: SURVEILLANCE**

Surveillance for differentiated thyroid cancer can be divided into biochemical and anatomic components (Figure 5). Biochemical surveillance uses thyroglobulin and TgAb testing. Anatomic surveillance is primarily done with neck ultrasonography.

At 6 to 12 months postoperatively, thyroglobulin and TgAb testing should be performed with an assay highly sensitive for TgAb. If TgAb levels are detectable, this same highly sensitive assay should be used for long-term surveillance of antibody levels. If the TgAb level is undetectable, thyroglobulin levels can be used reliably for biochemical surveillance in most patients. Use of a thyroglobulin assay with detectability to below 0.2 ng/mL allows confidence in determination of a biochemically complete response to therapy and is preferred over less sensitive assays. Thyroglobulin and TgAb levels should be obtained every 3 to 12 months, depending on the patient’s ATA risk category. If the thyroglobulin or TgAb level increases 50% or more above the baseline for a given patient and is well above the limit of detection, ultrasound evaluation should be obtained.

Alongside regular biochemical surveillance, imaging with ultrasound is recommended 6 to 12 months after the initial therapy and periodically thereafter even if thyroglobulin/TgAb levels remain stable. Central lymph nodes less than 0.8 cm in the anterior-posterior dimension and lateral lymph nodes less than 1 cm in the anterior-posterior dimension should be monitored with serial imaging if thyroglobulin/TgAb markers are stable. If lymph nodes exceed these dimensions, they should undergo FNA biopsy with thyroglobulin washout. Patients with biopsy-proven or thyroglobulin washout-proven metastatic disease should be referred for additional surgery.

In the event that thyroglobulin/TgAb levels are rising but enlarged lymph nodes are negative on FNA biopsy and thyroglobulin washout, additional imaging with CT or magnetic resonance imaging (MRI) should be performed. Any findings on additional imaging should be considered for biopsy or surgery. However, if all imaging has normal findings in the setting of rising thyroglobulin/TgAb levels, an I-123 whole-body scan is indicated. Disease identified on an I-123 scan can be treated with I-131 up to 150 mCi. In patients with thyroglobulin levels exceeding 10 ng/mL and no findings on

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**MACIS Prognostic Score for Papillary Thyroid Carcinoma**

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<td>Age</td>
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**Figure 4. Screenshot of thyroid cancer staging: MACIS (metastasis, age at presentation, completeness of excision, invasion, size) score calculator (full-size, color version available at www.thepermanentejournal.org/files/Summer2010/16035-4.pdf).**

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**Note:**
- Final prognostic score was defined as MACIS = 3.1 (if age ≤ 39 years) or 0.08 × age (if age ≥ 40 years), + 0.3 × tumor size (in centimeters), + 1 (if incompletely resected), + 1 (if locally invasive), + 3 (if distant metastases are present).
- Twenty-year cause-specific survival rates are as follows for each MACIS score: MACIS < 6 = 99%; MACIS 6-6.99 = 89%; MACIS 7-7.99 = 56%; MACIS ≥ 8 = 24%.

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Figure 5. Thyroid cancer: Surveillance (full-size, color version available at: www.thepermanentejournal.org/files/Summer2016/16035-5.pdf).

CT = computed tomography; EBRT = external beam radiation therapy; 18FDG = fludeoxyglucose F 18; FNA = fine-needle aspiration; I = iodine; IR = interventional radiology; mets = metastases; MRI = magnetic resonance imaging; NED = no evidence of disease; path = pathology; PET = positron emission tomography; RAI = radioactive iodine; T4 = thyroxine; Tg = thyroglobulin; TgAb = thyroglobulin antibody; TSH = thyroid-stimulating hormone, mIU/L; US = ultrasound; USC = University of Southern California Endocrine Laboratories; uTG = ultrasensitive thyroglobulin; X 2 = twice.
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**Imaging Surveillance**

- **Possible US mets as defined by > 0.8-cm central or > 1.0-cm lateral nodes**
  - **negative**
    - Tumor marker stable
    - Repeat monitoring of tumor markers based on risk
  - **positive**
    - Tumor marker rising
    - FNA negative for path or Tg washout
    - FNA positive for path or Tg washout

**EXCELLENT RESPONSE**
- No clinical, biochemical, or structural evidence of disease after therapy (remission, NED).
- TgAb negative: typically, unstimulated Tg < 0.2 ng/mL.
- TgAb positive: > 50% drop without structural or functional disease.
- Recurrence rate: 1%-2%.

**BIOCHEMICALLY INCOMPLETE RESPONSE**
- Persistent Tg/TgAb in the absence of localizable disease. Detectable nonstimulated Tg or positive TgAb without structural disease: typically, nonstimulated Tg > 1 ng/mL, < 50% drop in TgAb.
- Outcomes: 56%-68% move to NED, 19%-27% remain in the biochemically incomplete response group, 8%-27% develop structural recurrence.
- No deaths at 10 years.

**STRUCTURALLY INCOMPLETE RESPONSE**
- Persistent or newly identified locoregional or distant metastases. Structural or functional (RAI scan, 18FDG-PET) evidence of locoregional or distant metastases, either biopsy proven or highly likely to be metastatic disease.
- Outcomes: 29%-51% move to NED after surgery.
- 15-year postoperative mortality: 0% if biochemically incomplete response, 11% if locoregional incomplete response, 57% if structurally identified distant metastases.

**INDETERMINANT RESPONSE**
- Nonspecific lesions and indeterminate Tg/TgAb values. Continued observation with serial imaging of nonspecific lesions and serial laboratory monitoring of Tg/TgAb. Nonspecific findings becoming suspicious over time or rising Tg or TgAb should be evaluated.
ultrasound, CT or MRI, and I-123 scan, the clinician should consider positron emission tomography-CT and case discussion with his/her local tumor board.

External beam radiation therapy is recommended for RAI-refractory disease or for treatment of symptomatic metastatic lesions. Tyrosine kinase inhibitors and clinical trials should be considered for patients with progressive, RAI-refractory disease. Patients who are candidates for tyrosine kinase inhibitors should be thoroughly counseled on the potential risks and benefits of this therapy as well as alternative therapeutic approaches, including supportive care.

To facilitate understanding of probable long-term outcomes and thereby guide surveillance frequency, one should ensure that responses to therapy follow ATA recommendations and be documented as “excellent response,” “biochemically incomplete response,” “structurally incomplete response,” or “indeterminate response” (Table 1).

Patients with an “excellent response” to therapy have no clinical, biochemical, or structural evidence of disease. For this designation, thyroglobulin levels must be below 0.2 ng/mL in the setting of negative TgAb levels, or the TgAb level must have dropped 50% or more from baseline. The recurrence rate in this group is believed to be 1% or 2%.

Patients with “biochemically incomplete responses” to therapy have persistent thyroglobulin/TgAb levels in the absence of localizable disease. Studies have shown no increase in disease-specific mortality for this group. At 5 to 10 years, 56% to 68% of these patients will move into the “excellent response” category, 19% to 27% will remain in this category, and 8% to 27% will experience a recurrence.

Patients with “structurally incomplete responses” to therapy have persistent or newly identified locoregional or distantly metastatic disease, either biopsy-proven or likely disease as determined by imaging. In 5 to 10 years, 29% to 51% of these patients will move into the “excellent response” category. Mortality rates for this group are highest, with death occurring in 11% of those with locoregional disease and 57% of those with distant metastases.

Finally, patients with “indeterminate responses” to therapy are those with nonspecific lesions and thyroglobulin/TgAb levels between 0.3 and 1 ng/mL. Most of these patients do well; at 5 to 10 years, 80% to 87% will move into the “excellent response” group while 13% to 20% will move into the “biochemically” or “structurally incomplete response” group.

All patients require TSH monitoring at least annually. Patients who are determined to be biochemically and structurally free of disease and those with indeterminate responses should have TSH levels maintained at 0.4 mIU/L to 2.0 mIU/L. Patients with biochemically or structurally incomplete responses to therapy should have TSH levels maintained at below 0.1 mIU/L if reasonable in the context of coexisting conditions and patient age.

### PRIMARY HYPERPARATHYROIDISM: PREOPERATIVE PREPARATION

Overproduction of PTH resulting in abnormal calcium homeostasis covers a wide spectrum of presentations, including the following:

- hypercalcemia with elevated PTH level
- hypercalcemia with normal but inappropriate PTH level
- eucrealcemia with elevated PTH level in the absence of secondary causes.

Symptoms may or may not be present and include but are not limited to osteoporotic fractures, renal stones, constipation or abdominal pain, peripheral neuropathy, headaches, or psychiatric symptoms. One should suspect primary hyperparathyroidism (PHPT) in patients with hypercalcemia, inappropriately low bone density for age, or family history (hyperparathyroidism-jaw tumor syndrome, multiple endocrine neoplasia, and familial isolated hyperparathyroidism).

Secondary hyperparathyroidism often results from prolonged renal disease, especially after kidney transplantation when prolonged pretransplant parathyroid stimulation could result in autonomous PTH production and hypercalcemia. Patients treated with lithium, especially for prolonged periods, may present with secondary hyperparathyroidism; lithium alters calcium sensing, causing four-gland hyperplasia. Some patients could harbor an unrelated underlying adenoma, and PHPT is detected in associated monitoring.

The ideal workup includes a simultaneous fasting serum calcium test and PTH measurement (Figure 6). When in doubt, one should repeat the PTH estimation. The most common causes of hypercalcemia other than PHPT are thiazide diuretics (through decreased resorption of calcium in the kidney) and malignancy (through a variety of mechanisms). Rarely, excess calcium ingestion or granulomatous processes (including but not limited to tuberculosis and sarcoidosis) can cause high serum calcium levels with suppressed PTH.

### Table 1. Relationship of response to therapy at 6 to 18 months to initial risk stratification and outcomes at 5 to 15 years

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<th>Measure</th>
<th>Response to therapy at 6 to 18 months, %</th>
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<td><strong>Initial risk stratification</strong>&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>Low</td>
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<td>High</td>
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<td><strong>Outcomes at 5 to 15 years</strong></td>
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<td>No evidence of disease (NED)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>97-99</td>
</tr>
<tr>
<td>Indeterminant response (IDR)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>80-87</td>
</tr>
<tr>
<td>Biologically incomplete response (BIR)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>56-86</td>
</tr>
<tr>
<td>Structurally incomplete response (SIR)&lt;sup&gt;e&lt;/sup&gt;</td>
<td>29-51</td>
</tr>
</tbody>
</table>

<sup>a</sup> Blank boxes indicate that the proportion of patients in the category is not reported in the literature.

<sup>b</sup> Modified 2009 American Thyroid Association Risk Stratification System (2015), assessed 6 to 8 weeks postsurgically.

<sup>c</sup> No clinical, biochemical, or structural evidence of disease (thyroglobulin antibody [TgAb] negative: unstimulated thyroglobulin < 0.2 ng/mL; TgAb positive: > 50% drop in TgAb from preoperative level and no structural or functional disease).

<sup>d</sup> Nonspecific lesions and indeterminate thyroglobulin and TgAb values.

<sup>e</sup> Persistent thyroglobulin or TgAb with no localizable disease; detectable nonstimulated thyroglobulin or positive TgAb without structural disease; typically, nonstimulated thyroglobulin level > 1 ng/mL and < 50% drop in TgAb.

<sup>f</sup> Structural or functional (radioactive iodine, fludeoxyglucose F 18-positron emission tomography) evidence of persistent or newly identified locoregional or distant metastases. Of patients with structurally incomplete response, 29% to 51% move to NED after follow-up surgery. The 15-year mortality for structurally incomplete response is 11% for locoregional disease and 57% for structural distant metastases.
Evidence-Based Workflows for Thyroid and Parathyroid Surgery


CT = computed tomography; GFR = glomerular filtration rate; HPT = hyperparathyroidism; MIBISPECT = technetium Tc 99m sestamibi single-photon emission-computed tomography scintigraphy; PTH = parathyroid hormone; SPECT CT = single-photon emission computed tomography; TAV = telephone appointment “visit”; US = ultrasound.

HPT = hyperparathyroidism; ioPTH = intraoperative parathyroid hormone (pg/mL); US = ultrasound; X 2 = twice.

Primary HPT

Baseline ioPTH

Focused exploration

Consider 4-gland exploration (30%-35% of multiglandular disease)

HPT = hyperparathyroidism; ioPTH = intraoperative parathyroid hormone (pg/mL)

Old goal: reduce by at least 50% and in normal range, ideally < 40

Surgeons might consider 4-gland exploration in lieu of ioPTH

Keep in mind that ioPTH is less accurate with negative scan and normocalcemic HPT

Consider ioPTH draw X 2 at 5-10 minute intervals after removal of parathyroid gland(s)

ioPTH > 65 persistent disease

New thinking: ioPTH > 40 suggests persistent disease

If surgery not successful, discuss next steps with endocrinologist

Continue exploration

SURGERY CONSULT

• Recommend all surgeons do their own US
• Review of US and Sestamibi by surgeon immediately before surgery is strongly encouraged
Diagnostic serum testing should include measurement of serum creatinine to rule out renal disease, 25-hydroxyvitamin D, phosphorus, ionized calcium, albumin, and alkaline phosphatase. The latter may be elevated in predominant bone disease, identifying high turnover and a resulting risk of hungry bone syndrome.

In determining whether surgical removal of parathyroid tissue is warranted, the clinician can use several criteria depending on the presence or absence of symptoms. A 24-hour urine collection for calcium and creatinine will allow the calculation of renal calcium clearance. High urinary calcium loss may warrant surgical intervention; this is often present in PHPT. Low urinary calcium loss suggests familial hypocalciuric hypercalcaemia, a benign condition for which surgery is not indicated.

Once the diagnosis of PHPT has been established, surgery is the treatment of choice in the absence of a contraindication, such as limited life expectancy, or evidence of end-organ damage (eg, renal compromise, osteoporosis), especially in the presence of evidence of disease progression.

If the patient is asymptomatic, we adhere to the guidelines for surgery from the Management of Asymptomatic PHPT Fourth International Workshop in 2013. We would consider surgery if any of the following is present (see Figure 6):

- hypercalcemia: serum calcium level exceeding 1 mg/dL above the upper limit of normal
- skeletal compromise
  - low bone mineral density determined by dual-energy x-ray absorptiometry: T-score at or below −2.5 at the lumbar spine, total hip, femoral neck, or distal one-third radius (standard bone density measurement sites); use Z-scores for premenopausal women and men younger than age 50 years
  - vertebral fracture demonstrated using radiography, CT, or vertebral fracture analysis
  - history of fragility fracture (considered a skeletal complication of PHPT)
- renal compromise
  - glomerular filtration rate below 60 mL/min/1.73 m²
  - 24-hour urine calcium level above 400 mg/day and increased stone risk by biochemical stone analysis
  - nephrolithiasis or nephrocalcinosis by x-ray, ultrasound, or CT
- age under 50 years.

Meeting only a single criterion indicates the need for surgery. Other general criteria that the workshop itemized as an indication for surgery include

- Medical surveillance is neither desired nor possible
- The disease has progressed
- The patient prefers surgery in the absence of meeting the aforementioned criteria (as long as there are no contraindications).

The task force members thought that the defining criteria for a neurocognitive component (including but not limited to fatigue and depression) were not definitive.

Once the decision to proceed with surgical consultation is made, a preliminary thyroid sonogram is acquired to identify thyroid nodules and potentially localize a parathyroid adenoma. Ruling out medullary thyroid cancer (associated with MEN2A) in a nodule and workup of thyroid nodules before surgery may change the scope of the surgery. If the sonogram is nonlocalizing, most experts proceed to parathyroid scintigraphy using technetium Tc 99m pertechnetate sestamibi washout imaging with or without SPECT (or SPECT CT) to improve localization together with sonography. Multiphasic CT may also be considered if the combination of sonography and scintigraphy is nonlocalizing or discordant. A presurgical discussion about the likelihood of hyperplasia or multiple adenomas is recommended because of its potential to alter the surgical approach.

**HYPERPARATHYROIDISM: INTRAOPERATIVE AND POSTOPERATIVE MANAGEMENT**

**Parathyroid Localization Studies**

In advance of most surgical procedures, the surgeon knows what will be resected and from which location (Figure 7). Parathyroid surgical therapy differs because the glands are small and of variable number and location. Although localization studies have improved greatly in the past three decades, we are sometimes unable to reliably determine the number and location of all diseased glands preoperatively.

With the advent of an inexpensive and relatively rapid intraoperative PTH assay, localization studies have become increasingly important because minimally invasive procedures may be performed in approximately 85% of cases. As localization studies continue to be refined and new modalities are developed, our algorithm will evolve: we currently recommend a combination of sonography and sestamibi washout scintigraphy as first-line localization studies.

Parathyroid surgeons should become facile with in-office sonography. They have an excellent grasp of the anatomy and both typical and atypical locations of the parathyroid glands; therefore, using basic sonography skills, parathyroid surgeons may quickly become proficient at parathyroid sonography. Sestamibi washout scintigraphy is helpful should the sonogram be nonlocalizing, especially in mediastinal disease, in which there is no utility of sonography. Sestamibi washout scintigraphy is limited in the presence of multiglandular parathyroid disease or synchronous hyperfunctioning thyroid nodules. Multiphasic enhanced neck CT may be of benefit when the sonography and scintigraphy are nonlocalizing, discordant, or both but has a distinct disadvantage of a very high radiation dose; it is thus not currently recommended as an initial localizing study. Additional studies—MRI, FNA with sonographic guidance, and venous sampling—may be used, especially in revision cases for which we recommend having concordant results with at least two modalities before reexploration whenever possible.

**Intraoperative and Postoperative Management**

A skilled parathyroid surgeon navigates the subtleties and complexities of hyperparathyroidism. Before taking the patient to the operating theater, the surgeon will have thoroughly reviewed the case and its corresponding localization studies to be certain of the diagnosis of PHPT. If a localization study is not validated in the operating room and four normal glands are found, a surgeon who is certain of the diagnosis may confidently expand the exploration, find the abnormal gland, and conclude surgery successfully.
A baseline intraoperative PTH measurement is critical for a focused exploration and also helps determine when to stop in a bilateral exploration; more than 4 glands are present in approximately 6% of cases. Owing to variable PTH kinetics, no perfect criterion exists for terminating an operation. The more stringent the criteria, the higher the number of unnecessary explorations that will occur. We now recognize that a drop in intraoperative PTH level exceeding 50% from the preexcision value does not result in an adequate cure rate, and we recommend continued exploration if the final PTH exceeds 65 pg/mL. In addition, current thinking suggests that patients with values exceeding 40 pg/mL may have hyperplasia. It is almost always better to perform a bilateral exploration than to return at a later date to face a scarred operative field, where finding the diseased gland is more challenging and could result in greater complications.

The nature of renal hyperparathyroidism mandates bilateral exploration. A hyperplastic process involving all the glands is generally present even when a localization study identifies only one or two abnormal glands, and hyperplastic glands can vary greatly in size. Postsurgical hypercalcemia should be expected in most cases of renal hyperparathyroidism. Monitor patients who have clinically significant bone disease with special vigilance.

CONCLUSION

These workflows synthesize the best evidence currently available about caring for patients with thyroid nodules and PHPT and represent an attempt to standardize the care of patients with thyroid and parathyroid diseases. The evidence-based decision points and workflows presented here support an initiative of specialty care redesign to provide consistency in delivery of care and outcomes for our patient population.

Disclosure Statement

The author(s) have no conflicts of interest to disclose.

Acknowledgment

The authors would like to thank Violeta Rabrenovich for material support of this work. Jennifer Green provided editorial assistance. Kathleen Louden, ELS, of Louden Health Communications provided editorial assistance.

How to Cite this Article


References


The Third View

The practical surgical question as to whether the cretinous symptoms following thyroidectomy are due to—1) Chronic asphyxia, as believed by Kocher; 2) Injury of the sympathetic and other nerve trunks 3) Arrest of function of the thyroid gland—is almost settled in favor of the third view, and with it also the pathology of Myxoedema.

— Sir Victor Alexander Haden Horsley, FRS, 1857-1916, English neurosurgeon and neuroscientist