Differentiated thyroid cancer

Differentiated thyroid cancers, including papillary and follicular variants, make up 90% of all cases. In North America, the annual incidence has increased approximately fourfold with almost the entire change due to papillary thyroid cancer.\(^1\)\(^,\)\(^2\) Approximately 50% of the increased incidence consists of cancers 1 cm or smaller and almost 90% consists of cancers 2 cm or smaller. In the past two decades powerful new tools have become available for the routine followup of treated thyroid cancer patients, allowing both \(^{131}\)I scanning and therapy to be more selectively prescribed.\(^2\)\(^,\)\(^3\) A risk-appropriate followup of differentiated thyroid cancer may now be visualized as consisting of two phases, followup/therapeutic decision-making in the immediate post-surgical phase and long-term risk-appropriate followup post initial therapeutic intervention.

But in terms of long-term relapse risk, it must always be remembered that thyroid cancer shares a characteristic with melanoma, renal cancer and hormone receptor-positive indolent breast cancer in elderly women. Up to 30% of appropriately treated patients ultimately develop recurrences and while the majority occur within the first five years, one-third of these will appear decades after initial therapy.\(^5\)^\(^,\)\(^10\) In addition, in relation to overall thyroid cancer-related deaths, more than 75% will still represent well-differentiated thyroid cancers, and there is also good evidence that anaplastic thyroid carcinoma can undergo dedifferentiation from well-differentiated thyroid cancer.\(^2\)\(^,\)\(^3\) Such considerations mean that a risk-appropriate long-term followup strategy for thyroid cancer patients is paramount.

RISK-APPROPRIATE POST-SURGICAL FOLLOWUP

In current practice, most patients with a preoperative fine-needle aspiration biopsy of malignancy undergo total thyroidectomy, while an initial benign or uncertain diagnosis more typically leads to lobectomy. It is now generally accepted that patients with small (<1 cm), unifocal, intrathyroid, node-negative, low-risk papillary tumours may safely be treated by lobectomy only.\(^7\) Subsequent quantitative assessment of postsurgical recurrence risk is guided both by TNM tumour grading and AJCC criteria (Tables 1). Current US and UK guidelines\(^2\)\(^,\)\(^3\) recommend that any decisions regarding possible completion thyroidectomy depend on an assessment of:
- the age and sex of the patient (>45 or male sex are both poorer prognostic features).
- size of the malignant nodule (>2 cm) and if entirely confined within thyroid gland.
- presence of lymph node involvement, distant metastases or disease in the remaining lobe on ultrasound.
- aggressive histologic variants such as poorly differentiated or tall, columnar, insular cell types.
- past history of exposure to significant ionizing radiation or positive family history.

While papillary cancers tend to spread late to regional lymph nodes or lungs, follicular disease is more likely to metastasize early via the hematogenous route to bone or brain. Thus, follicular cancers are likely to present with a higher risk of recurrence.\(^2\)

Authors’ note: Drs Brigden, Rachinsky and Singh wish to dedicate this article to Dr. Albert Driedger, in recognition of the advice, leadership and friendship he has provided both provincially and nationally during more than 40 years of thyroid cancer practice.
**TABLE 1. TNM classification system for differentiated thyroid carcinoma**

<table>
<thead>
<tr>
<th>Stage</th>
<th>T, N, M</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage IVA</td>
<td>T4, N1a, MO</td>
</tr>
<tr>
<td></td>
<td>T1, N1a, MO</td>
</tr>
<tr>
<td></td>
<td>T1, N1b, MO</td>
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<tr>
<td></td>
<td>T2, N1b, MO</td>
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<tr>
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<tr>
<td></td>
<td>T4a, N1b, MO</td>
</tr>
<tr>
<td>Stage III</td>
<td>T3, N0, MO</td>
</tr>
<tr>
<td></td>
<td>T1, N1a, MO</td>
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<tr>
<td></td>
<td>T4a, N0, MO</td>
</tr>
<tr>
<td>Stage II</td>
<td>Any T, any N, MO</td>
</tr>
<tr>
<td></td>
<td>T2, N0, MO</td>
</tr>
<tr>
<td>Stage I</td>
<td>Any T, any N, any M</td>
</tr>
</tbody>
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AJCC=American Joint Committee on Cancer; T=tumour; N=node; M=metastasis.

**Figure 1. Post thyroidectomy risk-appropriate followup**

- Low risk
  - Micronodular disease (unifocal or multifocal)
  - T1, T2 tumours with no nodal disease or extrathyroidal extension

- Intermediate or high risk
  - Male sex or age greater than 45
  - Familial history or radiation exposure
  - T3, T4 tumours
  - Aggressive histological variants
  - Extrathyroidal extension or nodal involvement

- May not require ¹³¹I therapy
- Will likely require ¹³¹I therapy

For total thyroidectomy patients, subsequent treatment options depend on risk for future cancer recurrence, usually classified as low, intermediate or high.²,³ (Figure 1) Intermediate and high recurrence risk patients for thyroid cancer should undergo ¹³¹I ablation. Equally efficacious radioiodine ablation protocols include thyroid hormone withdrawal (therapeutic goal, thyroid-stimulating hormone [TSH] >30 mIU/L) or utilization of recombinant TSH (rhTSH, Thyrogen) injections. The rhTSH protocol has significant advantages: a shorter preparation time and avoidance of hypothyroid symptoms. Moreover, since a euthyroid state is preserved during ¹³¹I ablation using rhTSH, there is no accompanying hypothyroid decrease in glomerular filtration rate (GFR) that substantially increases the total body radiation dose.²

The serum thyroglobulin (Tg) value is strongly dependent on circulating TSH level; a maximal value is obtained when the TSH is elevated (so-called stimulated thyroglobulin) and a low or undetectable value (usually <1–2 ng/mL) is a strong predictor of good outcome. All patients should have a stimulated Tg performed at the time of radioiodine ablation when their TSH levels are elevated. For those treated with hormone withdrawal, sampling can occur immediately prior to ¹³¹I therapy; those who receive rhTSH will achieve maximum stimulation Tg on the fifth day post first injection.²,³ The best definition of successful ablation is an undetectable or appropriately low (<1–2 ng/mL) serum Tg level following TSH stimulation accompanied by a normal neck ultrasound at 12 months post therapy.⁴

Regardless of hormone withdrawal or rhTSH protocol, all patients should go on a restricted-iodine diet for 12–14 days (10 days prior to radioiodine administration and ~2 days after).⁴,⁵ The post-therapy scan ¹³¹I should be performed around day 5–7 postablation. At this time another risk-based stratification may be undertaken based on post-therapy imaging results, stimulated serum Tg level and any knowledge of metastatic disease.²,³ (Figure 2) **TARGET TSH RANGES AND DENTAL PROPHYLAXIS**

Ideally while on thyroxine therapy, serum TSH, Tg and thyroglobulin antibodies (TgAb) should be determined every six months, coupled with a clinical neck examination.²,³ Approximately 25% of thyroid cancer patients present with TgAb, which may falsely lower serum Tg determinations by binding to Tg. Serial serum TgAb quantification may serve as a reasonable surrogate marker of residual normal thyroid tissue under such circumstances.² Overly aggressive thyroxine therapy includes potential risks such as possibly accelerated bone loss, atrial fibrillation and cardiac dysfunction.²,³ Patients whose TSH levels may be chronically depressed should be counselled to ensure adequate daily intake of both calcium (1000 mg/day) and vitamin D (800 units/day). Therefore, for patients judged to be at low recurrence risk who did not receive ¹³¹I, it is reasonable to target hormone replacement to achieve TSH levels in the lower half of the reference range, i.e. 0.5–1.5 µg/mL. For patients at intermediate or high risk, a minimum value of at least 0.1 µg/mL is currently recommended.²,³⁴
Patients should be instructed regarding thyroid hormone administration since minerals, food and other medications may interfere with absorption, producing significant variations in TSH levels. The best time to take L-thyroxine is first thing in the morning, with avoidance of other oral intake for 45-60 minutes. Repeat TSH testing after any dosage changes requires a minimum six-week delay since thyroid hormone dosage takes time to be fully reflected in the TSH level. In following up patients post ¹³¹I therapy, it is important to remember that even in the absence of frank sialadenitis, reduced saliva production may potentially occur, so vigorous lifelong oral hygiene and dental prophylaxis is mandatory.

SUBSEQUENT LONGITUDINAL FOLLOWUP

At year 1 post initial ¹³¹I scan, appropriate clinical examination should be performed along with a neck ultrasound, and Tg and TgAb determinations before and after rhTSH stimulation. Several studies have suggested that whole-body ¹³¹I scanning is no longer necessary if rhTSH-stimulated Tg concentrations are <2 µg/L and the neck ultrasound is normal. However, one year post-ablation, approximately 20% of patients who are clinically free of disease, with serum Tg levels of <1–2 µg/L while on TSH suppression, will have a serum Tg level >2 µg/L post rhTSH or thyroid hormone withdrawal. One-third of these patients will subsequently have progressive elevation of Tg levels and be identified with persistent or recurrent disease while the remaining two-thirds will persist clinically free of disease with a stable or decreasing stimulated serum Tg over time. Clinical followup in these patient groups should be tailored to ensure serial results. Patients with significantly elevated Tg will likely undergo surgery or a second ¹³¹I therapy (if surgically resectable disease is identified on neck ultrasound). Patients who have persistently elevated Tg in the face of negative ¹³¹I scanning at the time of radioiodine therapy should subsequently be investigated by positron emission tomography – computed tomography (PET/CT) scan.

At years 2 and upwards, continue with appropriate clinical examination and measurement of TSH, Tg and TgAb yearly or as appropriate with additional neck ultrasounds based on risk profile and clinical findings. Radioiodine imaging might be performed if serum Tg increases or there is other clinical evidence suggesting recurrence, or alternatively, an additional radioiodine dose could be administered without prior low-dose diagnostic radioiodine scanning. Because of the significant incidence of late recurrences, where clinically feasible, annual followup should probably be carried out indefinitely. However, after 10 years, some practitioners lengthen the interval followup period. Such followup does not necessarily require specialist care and may become part of patient-centred care provided by other informed primary health care practitioners. Followup of patients with good prognosis initially treated with subtotal thyroidectomy only: serial Tg determinations (without TSH stimulation) and annual neck ultrasound evaluations of contralateral residue thyroid tissue and cervical nodes are recommended. Annual or lengthier followup intervals are based on subsequent serial results.

Adrenal incidentalomas

Adrenal incidentalomas occur in approximately 4% of patients and are defined as serendipitously discovered adrenal lesions >1 cm in size on radiologic examination done for reasons other than to investigate for primary adrenal disease. The mean age of such patients is 60 years. The mean diameter on CT scan is typically 3–3.5 cm and more than 80–85% are benign nonfunctioning adenomas, while subclinical Cushing’s syndrome (9%), phaeochromocytoma (4%) and aldosteronomas (1–2%) account for the majority of the remainder. Only 50% of patients with aldosteronoma have hypokalemia and up to 50% of patients with incidentally discovered phaeochromocytomas may also be normotensive. Less than 10% of all incidentalomas are actually malignant in nature. Sex hormone-producing adrenal tumours are rare and typically present with accompanying clinical symptoms.

Followup of the incidentally discovered adrenal mass may be divided into the initial and late categories.

INITIAL FOLLOWUP

Initial followup of the incidentally discovered adrenal mass aims to distinguish functioning from nonfunctioning status, as well as benign from malignant tumours. As illustrated in figure 3, the initial investigation should include a 24-hour urine for urinary-free cortisol or 1 mg dexamethasone suppression test, 24-hour urine for metanephrines (preferable to catecholamines which, may be intermittently secreted) and if
hypertensive, an upright plasma aldosterone concentration to plasma renin ratio (ARR). Patients with initial abnormal endocrine screening would typically have a confirmatory test followed by appropriate surgical and/or medical management.6,7

When initial endocrine testing is normal, modern imaging can be most helpful in separating potentially benign from malignant tumours. Adenomas tend to have smooth margins and homogeneous density whereas carcinomas are usually heterogeneous with an irregular shape and calcifications or necrosis.8,9 Adenomas typically contain a greater proportion of intracellular fat compared to malignant incidentalomas, resulting in increased attenuation on unenhanced CT. An attenuation of greater than 10 Hounsfield units on unenhanced CT has a sensitivity and specificity of 71% and 90% respectively.6,7

For all masses >6 cm in size or between 4–6 cm and not manifesting benign appearance on CT scanning (most adenocortical carcinomas are greater than 4 cm in size), laparoscopic adrenalectomy represents the gold standard.6,7

LONG-TERM FOLLOWUP

For nonfunctioning adenomas >4 cm in size, a followup protocol is usually recommended. In choosing the appropriate followup for an individual patient, the following needs to be considered:6,9,10

- The annual risk of developing subclinical or clinical hyperfunction during followup is low, probably in the range of 0.9–1.2%/year.
- If no transformation to functioning status has occurred within 4 years, subsequent evolution is highly unlikely.
- The risk of malignant transformation is also low (in the range of 0.1%/year) and is almost always accompanied by an absolute annual increase in size of greater than 0.5–1 cm or 25% overall.
- The subsequent risk of malignant transformation is very small in masses that are stable over 6–12 months.
- Clearly benign etiologies at discovery (hemorrhages, cysts, myelolipomas) may not necessarily require any further evaluation.

Based on the above, most of the published consensus or clinical guidelines recommend annual hormonal screening for up to 4 years accompanied by several repeat radiologic assessments.6,8,9 First followup scan has been suggested in 6 months for radiologically suspicious lesions or 12 months for seemingly benign masses. Subsequent imaging should be directed by clinical judgment.6

Neuroendocrine cancers

Neuroendocrine cancers (NETs) are uncommon malignancies that can originate from neuroendocrine cells and can arise from anywhere in the body, including the foregut (respiratory tract, stomach, duodenum, pancreas), midgut (small bowel, appendix, ascending colon) or hindgut (transverse colon, descending colon, rectum).11,12,13 If functional, they are generally characterized by their ability to produce peptides that may lead to symptoms such as flushing, diarrhea or bronchoconstriction.11,12 NETs form a heterogeneous group of malignancies whose behaviour can range from incredibly indolent to aggressive. The incidence of NETs is known to be increasing, either due to better detection or true increase in disease burden.12,13

NETs are often difficult to detect and diagnose as they may go undetected for years without obvious signs or symptoms. Since many patients will have had a long history before definitive diagnosis, they obviously may be very concerned regarding potential followup plans. Although no randomized data exist, there are a number of expert consensus guidelines.13,14

GENERAL PRINCIPLES FOR FOLLOWUP OF NEUROENDOCRINE CANCERS

- Followup must be individualized according to tumour characterization and rate of growth.
- Patients may be followed more closely in the first year after diagnosis to establish pace of tumour growth.
- While NETs are generally slow-growing malignancies, Ki-67 represents an important pathologic marker that may predict subsequent growth rate/clinical behaviour.11,12,13
• High-proliferating tumours that have a Ki-67 index >10–15% are usually larger than 2 cm, exhibit extensive angioinvasion, and show greater potential for metastatic disease.
• Poorly differentiated or even well-differentiated NETs with a high Ki-67 may progress rapidly and should be followed closely.
• Clinical followup should consist of history and physical examination (HPE), with particular emphasis on NET specific symptoms (such as flushing, diarrhea, abdominal pain, bloating, bronchospasm) and physical exam findings ( flushing, rash ).
• Investigations include standard laboratory testing, as well as the serum tumour marker chromogranin A (CgA), currently the most important biomarker.15 Artifactual high CgA levels may be seen with type A chronic atrophic gastritis, renal disease or the use of proton pump inhibitors. Other corroborative laboratory investigations include 24-hour urinary 5-HIAA (5-hydroxyindoleacetic acid), a measure of a serotonin breakdown product in urine. Urinary 5-HIAA may also be influenced by dietary factors.

FOLLOWUP OF NETS — FULLY RESECTED
Years 1–3
• HPE and routine bloodwork q 3–6 months
• Serum CgA q 6 months, Urinary 5-HIAA q 6 months (if functional tumour)
• CT or magnetic resonance imaging (MRI) q 6 months
• If results sufficiently abnormal, do further testing, including indium 111In-pentetreotide (OctreoScan)
• (OctreoScan q 2 years is preferred if available)

Years 4 and beyond
• HPE and routine bloodwork q 6–12 months
• Serum CgA q 12 months, urinary 5-HIAA q 12 months (if functional tumour)
• CT/MRI q 12 months
• If results sufficiently abnormal, do further testing, including OctreoScan

FOLLOW UP OF NETS — POST DE-BULKING SURGERY (MACROSCOPIC RESIDUAL DISEASE PRESENT) OR NON-DE BULKED METASTATIC DISEASE
Year 1
• HPE and routine bloodwork q 3 months
• Serum CgA q 3 months, urinary 5-HIAA q 3 months (if functional tumour)
• CT/MRI q 3 months
• OctreoScan at baseline if possible

Years 2 and beyond (if accelerated growth, Ki-67 >30% or poorly differentiated, then continue as per year 1)
• HPE and routine bloodwork q 6 months
• Serum CgA q 6 months, urinary 5-HIAA q 6 months (if functional tumour)
• CT/MRI q 6 months
• OctreoScan yearly if possible
• If results sufficiently abnormal, do further testing, including OctreoScan

References