



Donna Morrison. *Buds of Beauty*. Watercolor, 21" × 24".

The diagnosis and treatment options for papillary thyroid carcinoma, follicular carcinoma, and Hürthle cell carcinoma are reviewed.

Workup of Well-Differentiated Thyroid Carcinoma

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Background: Well-differentiated thyroid carcinoma (WDTC) includes three main entities: papillary thyroid carcinoma (PTC), follicular thyroid carcinoma (FTC), and Hürthle cell carcinoma (HCC). A thorough knowledge of the natural history and presentation of these carcinomas is vital to the thyroid surgeon.

Methods: This review details the preoperative workup of patients having or suspected to have WDTC. We review the history, physical examination, laboratory, and radiographic evaluations that optimally prepare the surgeon to determine the ideal surgical thyroid and neck treatment for patients with WDTC.

Results: A fiberoptic evaluation of the larynx is integral to the physical examination, and a laryngeal assessment is performed for all patients who will undergo thyroid surgery. It must be noted that vocal cord paralysis can be subtle and does not always present with clear dysphagia or voice change. Ultrasound and FNA are the primary tools of preoperative assessment. Given that patients with preoperative FNA positive for papillary cancer are expected to have clinically significant nodal disease in one third of cases, radiographic evaluation must be appropriately aggressive. The combination of US and CT allows assessment of the central and lateral neck nodes and the thyroid's relationship to central neck viscera.

Conclusions: The overriding principle in the surgical treatment of WDTC is that the surgeon recognizes and encompasses all gross disease in the thyroid and neck nodes at first surgery. The extent of thyroidectomy is tailored not only to the patient's risk group and gross operative findings but also to the progress of the specific surgery in terms of parathyroid and recurrent laryngeal nerve preservation.

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Abbreviations used in this paper: PTC = papillary thyroid carcinoma, FTC = follicular thyroid carcinoma, HCC = Hürthle cell carcinoma, FNA = fine-needle aspiration, US = ultrasound, CT = computed tomography, TSH = thyrotropin.

Introduction

Among thyroid cancers, well-differentiated thyroid carcinoma has a good prognosis when the diagnosis, staging, treatment, and risk of recurrence are carefully managed. Careful preoperative assessment, including laryngeal examination and appropriate preoperative imaging with recognition of the differences among the types of well-differentiated thyroid carcinoma are key factors in optimal patient care.

Patient History and Physical Examination

The workup of any carcinoma begins with a thorough history and examination. Access to previous investigations, laboratory tests, and relevant operating notes is important at this patient review. Following a full clinical and surgical history, the physician needs to address questions of particular relevance when assessing a potential thyroid carcinoma patient for the first time.

A discussion about any symptoms potentially indicative of vocal cord paralysis including hoarseness of voice, dysphagia, odynophagia, and aspiration of fluids is especially important. Also, the physician inquires about coughing, shortness of breath, stridor, or hemoptysis, all of which may suggest tracheal invasion by a thyroid carcinoma. Significant weight loss or systemic discomfort, as well as any previous thyroid disease or surgery to the head and neck, is also discussed during the history-taking process. Due to the increased risk of thyroid carcinoma in patients with prior exposure to ionizing radiation, particularly to the head and neck region during childhood, any previous history of radiation exposure or external-beam irradiation must be elucidated.^{1,2} It is also important to identify any family history of thyroid cancer, since 5% to 10% of patients with papillary thyroid carcinoma and 25% of patients with medullary thyroid cancer may have a family history of thyroid cancer.³

A full head and neck examination and respiratory examination are required. Any nodularity, increase in size, or tenderness is noted when examining the thyroid, and a thorough assessment for any associated lymphadenopathy is important. Fixation of the mass to the airway and deviation of the trachea and larynx should be noted.

A fiberoptic evaluation of the larynx is integral to the physical examination, and a laryngeal assessment is performed for all patients who will undergo thyroid surgery. It must be noted that vocal cord paralysis can be subtle and does not always present with clear dysphagia or voice change. Vocal cord paralysis is associated with voice change in only one third of patients and will be identified on computed tomography (CT) of the neck in only 25% of patients.⁴ Symptomatic

assessment of vocal cord paralysis is inaccurate, with only 40% of patients with unilateral paralysis being asymptomatic.⁵⁻⁷ Thus, visual inspection of the vocal cords is imperative during the initial preoperative workup. Knowledge of vocal function is critical during preoperative planning, given that the presence of vocal cord paralysis may indicate a more aggressive carcinoma with infiltration of the recurrent laryngeal nerve and invasion of the airway. This knowledge is also important when an invaded nerve is found during surgery as its management is dependent on its preoperative function.⁸ Preoperative laryngeal examination is particularly vital in revision cases where preoperative vocal cord paralysis rate can be as high as of 6.7% and can be asymptomatic.^{9,10}

Types of Well-Differentiated Thyroid Carcinoma

Well-differentiated thyroid carcinoma includes three main entities: papillary thyroid carcinoma (PTC), follicular thyroid carcinoma (FTC), and Hürthle cell carcinoma (HCC). A thorough knowledge of the natural history and presentation of carcinomas is vital to the thyroid surgeon. The most common of the well-differentiated thyroid carcinomas is papillary carcinoma.

Papillary Thyroid Carcinoma

The main diagnostic features of PTC are its nuclear changes, which include subtle irregularities in the nuclear contour and size, deep nuclear grooves, and pseudo inclusions resulting from cytoplasmic invaginations. These nuclear features enable the diagnosis of PTC to be made on cytological examination and frozen section. On gross examination, PTCs can be of variable sizes with ill-defined margins, and they are commonly firm with a white cut surface. PTC is also associated with the microscopic feature of psammoma bodies that can be calcified and can appear as microcalcifications on ultrasound (US) scans in up to 50% of patients. Due to their well-differentiated nature, PTC cells often retain their ability to concentrate iodine and occasionally produce thyroid hormone.¹¹⁻¹³ They also produce and secrete thyroglobulin and can express thyrotropin receptors on their surfaces.¹⁴

PTC represents a large group of well-differentiated thyroid carcinomas with several histologic variants including microcarcinomas, follicular variants, encapsulated variants, diffuse sclerosing variants, oxyphilic cell variants, and two more aggressive variants — the tall cell variant and the columnar cell variant.

The most common presentation of PTC is a young woman with either a palpable neck mass in the thyroid or a palpable cervical lymph node.¹⁵ One of the features of PTC is its tendency for multifocality, ranging

from 18% to 46%, depending on the series.¹⁶⁻²⁰ Lymph node involvement is common, occurring in 30% of patients. Extrathyroidal extension occurs in 8% to 32% of cases. The most common site of extrathyroidal extension is the surrounding muscle (8%), followed by the recurrent laryngeal nerve (6%) and trachea (5%).^{17,19,20} Distant metastasis occurs in only 1% to 25% of PTC patients, representing the lowest rate of all the well-differentiated thyroid carcinomas.²¹ A recent study has found the survival rate of PTC at 1 year to be 97.5%, while the survival rate at 5, 10, and 15 to 20 years is 92.8%, 89.5%, and 83.9%, respectively.²²

Follicular Thyroid Carcinoma

FTC is diagnosed microscopically through the identification of capsular or vascular invasion. This feature differentiates FTC from follicular adenoma. Therefore, a diagnosis of FTC cannot be confidently made with fine-needle aspiration (FNA) or frozen section. Macroscopically, FTC tends to comprise solitary tumors of varying sizes with thick fibrous capsules that have a tan cut surface. FTC is considered a more aggressive well-differentiated thyroid cancer when compared to PTC.²³ The 5-, 10-, and 20-year survival rate for FTC has been found to be 85%, 80%, and 76%, respectively.²⁴ Several prognostic features that decrease the overall survival of FTC include age, size of tumor, distant metastasis, extrathyroidal extension, and histologic type. In high-risk groups (age >45 years, stage >T1, distant metastasis, high histologic grade), the 10-year survival rate can be as low as 56%.²⁴

The two main subgroups of FTC are minimally invasive and widely invasive. Minimally invasive FTCs have been shown in several studies to have a more favorable prognosis.²⁴⁻²⁷ FTC has a higher rate of hematogenous spread than PTC. It is important for the surgeon to recognize that at the time of diagnosis of FTC, 10% to 15% of cases have distant metastasis.^{19,28,29}

Hürthle Cell Carcinoma

HCC can be considered a subtype of FTC and is characterized pathologically by the presence of oncocytes rich in mitochondria (Hürthle cells). The Hürthle cell's rich mitochondrial content makes HCCs appear brown on their cut surface. Microscopically, a diagnosis of HCC is made through identification of capsular or vascular invasion, similar to that of FTC. Similarly, the diagnosis of HCC cannot be made on either FNA or frozen section.

Although HCC rarely presents with distant metastases, it has the highest incidence of distant metastasis of all the well-differentiated thyroid carcinomas. Approximately 34% of patients will develop distant metastasis at some time during their illness.³⁰ It also has a higher rate of lymph node metastases compared to FTC.^{28,31}

Evaluation of the Thyroid Nodule

Initial Diagnostic Approach

As a basic diagnostic step, all patients undergoing thyroid surgery have their thyroid function assessed with a set of function tests, particularly thyrotropin (TSH). We do not advocate routine preoperative assessment of thyroglobulin or calcitonin. US and FNA are the gold standards in the evaluation of a thyroid nodule for clarifying the anatomy and obtaining a cytological diagnosis. A definitive result with FNA is not always possible, but improved imaging techniques have enabled the use of US to guide FNAs to increase their accuracy. Ultrasonography can increase this accuracy to more than 95% by ensuring appropriate needle position.³² We believe that all thyroid nodules larger than 1 cm require FNA.

Imaging of the Thyroid Gland

Ultrasonography

Ultrasonography is often the first imaging modality employed to evaluate a thyroid nodule since it is readily accessible, inexpensive, and noninvasive, and it requires no radiation exposure. Ultrasonography is effective at delineating intrathyroidal architecture, distinguishing cystic from solid lesions, determining if a nodule is solitary or part of a multinodular gland, and accurately locating and measuring a nodule.³³ It has the added advantage of demonstrating any associated lymphadenopathy in the paratracheal region, the most commonly involved lymph node region for metastasis.³⁴ However, a US scan is unable to provide any functional information or predict malignancy, and it is dependent on an ultrasonographer for the quality of images, regions of the neck covered, and interpretation. Several ultrasonographic features have been identified that suggest a higher risk of malignancy within a nodule, including microcalcifications and central blood flow.³⁵ Serial US examinations enable the clinician to monitor disease progression, assess therapeutic response, and identify recurrence. US scans can be misleading if lateral neck nodal regions are not fully inspected for nodal disease, and a sensitivity of only 37% in the detection of regional nodal disease has been reported.³⁶

Computed Tomography and Magnetic Resonance Imaging

In thyroid carcinoma, CT is particularly useful in identifying and delineating the full extent of any cervical lymphadenopathy and the relationship of the thyroid to surrounding cervical viscera.

Contrast CT in the assessment of thyroid carcinoma is associated with a short delay in scanning and radioactive iodine treatment for up to 6 to 8 weeks. For this reason it should be used judiciously and appropri-

ately. CT can be performed without the administration of intravenous contrast, with somewhat more limited resolution. We limit the use of contrast CT to patients with associated lymphadenopathy on examination or US and to patients whose FNA is positive for PTC. The surgeon must appreciate that patients with preoperative FNA positive for papillary cancer are expected to have clinically significant nodal disease in one third of cases. Radiographic evaluation must be appropriately aggressive. We find that the combination of US and CT in these situations allows us to clearly assess the central and lateral neck nodes and the thyroid's relationship to central neck viscera. Lateral neck nodal disease sometimes not well investigated by US, as well as nodal disease in the parapharyngeal, retrolaryngeal, retrotracheal and retrosternal regions, are clearly and reliably seen on contrast CT. This radiographic combination of US and contrast CT produces an effective preoperative nodal map that enables us to direct our nodal dissection at the time of surgery. We feel the added accuracy of this combined assessment allows for comprehensive nodal resection at first surgery, which is likely of greater value to patients with papillary cancer than prompt postoperative I131.

The resolution, standard representation of neck anatomy, and ease of interpretation of CT make it a superb modality for preoperative assessment in patients with FNA-revealing papillary cancer. MRI can also be used to evaluate the thyroid gland by utilizing a dedicated neck or surface coil. This provides excellent soft tissue resolution, with nodules as small as 4 mm being detected.³⁷

Radioisotopic Scanning

Thyroid scintigraphy is of extremely limited use for the thyroid carcinoma surgeon. The two-dimensional nature of scan, the erroneous superimposition of normal and abnormal tissue that limits interpretation, and the lack of reliability in differentiating benign from malignant nodules render it of little use in the evaluation of a thyroid carcinoma. For these reasons, we do not use preoperative thyroid scintigraphy in the evaluation of thyroid carcinoma.

Fine-Needle Aspiration Biopsy

FNA has become the gold standard in deciding whether to proceed with surgical treatment of thyroid carcinoma. The sensitivity and specificity of FNA for thyroid cancer are high, ranging from 65% to 98% and 72% to 100%, respectively, making FNA the test of choice for routine diagnosis and management of thyroid nodules.³⁸⁻⁴³

The four main groups of FNA results are benign, malignant, indeterminate (suspicious), and nondiagnostic (unsatisfactory).⁴⁴⁻⁴⁶ The benign group includes colloid nodules, benign cysts, and thyroiditis. The indeterminate (suspicious) group consists of cytology that

is atypical but not diagnostic for malignancy. The non-diagnostic (unsatisfactory) group is made up of aspirates with too few cells for diagnosis. Knowledge of the implication of each group to the patient, as well as to the appropriate management of the disease, is imperative for the thyroid surgeon.

Benign: The benign FNA cytological classification is the most common result, representing approximately 70% (50% to 90%) of cases.⁴⁷⁻⁴⁹ One may follow such a nodule without surgical intervention. If the nodule changes in follow-up, is large, or has other worrisome clinical characteristics, repeat FNA or surgery can be considered. This classification often includes a benign macrofollicular adenoma, multinodular goiter, or thyroiditis.

Malignant: The malignant group represents approximately 4% (1% to 10%) of all the thyroid FNA specimens. PTC represents the most common malignant FNA result since its diagnostic nuclear features allow cytological diagnosis.⁵⁰ In certain circumstances, these nuclear features are seen but are not sufficient to confirm a diagnosis of PTC; in these situations, a definitive diagnosis cannot be established so the sample is classified as suspicious. Other thyroid malignancies diagnosed on FNA include medullary carcinoma and highly malignant carcinomas (anaplastic carcinomas and high-grade metastatic lesions).^{51,52}

Suspicious: This classification is used when a definitive diagnosis cannot be made cytologically. This group represents 10% (5% to 20%) of all FNA results. Due to the inability to see vascular or capsular invasion on a cytological sample, the most common diagnosis in this group includes follicular neoplasms and Hürthle cell neoplasms. PTCs also form part of this group when some nuclear features are seen, but cytological evidence is insufficient to make a definitive diagnosis. Factors that increase the probability of malignancy for follicular neoplasms are nodule size greater than 4 cm, solitary nodule, male sex, and fixed nodule on palpation.^{53,54} This suspicious category presents the thyroid surgeon with a unique situation since only approximately 20% of suspicious aspirates are subsequently found to be malignant.⁵⁵ Several options are available in this situation. If the aspirate is suspicious for PTC, a hemithyroidectomy can be performed and sent for frozen section. If the frozen section confirms the diagnosis, a total thyroidectomy is then performed. If this approach is chosen, patients are counseled preoperatively of this outcome; they are informed that a frozen section is only a representative sample of the tumor and that final pathology may differ from the frozen section. Unfortunately, due to the nature of FTC and HCC, a diagnosis for these cannot be made on frozen section. Thus, for follicular or Hürthle cell neoplasms, the best surgical option is a hemithyroidectomy without frozen section followed by a completion thyroidectomy if the final pathology is positive for malignancy.

Well-Differentiated Thyroid Carcinoma Workup Recommendations

- Physical examination, including laryngeal examination
- TSH
- FNAB
- If FNA+ for papillary cancer: US and CT to assess nodal disease
- Not recommended: I131 scan, thyroglobulin, calcitonin

Nondiagnostic: Nondiagnostic aspirates are samples that do not render enough cytological material for a diagnosis. It is important that the patient understand that there is no reassurance that “no malignant cells were seen” but only that no diagnostic material was present in the present sample. However, patients can be reassured that respiration yields diagnostic information in 50% of cases and that a US-guided FNA can increase this further. Surgical excision is reasonable in nodules needed twice as nondiagnostic (Table).

US-Guided FNA

US-guided FNA is helpful in cases where nodules are smaller than 1.5 cm or when a previous aspiration attempt was unsuccessful. Recent work has shown that a diagnosis was achieved in 91.5% of cases when US-guided FNA was used compared with 85.9% of cases when palpation alone was used.⁵⁶

Thyroidectomy

Final Steps Prior to Surgery

Successful thyroid surgery implies meticulous attention to detail and is accomplished through rigorous preoperative workup. Paralytic agents are not used when monitoring and stimulation of the recurrent laryngeal nerve are planned. Due to the high rate of lymph node metastasis in PTC, we believe that these patients need preoperative evaluations that include both US scan and neck CT. This creates a comprehensive cervical nodal map on which to plan surgery. As previously mentioned, all patients also have preoperative laryngoscopy to assess for vocal cord paralysis. Patients found to have vocal cord paralysis are further evaluated for laryngeal, tracheal, and esophageal invasion with fine-cut neck and airway CT so that surgery can be planned accordingly. If any evidence of such invasion is found, bronchoscopy and esophageal endoscopy can be performed at the time of thyroidectomy.

Extent of Thyroidectomy

When considering the extent of thyroidectomy for well-differentiated thyroid carcinoma, several factors are taken into account. Age, presence of distant metastatic disease, and degree of invasiveness are probably

the most important prognostic determinants. These are used to determine the extent of treatment and follow-up care. The extent of surgery for well-differentiated thyroid carcinoma is a controversial issue. No randomized, controlled trials have compared survival after partial vs total thyroidectomy for well-differentiated thyroid carcinoma. However, several retrospective studies support both sides of the argument. Some suggest a decrease in recurrence rate and improved overall survival following near total or total thyroidectomy,⁵⁷⁻⁵⁸ while others report no benefit.⁵⁹⁻⁶² Although several prognostic risk-stratification systems have been devised to predict survival in well-differentiated thyroid carcinoma, the majority of surgeons in the United States still perform a total thyroidectomy regardless of patient risk group.⁶³ Advantages of performing a total thyroidectomy include removing contralateral microscopic disease, enabling accurate serial postoperative thyroglobulin in measurements, and allowing the administration of radioactive iodine to ablate any remaining thyroid tissue.

Another consideration in the management of well-differentiated thyroid carcinoma is the extent of lymph node dissection. Studies have shown that despite the strong association of PTC with lymph node metastases at the time of presentation, it seems to have no significant prognostic implication in younger patients.^{64,65} Microscopic disease appears to be of limited clinical importance. This is best highlighted by studies showing a low rate of development of clinical disease despite a high prevalence of microscopic foci in the contralateral lobe and neck.^{66,67} These observations have led to the abandonment of the past recommendations of elective neck dissections in patients with N0 disease.^{28,68} Although nodal metastases do not seem to worsen the overall prognosis in many patients with well-differentiated thyroid carcinoma, studies have identified that age (>45 years) in the face of nodal metastasis increases the risk of local recurrence and cancer-specific mortality.⁶⁹⁻⁷¹

The overriding principle in the surgical treatment of well-differentiated thyroid carcinoma is that the surgeon encompasses all gross disease in the thyroid and neck nodes at first surgery. Grossly enlarged lymph nodes should be excised, but a full formal neck dissection is unnecessary. The lymph nodes most commonly and initially involved with thyroid metastasis are the paratracheal nodes. Lateral neck regions involved in well-differentiated thyroid carcinoma include level IV (52%), followed by the level III (45%), level V (33%), and level II (30%).³⁴ Given the frequency of involvement of the paratracheal region and the significant morbidity of revision surgery in the central neck, we advocate aggressive inspection and palpation of this region in all patients with PTC on FNA and formal paratracheal dissection in any patient with nodal disease identified on preoperative CT or US scan or intraoperative inspec-

tion. Care is taken to preserve or autotransplant the inferior parathyroid gland. Gross invasion of the trachea is managed with segmental airway resection. Patients without contralateral nodularity or gross lymphadenopathy in the low-risk prognostic group can be treated effectively with ipsilateral total lobectomy and isthmusectomy. However, most agree that patients in the high-risk group are managed with a total thyroidectomy to optimize survival.

It is also important to note that the extent of thyroidectomy is tailored not only to the patient's risk group and gross operative findings but also to the progress of the specific surgery. Total thyroidectomy is a safe procedure in skilled hands and is offered when it does not cause significant morbidity. Total thyroidectomy is performed if initial dissection of the first lobe reveals two parathyroids of good color associated with good vascular pedicles and a recurrent laryngeal nerve that has been identified and well stimulated electrically at the end of the dissection. Elective contralateral lobe resection is deferred if problems with the parathyroids or recurrent laryngeal nerve are perceived. If necessary, subsequent elective completion thyroidectomy for the contralateral lobe is performed safely and with low morbidity at a later date.⁷²

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