Papillary Thyroid Carcinoma

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Contents

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Case Presentation

Patient is a 47-year-old woman who presents with a 9 mm right thyroid nodule found after she requested a thyroid ultrasound because her sister was diagnosed with papillary thyroid cancer last year. She has no symptoms referable to the nodule, although she notes some issues with intermittent hoarseness. Her past medical history is significant for treatment of Hodgkin lymphoma as a child with external beam radiation to her chest and low neck. Her family history is significant for a goiter in her maternal grandmother but no other first-degree relatives with thyroid cancer. She takes levothyroxine for hypothyroidism, 100 micrograms daily. She has had no surgery or prior trauma in the head or neck region. Physical examination reveals vital signs in the normal range and a healthy appearing woman who appears her stated age. The neck has no masses or swelling on observation and on palpation, the thyroid gland has a normal thyroid texture and is not fixed. There is no palpable lymphadenopathy Papillary thyroid carcinoma (PTC) patient history in the lateral neck on the left or right.

Questions

1. The most likely type of thyroid cancer in this patient is.
   (a) Follicular thyroid cancer
   (b) Papillary thyroid cancer
   (c) Medullary thyroid cancer
   (d) Anaplastic thyroid cancer
2. The presence of thyroid cancer in her sister as the only first-degree relative with a history of thyroid cancer suggests she has familial thyroid cancer syndrome.
   (a) True
   (b) False
3. Her history of radiation to the thyroid region is meaningful. She should be counseled that "It is more likely that this biopsy will show you have a cancer, but it does not mean that cancer will be more aggressive than if you had not received radiation."
   (a) True
   (b) False
4. The next step in workup of her thyroid nodule is
   (a) Check serum TSH
   (b) Needle biopsy of the thyroid gland
   (c) Nuclear medicine evaluation of the thyroid nodule
   (d) Neck CT scan with and without contrast
5. Her full workup is completed and reveals 9-mm hypoechoic nodule with microcalcifications and regular, smooth borders located in the central aspect of the right thyroid gland. There is no contact of the nodule with the thyroid capsule. The left hemithyroid and isthmus are without nodules or lesions. The lateral necks show no abnormal appearing lymph nodes. Needle biopsy result was Bethesda V – suspicious for papillary carcinoma.

(a) Nuclear medicine evaluation of the thyroid is not indicated.
(b) Neck CT scan with and without contrast must be performed.
(c) No further workup is required.

6. Because the patient reports intermittent hoarseness, you decide to obtain a complete laryngeal exam. It is normal. Her options at this point include
   (a) Total thyroidectomy.
   (b) Hemithyroidectomy.
   (c) Active surveillance.
   (d) All are within the range of current guidelines.
7. Imagine now that her laryngeal exam instead shows a compensated left vocal cord paresis: the left vocal cord rests in a slightly paramedian position and does not move through its full range, but the right vocal cord moves over just past midline to meet it nearly fully. This finding suggests which treatment(s) might best be discussed with her as first-line management?
   (a) Total thyroidectomy
   (b) Hemithyroidectomy
   (c) Active surveillance
   (d) Either (a) or (b)
8. She asks for information about her prognosis. Her 9-mm papillary thyroid cancer confined to the thyroid gland suggests her prognosis is
   (a) Excellent. She is very unlikely to die from her thyroid cancer. However, there is always a small chance that her cancer may recur if removed, or grow and eventually need surgery if she does active surveillance.
   (b) Good. She is at higher risk than others of having recurrence after surgery/cancer growth or spread on active surveillance because of her sister's cancer and her childhood radiation.
   (c) Fair. It would be better if she had not had childhood radiation.
9. As you discuss the prognosis of her 9-mm papillary thyroid cancer confined to the thyroid gland with her, you remember that her cancer was found on a thyroid ultrasound she requested, because her sister had recently been diagnosed with cancer. You explain what may have happened:
   (a) Ultrasound can detect subclinical thyroid cancers.
   (b) Not all ultrasound detected thyroid cancers go on to become clinically evident during the patient's life.
   (c) Thyroid cancer is commonly found at autopsy in people who died of other causes.

(d) Though it is possible her cancer will grow or spread, the data suggest that for the large majority of people, it will not.
(e) All of the above.

10. Imagine now instead that this patient presented with a 2-cm thyroid nodule abutting the trachea by ultrasound. Her vocal cord function is normal. Your physical exam suggests fullness in the right neck. The next imaging step to consider is
    (a) Cross-sectional imaging of the neck and chest, without contrast
    (b) Cross-sectional imaging of the neck and chest, with contrast
    (c) Lateral neck ultrasound and further ultrasound exam of the trachea
11. The imaging shows several rounded lymph nodes in right neck levels III and IV, but they are just 1 cm. The imaging of the trachea suggests the disease might be in the wall of the trachea on the right. The next steps are
    (a) Needle biopsy of the lymph nodes
    (b) Bronchoscopy and esophagoscopy to fully evaluate the vital central neck structures
    (c) Both (a) and (b)
12. Imagine the workup for the lateral neck adenopathy and the tracheal involvement is negative, she has only a 2-cm papillary thyroid cancer. There is no spread to the lymph nodes, and the trachea is not involved. Her thyroid gland treatment options are
    (a) Active surveillance
    (b) Hemithyroidectomy
    (c) Total thyroidectomy
    (d) (b) or (c)
13. Imagine the workup is positive and the patient undergoes total thyroidectomy and right central and lateral neck dissection. The trachea is not involved. The patient has classical variant of papillary thyroid cancer and four positive lymph nodes, all with microscopic disease. The initial step in follow-up is
    (a) Radioactive iodine.
    (b) Check thyroglobulin and do an ultrasound about 6 months after surgery.
    (c) Do a neck ultrasound about 6 months after surgery.
14. After initial follow-up, the patient is followed regularly. She is likely to be followed with
    (a) Periodic Neck CT scan
    (b) Periodic serum thyroglobulin
    (c) Periodic neck ultrasound
    (d) (a) and (b)
    (e) (b) and (c)

15. After several years, she develops metastases to the lungs. They are not avid on PET scan. Commonly used first-line option(s) for management are
    (a) Radioactive iodine
    (b) External beam radiation
    (c) Tyrosine kinase inhibitors
    (d) (b) or (c)

5.1 Introduction

A familiarity with papillary thyroid carcinoma (PTC) is essential for any endocrine surgeon. PTC is by far the most common endocrine malignancy, and the incidence of this disease is rapidly increasing across the world [1, 2]. While the reasons for this are debated, there is little doubt that the increased sensitivity and application of medical imaging is largely responsible for the rise [3–8]. It is now apparent that there is a large reservoir of occult PTC in the otherwise well population. Series of benign thyroidectomy surgery report an unexpected malignancy rate of around 5–10% and autopsy series of people who died of other causes never knowing they had a thyroid cancer have found rates of up to 30% [9]. The autopsy prevalence has remained stable over time, and meta-analysis has shown that autopsy prevalence is higher when glands are more closely sectioned or examined [10]. Therefore, the modern endocrine surgeon will spend much of their time managing patients with suspected, proven, or treated PTC.

Over recent decades, a significant change in our understanding of the biology of PTC has resulted in a revolution in management approach. An appreciation of the background to this contemporary approach to the management of PTC will allow the modern endocrine surgeon to best serve their patients and provide a treatment approach that balances risk of recurrence against functional outcomes and treatment side effects for the individual.

5.2 Clinical Presentation

The most common presentation of PTC is a female patient with a small thyroid nodule, with no symptoms. In developed countries, most patients present with cancers that are too small to feel (2 cm or less). If palpable, the majority will move up and down with the larynx on swallowing. In modern population-based data sets, the most common age range of patients is 45–54 years, and about 80% are female. A significant minority will present with regional spread to the lymph nodes of the central or lateral neck. Fewer than 5% of cases present with locally

invasive disease [11]. Local invasion may be a sign of de-differentiation of PTC toward a more aggressive disease type. When local invasion progresses, involvement of the critical structures of the central neck may result in important symptoms including dysphonia, dysphagia, hemorrhage, and even asphyxia.

During clinical assessment, the patient should be queried for symptoms that might suggest invasive local or regional disease – change in voice, and change in swallowing or breathing. The only known risk factors for papillary thyroid cancer are childhood or adolescent exposure to ionizing radiation and family history. In particular, if exposed to ionizing radiation prior to age 19, rates of papillary thyroid malignancy are higher [12]. Those exposed at younger ages (i.e., less than age 5) have the highest risk, and the risk increases with increasing dose. The increased risk of thyroid cancer persists for up to 60 years or more, but the cancer is no more aggressive than nonradiation-induced thyroid cancer [13–15]. Although rare, familial nonmedullary thyroid cancer (most commonly PTC) has also been described and is diagnosed when three *additional* first-degree relatives are also affected by thyroid cancer [16, 17].

In areas where high-resolution cross-sectional imaging is not readily available or not widely used, patients more commonly present with symptoms of their disease. However, in routine clinical practice, in areas with access to a wide array of imaging and health care services, an increasing number of patients will be referred with incidentally discovered disease that is small, and asymptomatic, as described above. Such patients will have undergone examination or imaging for a nonthyroid-directed reason, which identifies a thyroid finding [5]. In turn, this leads to more investigations and the diagnosis of PTC. This group tends to be older, as older adults tend to undergo imaging and receive more healthcare than younger people [18]. The most dramatic example occurred in South Korea, where thyroid ultrasound was offered as a retail add-on by individual health care providers during sanctioned cancer screenings for breast, stomach, and liver cancer, and this resulted in the largest increased incidence of PTC globally, without impacting mortality [19].

Evaluation of the patient with thyroid cancer should include asking about daily activities and voice usage needs. Patients should be educated about the disease and decisions about extent of treatment should be approached jointly. Most patients with PTC will require surgery to remove all or part of the thyroid gland, and that carries the risk of voice change and permanent hypoparathyroidism if the entire gland is removed. Damage to the recurrent nerve or superior laryngeal nerve will adversely affect vocal range, stamina, volume, and quality – making it difficult to talk for long periods or in noisy environments. If these changes in voice occur, it may have a significant impact on their ability to continue in their role. Chronic hypocalcemia

requires ongoing treatment and can affect clarity of thinking and muscle function. At the point of presentation, as with any cancer diagnosis, patients with PTC are likely to be highly anxious and fear for themselves as well as their family and others who depend on them.

5.3 Natural History

The natural history of PTC is excellent. The 10-year survival of papillary thyroid cancer of any size localized to the thyroid gland and treated with either hemithyroidectomy or total thyroidectomy is 99% [20]. Though a small proportion of cases are aggressive, the increasing incidence of papillary thyroid cancer across the world has primarily resulted from the detection of subclinical disease, meaning small cancers localized to the thyroid gland that had they not been found would have been unlikely to go on to become clinically apparent [6]. Cohorts of patients followed over time with cancers measuring up to 1.5 cm in size have shown that rates of growth are low and vary by age. Those diagnosed in their 20s will show advancement in their cancer up to 24% of the time, but those in the age 60 or over will have growth less than 3% of the time [21, 22].

In contrast to the hematogenous spread pattern for follicular thyroid cancer, PTC spreads primarily through the lymphatic route. It is now understood that PTC has a slow growth pattern, but paradoxically, a high rate of regional metastasis. This finding runs counter to many of the classical "rules" of oncology. For example, it is widely taught that if a head and neck squamous cell carcinoma negative for human papilloma virus metastasizes to the regional nodes, the chance of survival drops by half. In contrast, although only 20–30% of patients with PTC present with overt nodal disease (cN1), if elective dissection of the regional lymph nodes is performed, occult disease can be detected in over a third of cases who were thought to be cN0 [23]. Although this has long been used as a justification for elective lymph node surgery in the central neck compartment, the outcome of patients who received prophylactic central neck lymph nodes dissection was compared to those who did not, and showed no or minimal clinical difference [24, 25]. This is consistent with autopsy data suggesting that 16–18% of patients who die of other causes never knowing they had thyroid cancer have evidence of metastatic thyroid cancer at the time of their death [26, 27].

Fewer than 5% of patients with papillary thyroid cancer have distant metastases at the time of diagnosis: the most common site of spread is the lung. Although in the distant past, the majority of patients with PTC died of uncontrolled central neck disease, with improvements in management, death is

now more commonly associated with progressive distant than uncontrolled locoregional disease [28].

5.4 Diagnosis

Diagnosing and staging PTC requires a history and examination followed by imaging and biopsy. In the clinical history, features associated with involvement of central neck structures should be sought, as outlined above. In addition, past medical and surgical history, family history, comorbidities, and daily activities and life roles should be discussed to gain a full appreciation of the patient's situation.

Physical examination includes observation and palpation of the neck, both the thyroid and the regional lymphatics. Examination of the larynx is also an important part of the initial assessment, particularly if there is any concern related to voice change, or if the patient has had prior thyroid (or parathyroid) surgery. Although pre-existing vocal cord dysfunction is not typical in the absence of a pertinent history or voice finding, results should be available to clinicians involved in the management of thyroid malignancy so that any postoperative changes can be understood, and prognostic estimations of future vocal cord function can be offered.

Biochemical assessment of thyroid function (TSH, and in some locales, calcitonin) should be completed prior to nodule biopsy to guide interpretation of needle biopsy results.

First-line imaging for identified thyroid nodules is ultrasound. Not only is this relatively cheap and avoids ionizing radiation, but in trained hands, it is the most accurate method for assessing the thyroid and facilitates image-guided biopsy. A number of different risk stratification systems are available to guide the need for biopsy [29, 30].

Fine-needle aspiration (FNA) biopsy is the most common method of achieving a tissue diagnosis. This can be taken from the suspicious thyroid nodule or a pathological lymph node. Core biopsy is an alternative, which provides additional tissue and is favored by some groups. Standardized reporting schema now exist to facilitate communication between cytopathologists and other members of the disease management team [31], as discussed in ► Chap. 1.

For many patients, further investigation will not be required. Thyroid function testing, ultrasound, and needle biopsy results will provide adequate information to plan treatment. However, there are some notable exceptions to this. Patients with overt nodal disease may warrant cross-sectional imaging in the form of contrast-enhanced CT scan of neck and chest. Not only does this provide information regarding the presence or absence of metastatic disease in the lung, but it allows accurate characterization of the mediastinal lymph nodes behind

the manubrium, which are not visualized on ultrasound. The other setting where cross-sectional imaging is critical is in the setting of invasive primary disease. The relationship of disease to the critical structures of the central and lateral neck allows accurate presurgical planning. This is often combined with formal esophagoscopy and tracheoscopy to fully assess the extent of visceral involvement prior to surgery, which informs the process of presurgical consent. It is worth mentioning at this point that there has historically been concern about the use of iodinated contrast during CT scans and the potential impact that may have on subsequent use of radioactive iodine (RAI). However, these concerns are theoretical and have never been proven clinically. In addition, the need for accurate presurgical information to maximize the chance of a complete surgical excision far outweighs any such concerns. As such, when indicated, the surgeon should have no hesitation in ordering adequate imaging to fully stage all aspects of such advanced disease.

Fluorodeoxyglucose positron emission tomography (FDG-PET) scanning seldom has a role in the investigation of primary PTC. The disease tends not to be FDG avid. It may have a role in detection of de-differentiated disease: FDG avidity tends to increase as RAI avidity decreases.

5.5 Risk Stratification and Treatment

Treatment for PTC is highly controversial and has been for decades: most patients have extremely good outcomes, which translates to very low "event-rates" for clinical outcomes research. This makes planning and execution of prospective randomized controlled trials difficult, as large numbers and prolonged follow-up would be required for some of the important questions [32]. In the absence of prospective randomized evidence, opinions are based on detailed retrospective studies from single institutions or population-based databases that can provide representative results, but with fewer details. The inherent limits can result in conflicting results and interpretations.

Up until the first decade of the 2000s, most patients with PTC were recommended to undergo total thyroidectomy and RAI. Elective central neck dissection, including prophylactic dissection, was supported [33]. However, this chapter is written at a time where international opinion on the optimal management of PTC is slowly moving toward a more conservative approach [34]. Despite this, there remains significant disagreement between experts across the world and we hope to reflect this in a balanced summary below.

The surgeon dealing with PTC must have an appreciation of the impact that initial surgical therapy can have on the case overall. To effectively treat patients with adjuvant RAI, all

thyroid tissues must be removed, which is clearly the job of the surgeon. However, variation in surgical practice can also alter subsequent decision-making. For example, those surgeons who perform elective neck surgery identify nodal disease in a significant number of patients [23]. This potentially upstages the disease and may influence clinical decision-making in the postoperative period. Having an understanding of the interplay among surgery, staging, adjuvant therapy, complications, and outcomes is critical for all surgeons involved in the management of PTC.

No discussion about treatment for PTC can start without reviewing the concept of risk stratification. This approach was first suggested in the mid-twentieth century and has been more fully developed since. Initially, there was a recognition that prediction of survival in all thyroid cancers could be based on variables, the most important of which was histology [35]. However, refinements within differentiated thyroid cancers recognized advancing age, tumor size, presence of gross extrathyroidal extension, and distant metastases as predictive of survival.

A number of risk stratification systems were developed, which would allow young patients with small volume disease to be categorized as low risk, whereas older patients with advanced disease were recognized as high risk of cause-specific mortality [36–39]. These staging systems were eventually incorporated into the AJCC staging systems [40].

Despite advances in risk stratification, therapy for the majority of patients with PTC remained total thyroidectomy, consideration of elective central neck dissection, and postoperative adjuvant radioactive iodine (RAI) based on early data suggesting a recurrence and survival advantage [41].

Over the past three decades, a significant body of work from groups around the world has helped to refine that approach based upon the original risk stratification systems. For example, it is now accepted that in low-risk patients, there is little to gain from RAI, reducing the need for total thyroidectomy to facilitate this adjuvant therapy. In addition, although microscopic occult nodal disease is common, elective dissection of regional nodes has failed to demonstrate long-term advantage, and again in low-risk patients, there is a move away from this practice [24].

One of the issues with original risk stratification systems was their lack of translatability to clinical practice. The overwhelming majority of patients with PTC will not die. Therefore, systems designed to predict survival lacked clinical utility. Hence, in recent years, there has been a focus on predictors of recurrence rather than survival. In addition to the originally recognized factors, features including multicentricity, the presence of lymphatic and vascular invasion, microscopic extrathyroidal extension, and small volume nodal disease have been combined

into a recurrence risk continuum promoted by the American Thyroid Association [34].

Unfortunately, many of these additional features can only be described on postoperative pathology, so they cannot be used at the point of initial diagnosis. As a result, it is critical that the surgeon managing patients with PTC considers the whole case at the outset in order to plan effective treatment. If a patient is to receive RAI, a total thyroidectomy is required. Therefore, this should be considered when making initial treatment recommendations. If a hemithyroidectomy is undertaken and the pathology suggests RAI may provide recurrence benefit, completion thyroidectomy may be required.

The spectrum of risk, both for recurrence and survival, is shown in Table 5.1.

Many patients with PTC present with low-risk disease. In such cases, without evidence of nodal disease, there is no proven advantage of RAI. Therefore, such patients can normally be considered candidates for a thyroid lobectomy. This procedure removes the disease, protects the parathyroids and recurrent laryngeal nerve on the contralateral side, reduces the risk of requiring lifelong thyroxine, and is associated with excellent long-term outcomes.

In contrast, for those patients who present with gross extrathyroidal extension, advanced nodal or even distant disease, there is a well-proven role for RAI. In such patients, treatment should be aimed at eradicating macroscopic disease in the neck and facilitating adjuvant RAI. This requires a total thyroidectomy and compartment-oriented neck dissection.

For patients with nodal disease limited to the central neck, dissection of the central compartment is sufficient. For those

Table 5.1 Spectrum of risk of recurrence and survival in papillary thyroid cancer

		Predictors of survival	Predictors of recurrence
Lower-risk features		Younger age (<55y) Smaller tumor (<4 cm) No gross extrathyroidal extension M0	Unicentric N0 disease Classical histology Microscopic extrathyroid extension
Higher-risk features		Older age (>55y in advanced disease) Larger tumor (>4 cm) Gross extrathyroidal extension M1	Large volume N1 disease Vascular invasion pN1 with extranodal extension

with lateral neck disease, a compartment-oriented level II-V neck dissection is recommended to minimize the chance of recurrent disease [42]. In addition, for patients with advanced primary disease invading structures in the central neck, elective central neck dissection is recommended [43]. Not only does this provide optimal access to the disease, but in aggressive primary disease, rates of occult nodal disease are high. Outside this setting, elective neck dissection is not generally recommended.

In these two examples, the approach to management is fairly clear-cut. However, a great number of patients fall between these two extremes. Many patients present with PTC on the background of multinodular disease. In such patients, a decision is required about the likelihood of those additional nodules harboring disease and a balance must be struck between the need for surveillance of these nodules versus an upfront total thyroidectomy.

Analysis of the postoperative specimen may identify higher-risk features, such as more aggressive variants of PTC (tall cell, insular, solid, etc.), multicentric disease, small associated nodes in the perithyroid tissues, or microscopic extrathyroidal extension. Although treatment intensification (completion thyroidectomy to facilitate RAI) has never been shown to improve either recurrence or survival outcomes based on these individual features, given that total thyroidectomy and RAI was the standard of care for the majority of cases until relatively recently, many disease management teams may still recommend this approach for such intermediate-risk cases.

The surgeon is in a critical position to advise in such cases where definitive oncological evidence is lacking. Other highly pertinent information can be used to aid in decision-making. First is the complication rate of the surgeon themselves. As with many surgeries, association exists between volume and complications in thyroid surgery, with recent data suggesting that an annual volume of thyroidectomies in the low to mid-20s is required to minimize complication rates [44–46]. It is also understood that even high-volume surgeons have higher complication rates in total thyroidectomy versus thyroid lobectomy [44]. Often quoted rates of a 1% RLN injury and similarly low long-term hypocalcemia rates likely represent an underestimate for the average surgeon, based on population-based estimates, registry data, and careful institutional reports, which show short-term hypocalcemia following total thyroidectomy is around 20%, with long-term risk 1.8–5%, and vocal cord paralysis rates around 8% [47–49]. Overall complication rates of unilateral thyroid surgery are around 10% versus 20% for bilateral surgery [44]. Although complication rates are lower for high-volume surgeons, a higher rate is observed following bilateral versus unilateral surgery, even in expert hands.

Although an appreciation of the literature is useful, only the surgeon themselves can understand their individual complication rate through self-audit. This can then be balanced against

the potential for oncological benefit. This is particularly evident when the patient has been diagnosed following thyroid lobectomy and the disease management team is considering the need for completion thyroidectomy [50]. In this setting, if the patient suffered an RLN injury during the initial surgery, or one is detected during an initial procedure, which was planned as a total thyroidectomy, there is seldom a justification for completion surgery as this carries the risk of tracheotomy.

Another factor, which is central to the decision, is the opinion of the patient, who should be included explicitly in discussions about not just oncological outcomes but side effects of therapy. In particular, patients may be wary of the potential for additional surgical impact on laryngeal function. The long-term impact of hypocalcemia is also not to be underestimated. Lifelong calcium supplementation is highly inconvenient for patients and difficult to manage. These factors should be discussed with patients as possible side effects of total thyroidectomy in comparison with thyroid lobectomy. Additional surgical details on the indications and extent of both primary thyroid and nodal surgery are covered in ▶ Chaps. 11 and 12, respectively.

It should also be remembered that RAI is not without side effects. Although less in comparison with external beam radiotherapy (EBRT), RAI is associated with dry mouth, dry eyes, and swallowing dysfunction, which can compromise quality of life. Some groups have studied the use of EBRT in advanced local disease with some success [51]. In patients with unresected local disease, or in the setting of disease, which is excised with minimal margin (R1), radiotherapy may be considered in addition to RAI. However, such treatment is not without significant side effects, and management teams must consider the risk–benefit ratio carefully when recommending such an approach. PTC is ot generally considered sensitive to chemotherapy, and in large part, traditional chemotherapy has been superseded by advances in targeted treatments such as tyrosine kinase inhibitors, which are covered in ▶ Chap. 10.

Within a section dedicated to treatment of PTC, it is now critical to include consideration of "active observation" as a potential method of treatment. This approach was pioneered in Japan for small volume (1 cm or smaller) PTC [52, 53]. Such cases were diagnosed using US-guided FNA, and following counselling were offered surveillance, with surgery performed if the cancers grew or spread. When followed in this manner, only a small proportion of patients, predictable by age at diagnosis, demonstrate progression on ultrasound and go on to require surgery [22]. No patient who followed this strategy has succumbed to thyroid cancer and all patients with cancer growth or spread have been successfully rescued. In this manner, many patients can avoid surgery in the medium to long term without any negative oncological impact on the group as a whole. The ideal patient has a rim of normal thyroid tissue

around the cancer, can present for regular follow-up, has access to a medical team with the ability to follow with ultrasound, and the patient is interested in active surveillance [54]. This approach is being adopted now internationally with success in selected patients [21, 55–62]. Although currently 1 cm is generally considered the upper size limit to recommend a surveillance approach, groups are now investigating with success a similar approach in larger tumors (<2 cm) [58]. It seems likely that the option of treating patients with active surveillance will play a larger part in PTC management in the future.

In summary, when recommending treatment for PTC, a number of patient- and tumor-related factors must be considered. A select group of the smallest, lowest-risk PTC may be suitable for observation. For high-risk patients, aggressive treatment with total thyroidectomy and adjuvant RAI is justifiable. In contrast, for low-risk patients, a conservative approach with thyroid lobectomy achieves excellent oncological outcomes while minimizing the chance of surgical complications. For patients who lie between these extremes, additional factors relating to both the patient, their tumor, and the chance of surgical (and RAI) complications should be balanced to optimize oncological and functional outcomes in the long term (Fig. 5.1).

5.6 Follow-Up

The aims of follow-up include detection of recurrent disease, management of thyroid function (and calcium if required), detection of the complications of treatment, and provision of cancer survivorship support. Initial treatment ends either at the point of surgery or following RAI. Some patients are treated for benign disease, and PTC is diagnosed incidentally. Such cases often fall under low-risk category: in practice, the chance of recurrent disease is so low that this patient group can be discharged without any follow-up [43].

For the majority of patients, the end of treatment represents the start of long-term follow-up. The cornerstones of follow-up for most patients are clinical assessment, periodic ultrasound, and serum thyroglobulin monitoring if the patient has undergone total thyroidectomy.

Recently, risk stratification has been extended beyond the pre- and peritreatment period to follow up with the concept of dynamic risk stratification. This approach uses the 12-month ultrasound and thyroglobulin assessment to stratify patients into excellent response, indeterminate response, biochemically incomplete response, and structurally incomplete response groups [63]. Patients who fall into the lowest-risk category have <5% chance of recurrence in the long term. Patients who have a detectable thyroglobulin (biochemically incomplete

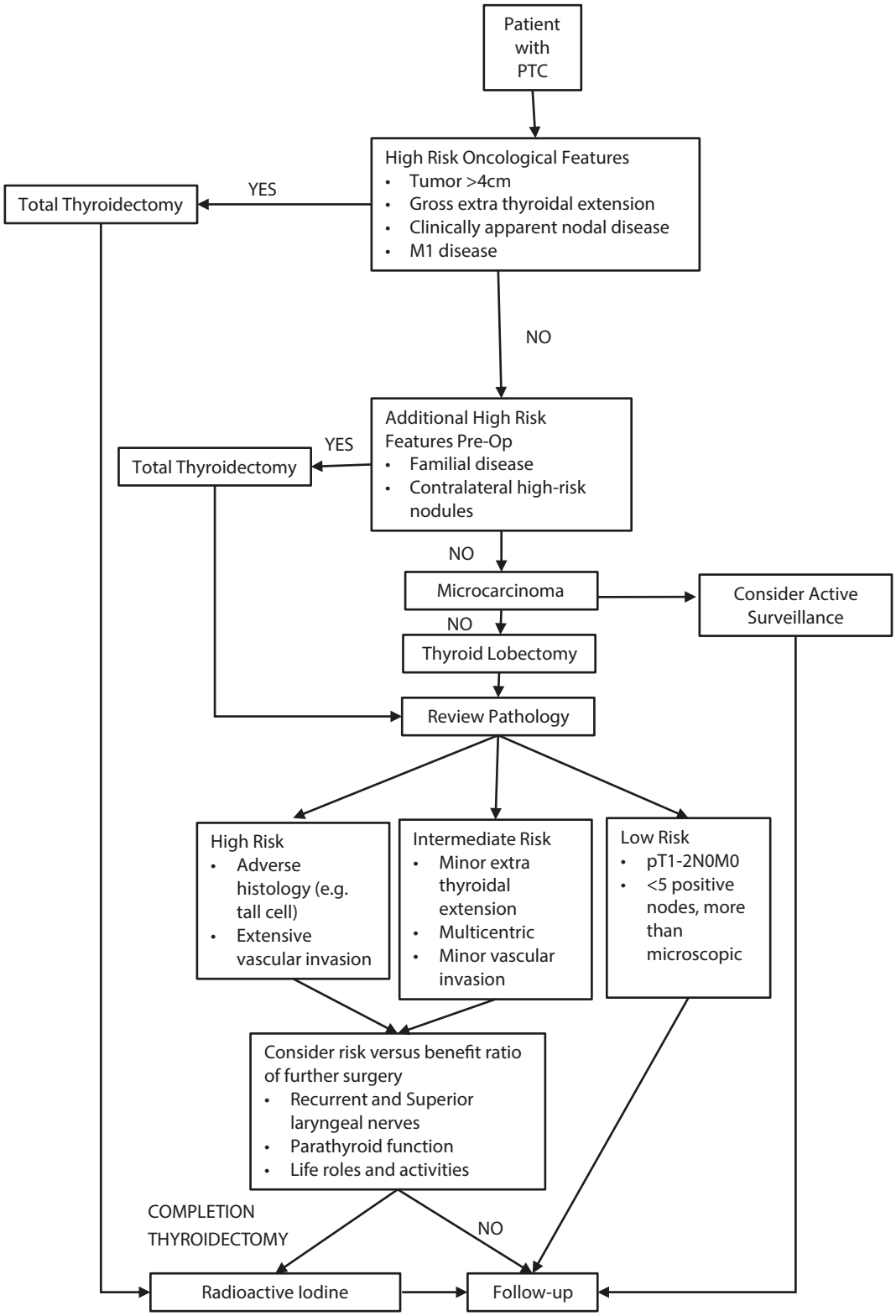

Fig. 5.1 Therapeutic approach to a patient with papillary thyroid carcinoma (PTC)

response) or indeterminate features on ultrasound (indeterminate response group) have around a 20% chance of recurrence. Those who have a structurally incomplete response to therapy have imaging findings consistent with persistent disease and, as such, rates of "recurrence" in this group are high [64]. These definitions were first provided for patients who had undergone total thyroidectomy and RAI. However, in recent years, modifications to this system have been provided for patients who underwent thyroid lobectomy alone [65].

Follow-up protocols can be tailored to the expected level of risk, with those low-risk patients who show an excellent response to initial treatment being reviewed less frequently than higher-risk patients, particularly if there is a less convincing response to treatment.

Patients will tend to be reviewed at 6–12 monthly intervals with ultrasound and thyroglobulin assessments. Any sustained rise in thyroglobulin will lead to a thorough search for evidence of structural disease, if not evident on ultrasound assessment.

Historically, patients were advised to keep their thyroid-stimulating hormone (TSH) suppressed, with a T4 level at the upper end of the normal range and the TSH below 0.1 mU/L. Although this TSH suppression has been shown to have a beneficial effect in patients with high-risk disease, this is not the case with patients at lower risk and may present problems in the elderly. The majority of patients do not require lifelong TSH suppression, and particularly during later stages of follow-up, a more normalized level of thyroid function is desirable. Avoidance of long-term TSH suppression minimizes the risks from cardiovascular disease and osteoporosis. Therefore, for initially high-risk patients and those patients considered to have a structurally incomplete response to initial therapy, suppression of TSH to <0.1 mU/L is reasonable. For patients with an indeterminate response, TSH levels 0.1–0.5 mU/L are acceptable. For low-risk patients, a TSH level 0.5–2 mU/L is acceptable [34].

The duration of follow-up required for patients with PTC is unclear. Although most recurrences occur in the early stages of follow-up, some can occur decades after initial therapy. It is reasonable to consider all patients for at least 5 years of surveillance. After that, if an excellent response to therapy has been achieved, there is little to gain from routine surveillance. In higher-risk patients, and in particular in those who have already recurred, longer-term surveillance is likely to be justified.

5.7 Outcomes

The vast majority of patients will not die from PTC and will have a long survivorship period following diagnosis. Indeed, despite the significant increase in the incidence of PTC, there has not been a proportional increase in the number of deaths,

suggesting that detection of subclinical disease has been the main cause of the increased incidence [6]. This well-recognized epidemiologic phenomenon is called "overdiagnosis", the detection of the disease on pre-clinical stage, when the patient is asymptomatic and the disease is very unlikely will become clinically evident [66–69].

As described above, risk stratification can be applied to cohorts presenting with PTC. Around 85% of adults presenting with PTC will be considered low risk, and 15% high risk; 30-year outcomes have now been reported by some groups and <5% of adults with PTC will die from disease. When risk stratified, less than 1% of low-risk adults will die from disease during this time versus up to 30% of high-risk cases [70]. It should be noted, therefore, that for the vast majority of patients, long-term survival is the rule.

Another outcome of interest is recurrence. In contrast to survival, recurrence is relatively common. It can be categorized as development of disease in sites, which are treatment naïve and recurrence in areas of previous treatment. By far the most common recurrence is in regional lymph nodes. The development of overt disease within previously untreated regional nodes is detected during follow-up in up to 20% of cases [71]. However, detection of disease does not mandate treatment. This is because we now appreciate that a significant number of patients who are cN0 do indeed harbor occult nodal disease at presentation, which can slowly progress and present on ultrasound or TG monitoring [23]. Although such patients do indeed have "recurrent" or perhaps more accurately "persistent" nodal disease, slow progression is the rule and serial monitoring has been shown to be clinically safe in the low volume (<1 cm) setting. Clearly, if such disease progresses, treatment will be required in the form of compartment-oriented neck dissection, and cure rates are high [72].

Distant recurrence is rare (<5%) in most series and is often first detected using serial measurements of thyroglobulin. Treatment usually involves RAI treatment, unless disease is considered RAI refractory, in which case, treatment options are more limited. Even in patients who develop distant disease, long-term survival with disease is the rule with generally slow progression of metastatic deposits over time.

Local recurrence can be defined as development of recurrent disease in the operated bed of the thyroid gland. This should be differentiated from contralateral lobar recurrence in a nonoperated thyroid lobe following contralateral lobectomy. True local recurrence is extremely rare (<2%) in contemporary practice following an extracapsular thyroid lobectomy [73]. However, when it occurs, structures including the RLN, airway, and esophagus are at high risk from both disease and from its treatment. Identification of the RLN, for example, in a previously operated thyroid bed is challenging and rates of injury in this setting are far higher than those reported in the

primary setting. In contrast, when disease manifests in a contralateral lobe following initial thyroid lobectomy, completion thyroidectomy is required. This procedure is associated with a risk profile similar to initial thyroid lobectomy, although there remains the potential for hypocalcemia (particularly if the contralateral lobectomy resulted in inadvertent parathyroid gland excision) and injury to the RLN. Clearly, if the initial procedure resulted in RLN injury, there is a risk of bilateral injury in this setting, which can be weighed against the oncological benefit of completion surgery.

The details of surgical management for patients with recurrent disease are beyond the scope of this chapter. In brief, for regional recurrence, which occurs in the nonoperated field, a compartment-oriented salvage neck dissection is recommended [42]. If recurrent nodes are detected within the previously operated neck, a more limited and targeted nodal resection is preferred. In the setting of local recurrence, careful staging including cross-sectional imaging and endoscopy is required. Salvage surgery may require resection of critical structures including the larynx or trachea. A careful balance should be struck among the morbidity of resection, the trajectory of disease, and the expected outcome of continued observation or nonsurgical treatments. These cases should be referred to units experienced in the management of recurrent PTC to optimize the chance of favorable outcome.

Alongside oncological outcomes, the surgeon must also consider the impact that treatment has on a patient's life. As shown above, most patients will love long lives following treatment and will therefore have to live with the after-effects of their therapy. Patients who present with invasive or metastatic disease are a small high-risk group who require aggressive primary treatment with neck dissection and adjuvant therapy. Clearly, this approach to treatment carries risks, but they are balanced against a meaningful risk of death. Such patients are in the minority. The vast majority of patients present with localized disease, are at low risk of recurrence, and almost no risk of death. For these patients, definitive evidence regarding the benefits of different approaches to treatment is lacking and a balanced approach, which includes explicit discussion with the patient, must be taken. Overall, the therapeutic choice is among total thyroidectomy, thyroid lobectomy, or active surveillance for the lowest-risk cancers.

The risks of unilateral thyroid lobectomy include damage to the recurrent laryngeal nerve, the external branch of the superior laryngeal nerve, and injury to the parathyroid glands. However, bilateral thyroidectomy not only doubles these risks but introduces the risk of long-term hypocalcemia and tracheotomy.

Given the generally indolent nature of PTC, the ability to accurately risk-stratify patients according to easily available

preoperative variables and our understanding about the risks of thyroid surgery, one can appreciate why some groups have now demonstrated that the risk of treatment may outweigh the risk or the disease in the lower-risk group [74].

Overall then, outcomes can be predicted based on the patient and the tumor. Low-risk patients have excellent oncological outcomes, irrespective of treatment approach. For this group, surgeons should balance the chance of surgical complications against the potential that more aggressive therapy has to provide an outcome advantage. In contrast, high-risk patients (although relatively rare) have a significant rate recurrence and are at risk of death. Therefore, a more aggressive approach to such patients is warranted.

Answers to the Questions

1. (b); 2. (b); 3. (a); 4. (a); 5. (c); 6. (d); 7. (c); 8. (a); 9. (e); 10. (b); 11. (c); 12. (d); 13. (b); 14. (e); 15. (a)

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