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Papillary thyroid cancer management

Contemporary debates in adult papillary thyroid cancer management

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An ever-increasing population of patients with differentiated thyroid cancer is engaging with healthcare systems around the world. Numerous questions about optimal management have arisen that challenge conventional paradigms. This is particularly the case for patients with low-risk disease, which comprise the majority of new patients. At the same time, new therapies for patients with advanced disease all are also being introduced, which may have the potential to prolong life. This review discusses selected controversial issues in adult papillary thyroid cancer management at both ends of the disease spectrum. These topics include: [i] the role of active surveillance for small papillary cancers; [ii] the extent of surgery in low-risk disease (lobectomy versus total thyroidectomy); [iii] the role of postoperative remnant ablation with radioiodine; [iv] optimal follow-up strategies in patients, especially those that have only undergone lobectomy; and [v] new therapies for advanced disease. While our current management is hampered by the lack of large randomized controlled trials, we are fortunate that data from ongoing trials will be available within the next few years. This information should provide additional evidence that will decrease morbidity in low-risk patients and improve outcomes in those with distant metastatic disease.

Essential points

- The rising incidence of differentiated thyroid cancer may be due to "overdiagnosis" but may also be due to environmental exposures, which thus far remain uncertain
- Many small papillary thyroid cancers are indolent, and many do not require surgery. Newer less invasive therapies (e.g., radiofrequency ablation, laser) are being developed.
- For low-risk disease, lobectomy provides outcomes similar to total thyroidectomy with decreased perioperative morbidity. Total thyroidectomy is indicated when there is preoperative evidence for more advanced disease, when more invasive disease is discovered intraoperatively, or when postoperative histology dictates completion thyroidectomy followed by adjuvant radioiodine therapy.
- Radioactive iodine therapy has not been shown to improve disease specific mortality or recurrence rates in patients with low-risk disease, particularly patients whose postoperative unstimulated serum thyroglobulin is <0.5 ng/mL.

- Postoperative unstimulated thyroglobulin and neck ultrasound remain the mainstays of follow-up of low-risk patients. However, persistent but low serum thyroglobulin levels have a very low positive predictive value for current structural disease.

- Newer therapies with multikinase inhibitors and redifferentiation strategies hold great promise in patients with advanced disease, but thus far, data from randomized trials do not unequivocally demonstrate improved overall survival.

Papillary thyroid cancer, the most common endocrine malignancy, offers important public health and individualized treatment challenges to policy-makers and clinicians. The rapidly rising incidence of papillary cancer, coupled with mostly excellent long-term survival, has created a large prevalent population of patients. While most of these patients do well, the biology of papillary cancer is extremely diverse, ranging from never-progressive/extremely indolent lesions to aggressive metastatic cancers. Patients at low risk of thyroid cancer death can still have important or even catastrophic morbidity (including invasion of trachea, esophagus, large cervical vessels, and recurrent laryngeal nerves). Our ability to identify those facing adverse outcomes remains imperfect. All treatments have risks. Finally, hardly any treatment decisions in papillary thyroid cancer care have rigorous randomized controlled trial evidence to support their adoption, although often contradictory observational research on papillary thyroid cancer treatment continues to proliferate. Thus, there are many ongoing debates about optimal papillary thyroid cancer management.

Clinicians managing papillary thyroid cancer patients have a multitude of sources to consult, including comprehensive but variably updated international treatment guidelines (1-5). Many other excellent recent summaries, including in *Endocrine Reviews* (6), focus on a comprehensive discussion of treatment for low-risk papillary cancers. In this paper, we aim to provide an up-to-date analysis of the key open debates in adult papillary thyroid cancer care across its spectrum of disease, offer a roadmap for optimizing personalized care in the face of evidence uncertainty, and explore how the evidence gaps may be bridged in the future.

The rising incidence of papillary thyroid cancer

The exponential, near worldwide increase in papillary thyroid cancer incidence has been well described. While this rising incidence began in the 1980s, the intense research focus on explaining the phenomenon developed in the early 2000s and continues today (7,8).

It is extremely likely that increased diagnosis of small, clinically silent tumors (often termed ‘overdiagnosis’) has occurred. The preconditions for overdiagnosis of thyroid cancer are clearly present. First, a reservoir of subclinical papillary cancer exists in many people; this has been most famously documented on autopsy specimens of cohorts who died of non-thyroid causes (9). Second, we have the technologic ability to identify these silent tumors, whether it be through advanced imaging techniques of ultrasound, computed tomography, magnetic resonance imaging or 18-fluoro-2-deoxyglucose positron emission tomography [^{18}F-FDG-PET] scans (10), or by systematic microscopic examination of thyroid tissue after surgical removal (11). Knowledge of small tumors being caught “early” and successfully treated, or conversely a fear of missing treatable disease when localized, are powerful motivators in both patients and clinicians to perform diagnostic procedures. When these procedures diagnose cancer, a positive feedback loop could be created to identify more disease and increase cancer incidence rates further (12).

While the phenomenon of overdiagnosis has probably occurred worldwide, the Korean experience is the most extreme example. Thyroid ultrasound became a common screening tool in the early 2000s (even though not part of the official cancer screening program) (13,14). The age-standardized incidence of papillary thyroid cancer (both sexes) rose from 6.3 cases/100,000 persons/year in 2001 to 60.1 cases/100,000 persons/year in 2013 (15). The

vast majority of diagnoses were of small, localized tumors (16); nodules as small as 3 mm diameter were documented to undergo fine needle aspiration (17).

There are many potential harms from cancer overdiagnosis. Otherwise healthy individuals may have significant psychologic distress from becoming a "cancer patient". Diagnosis usually leads to cancer treatments, with potential complications from unnecessary surgery or radioiodine treatment. Thyroid cancer patients have been documented to have significant impairments in quality of life (18,19), which could be related to either or both of these factors. There may be considerable personal financial costs related to cancer therapy, even leading to bankruptcy (20). In addition to personal costs, the societal financial costs of medical care through insurance programs (both government and private) are large (21). For thyroid cancer clinics, there may also be an opportunity cost from these medical services being overburdened with cases of extremely low-risk disease, preventing care and attention to patients at higher risk. Finally, patients with overdiagnosed cancers may be included in research studies assessing causes of disease or optimal treatments, and could therefore contaminate the research findings (22).

Difficult challenges exist in reducing overdiagnosis harm. Not all incidental diagnosis can be avoided; for example, small tumors may be identified during appropriate medical assessment for symptoms potentially due to thyroid cancer, or on histologic examination of surgical specimens resected for benign compressive goiter (23). Clinicians also face the dilemma of how to distinguish an "overdiagnosed tumor" from one that would cause clinical harm in the future if left unattended. Finally, some patients with small, incidentally identified cancers may feel psychological benefit from having a diagnosis made and treatment performed.

Therefore, we require a multi-pronged public health approach that attempts to reduce unnecessary diagnosis and the harm resulting from diagnosis. Table 1 conceptualizes possible solutions within a modified Haddon's matrix incorporating peri-diagnostic time-points and factors where interventions could be targeted (patients, diagnostic technology and definitions, and healthcare providers and environment). Some evidence suggests that initial efforts to prevent overdiagnosis are having an effect, with an apparent slowing of the incidence rise in the USA (24) and a reducing (but still very high) incidence rate in Korea (25).

A key question is whether all the increase in papillary cancer incidence is due to overdiagnosis. This is an important issue, because if environmental causes of thyroid cancer are driving part of the increased papillary cancer incidence, a singular focus on overdiagnosis prevention could be harmful by preventing earlier identification of clinically significant disease. Several lines of evidence support a "true" increase in thyroid cancer incidence. The incidence of large thyroid cancers as well as small tumors has increased (26-28). The incidence of advanced papillary cancers (e.g., those with lymph node or distant metastases (26,28,29), aggressive subtypes such as tall cell variants (30), or significant extrathyroidal extension (28,31)) have also increased. Finally, a rising papillary thyroid cancer mortality has been reported in the USA (32), and in Korea before 2004 (with a subsequent decline thereafter) (33). Counterarguments have been made: larger tumors may be incidentally diagnosed through imaging (34); modern surgical and staging approaches could conceivably lead to upstaging of disease over time; and prior US incidence-based mortality rates were higher in the 1970s than now (7). Thus, current upwards trending rates could represent statistical noise (although this argument assumes no improvements over time in directed or supportive treatments of advanced cancer patients).

With the possibility/probability that a portion of the rising thyroid cancer incidence is due to changes in environmental exposures, a steady expansion in efforts to define papillary cancer risk factors has occurred. However, much of the evidence remains preliminary. Table 2 discusses proposed risk factors examined in epidemiologic studies. One particular difficulty

in interpreting the literature is the potential for confounding by diagnosis, i.e., the inclusion of 'overdiagnosed' patients who might never manifest clinical disease (assuming that 'overdiagnosed' patients have different exposure profiles than patients with clinical disease). Ideally studies should be powered to include enough patients with clinically significant cancer to assess exposure-disease associations in these patients, and/or assess putative risk factors' associations with molecular markers of disease severity (e.g., *BRAF*^{V600E} mutations).

Initial therapy of papillary thyroid cancer

Should all cancers be treated?

Most patients with papillary thyroid cancer have an excellent prognosis. This is especially true for those with the smallest tumors, the papillary microcarcinomas (defined as diameter <10 mm). Given our knowledge of overdiagnosis and its associated harms, an important question is whether all diagnosed papillary cancers (particularly microcarcinomas) need treatment.

The pioneering work of Miyauchi and colleagues at Kuma Hospital, Japan has provided essential data on the natural history of papillary microcarcinomas. From 1993, most patients with biopsy-proven papillary microcarcinoma were offered either immediate surgery or observation (commonly called active surveillance; exclusion criteria were nodal or distant metastases, concern of high-grade malignancy on biopsy, and potential for tracheal or recurrent laryngeal nerve invasion) (59-64). The latest outcomes paper assessing 1263 patients who chose active surveillance reports no thyroid cancer deaths, no distant metastases, 3.8% development of nodal metastases at 10 years, and 8% with tumor enlargement ≥3 mm at 10 years (61). The risk of disease progression was highest in the youngest patients: 10-year disease progression for a patient age in their 20s was 36.9%, progressively declining with each decade of age to 3.6% for patients in their 70s (62). Numbers of patients in the active surveillance group who experienced complications from their treatment were significantly fewer than for patients who chose immediate surgery (reflecting fewer patients being exposed to surgery, even when treated in a very high-volume institution) (63). The 10-year cost of active surveillance vs immediate surgery appears to be lower, at least in the Japanese setting (64).

Other groups have published early data that supports active surveillance approaches for papillary microcarcinomas. The longest running program from the Cancer Institute Hospital, Japan (65-68) reports near identical results to the Kuma Hospital group for microcarcinoma patients (the latest report for 360 patients with mean follow-up 7.3 years documents no thyroid cancer deaths, no distant metastases, 1% development of nodal metastases, and 8% with tumor enlargement ≥3 mm) (68). The first American report from Memorial Sloan Kettering Cancer Center described tumor growth ≥3 mm diameter in 9 of 232 microcarcinoma patients (3.9%) during median follow-up of 2.1 years (69). Researchers from Asan Medical Center, Korea report that four of 192 papillary microcarcinoma patients observed without surgery over a median follow-up of 2.5 years had diameter increase by ≥3 mm (70). Finally, in 126 microcarcinoma patients followed with active surveillance for a median follow-up of 2.1 years at Samsung Medical Center, Korea, seven nodules grew ≥3 mm diameter, and one patient had nodal metastasis (71). In the latter three analyses, the change in tumor volume was proposed to be a more sensitive measure of growing tumors than tumor diameter.

The above data support a choice for biopsy-proven microcarcinoma, either immediate treatment or active surveillance. The current American Thyroid Association (ATA) guidelines for the management of thyroid nodules and thyroid cancer cautiously acknowledge this choice, and they also call for further studies to define the role of active surveillance (1). However, the guidelines also state that thyroid nodules without accompanying

lymphadenopathy should not undergo fine needle aspiration until ≥10 mm diameter (Recommendation 8), even when high suspicion ultrasound features are present (1); previous guidelines also discouraged biopsy of small lesions although were less prescriptive (72,73). Clinicians following the ATA guidelines for nodule diagnosis are therefore performing active surveillance by default on a subset of their patients, because some of them will have microcarcinomas. The active surveillance data suggest this "default" approach is safe for the vast majority of patients. Future research will improve clarity on which patients are at highest risk of disease progression with active surveillance for proven or potential papillary microcarcinomas, and thereby positively impact clinical management.

Papillary microcarcinoma has an arbitrary metric definition (<10 mm), but most patients with intrathyroidal papillary cancers ≥10 mm diameter also have an excellent prognosis. Two small studies have reported on the outcomes for active surveillance for papillary cancers ≥10 mm diameter. The Memorial Sloan Kettering study mentioned above included 59 patients with tumors 11-15 mm diameter; two had increase in tumor diameter ≥3 mm and five had tumor volume increase ≥50% (69). The Cancer Institute Hospital reported results for 61 patients with tumors 11-20 mm (mean follow-up 7.9 years) (68). There were no deaths, no patients with distant metastases, two patients with nodal metastases, four patients with increase in tumor diameter ≥3 mm, and seven patients with ≥50% increase in tumor volume.

Nonsurgical therapy for papillary microcarcinomas, including low power microwave ablation (74), radiofrequency ablation (75), and laser ablation (76) are novel and potentially useful therapies for papillary microcarcinoma.

Surgical approaches

For almost all papillary cancers needing treatment, surgery is the key therapy. The goals of surgery are to remove the primary tumor, minimize the risk of disease recurrence, provide accurate staging, and to allow radioiodine to be delivered, when appropriate. Accurate preoperative assessment is critical to surgical decision-making. The main surgical options are extent of thyroidectomy (either total thyroidectomy or lobectomy) and whether to perform neck nodal dissection (no dissection or central with or without ipsilateral dissection); the optimal approach remains controversial today.

Preoperative assessment

Ultrasound is widely accepted as the first-line imaging technique for preoperative assessment in papillary thyroid cancer. However, ultrasound accuracy is operator-dependent, and even with skilled sonographers, may not fully appreciate the extent of disease in certain neck locations (particularly the upper mediastinum, retropharyngeal space, and posterior to the thyroid for tracheal invasion and tracheoesophageal disease). A recent meta-analysis also suggested that the combination of ultrasound and contrast-enhanced computed tomography was superior to either technique alone in identifying cervical node metastases (77). Surgeons should therefore strongly consider preoperative cross-sectional imaging (i.e., contrast enhanced computed tomography) where there is any doubt as to ultrasound quality, if disease is suspected at locations where inadequate ultrasound images are likely (e.g., large posterior nodules), or for clearly aggressive cancers where cross-sectional imaging may assist in identifying additional nodal metastases). While it is true that administering intravenous contrast with computed tomography imaging will necessitate a delay in any radioiodine treatment, this time may be less than traditionally recommended (78) and any disease that is radioiodine-sensitive at the time of surgery is likely to remain so 1-3 months post-operation.

One tantalizing future possibility is the use of pre-operatively identified molecular markers (i.e., via fine needle aspiration) to guide treatment intensity. These could conceivably identity low and high-risk phenotypes and be used to prevent over-treatment of

likely indolent disease or under-treatment of tumors with high-risk molecular features. At present, data are insufficient to recommend this approach.

Lobectomy verses total thyroidectomy

The pendulum continues to swing regarding the extent of surgery required in papillary cancer. Ten years ago, the 2009 ATA thyroid cancer guidelines recommended total thyroidectomy for all papillary cancers >10 mm diameter and stated that lobectomy may be sufficient for low-risk, unifocal, intrathyroidal microcarcinomas (73). These recommendations were based on data from the US National Cancer Data Base, which suggested a survival advantage in patients with thyroid cancers ≥10 mm diameter who had more complete surgery (79). However, that study was extremely controversial, with other large population-based datasets analyses (80-82), including a re-examination of the National Cancer Data Base (83), showing no survival benefit from total thyroidectomy compared to lobectomy in low-risk patients. Single center cohorts also confirm an extremely low mortality and recurrence risk in patients undergoing lobectomy (84), at the expense of a small increased risk of recurrence in some (85-87), but not all studies (88). All current guidelines now suggest lobectomy for intrathyroidal papillary microcarcinoma. More controversially, these guidelines support either total thyroidectomy or lobectomy for most patients with papillary cancers 10-40 mm diameter and without extrathyroidal extension or clinical evidence of lymph node metastasis (1-5). Guidelines continue to support total thyroidectomy in those patients with the largest tumors or high risk pre-operative clinical features, and completion thyroidectomy for those patients with higher risk histologic features.

Lobectomy has the clear advantage of fewer surgical complications. Compared with total thyroidectomy, lobectomy patients experience less hypocalcemia and recurrent laryngeal nerve injury (89,90). Most lobectomy patients will also not need thyroid hormone replacement (90,91).

Despite data suggesting low risk of adverse cancer outcomes and lower chance of adverse surgical effects with lobectomy, the debate over optimal extent of surgery persists (92). The strongest argument for total thyroidectomy is to allow better individualized postoperative risk stratification and surveillance, including via radioiodine scanning and serum thyroglobulin measurement. Post-lobectomy dynamic risk stratification data show promising early results, but the numbers of supporting studies are small (93-96) and cutpoints for serum thyroglobulin response are not well defined (see *Tailoring follow-up strategies to the extent of initial treatment* section) (97). It is therefore understandable that some clinicians seek to minimize uncertainty by advocating more extensive treatment. Another suggested reason for total thyroidectomy is that adverse histologic features (e.g., tall cell variant of papillary cancer, follicular cancer with vascular invasion) can be found in lobectomy specimens, which may lead to completion thyroidectomy (although the data suggest that this applies to a minority of patients, when using very strict criteria for mandating completion thyroidectomy based on histologic features) (98). It has also been argued that because the contralateral lobe may harbor additional cancers (mainly microcarcinomas (99)), total thyroidectomy would prevent the need for reoperation. However, it is likely that many contralateral microcarcinomas would never progress clinically and seeking them in total thyroidectomy specimens could constitute a form of overdiagnosis. In studies from the Memorial Sloan Kettering Cancer Center that have compared local recurrence rates with lobectomy versus total thyroidectomy without radioiodine remnant ablation, no differences in locoregional recurrence rates were seen 289 patients (thyroid lobectomy (n=72) or total thyroidectomy (n=217) after a median of 5 years of follow-up (100), and similar findings were seen in a similar retrospective cohort of 789 patients (lobectomy n=261; total thyroidectomy n=528) with a median of 8 years of follow-up, with locoregional recurrence rates of <1% in both surgical groups (88). It is reasonable to suggest that a second surgery in the rare patient with

locoregional recurrence is preferable to subjecting all patients to what is likely unnecessary surgery in the majority. Furthermore, a recent population-based study found a higher rate of adverse quality of life issues and/or treatment related effects in patients who had undergone total thyroidectomy (excluding those who also had lateral neck dissections) compared with those who had undergone a lobectomy (OR, 1.49; 95%CI, 1.04-2.12) (19).

A key question for clinicians and patients considering conservative surgery is what specific disease-related features should preclude lobectomy or lead to completion thyroidectomy, taking into account patient preferences and health system expertise. A closely related consideration is whether radioiodine ablation should be performed, given that total thyroidectomy is almost always a prerequisite for this (101). Clearly, preoperative evidence of gross extrathyroidal extension, nodal metastatic disease, or distant metastases mandate a total thyroidectomy, and the presence of contralateral benign disease might favor a total thyroidectomy. It is critical for the surgeon to discuss the possibility of the need to convert a planned lobectomy to a total thyroidectomy with or without central neck dissection, based on intraoperative findings that were not apparent on preoperative imaging (e.g., extrathyroidal extension, recurrent nerve involvement, clearly pathologic adenopathy). The identification of very low risk histologic diagnoses (e.g., non-invasive follicular tumors with papillary-like features (102)) would argue against completion thyroidectomy following diagnosis on lobectomy. Figure 1 describes a framework for planning the surgical approach for preoperatively diagnosed papillary thyroid cancer. As mentioned above, we anticipate that in the future, pre- or postoperatively available somatic genomic/molecular profiles will be validated to assist with the personalization of surgical treatment decisions. At present, the data are insufficient to recommend using *BRAF*-mutation (or any other gene's) status in this decision-making, although the ATA differentiated thyroid cancer guidelines include *BRAF*-status as part of their modified Initial Risk Stratification criteria (1).

Extent of neck dissection

After resolving the extent of thyroidectomy, the next key surgical issue is to determine the extent of neck nodal dissection, if any.

Where no clinical evidence of nodal disease metastasis exists (either pre- or intra-operatively), the treating surgeon must decide whether to perform 'prophylactic' central node dissection of level VI of the neck (prelaryngeal, pretracheal and paratracheal lymph nodes bound superiorly by the hyoid, laterally by the carotids, and inferiorly by the innominate artery on the right and the corresponding axial plane on the left (103)), which may be a bilateral dissection but is often performed only on the ipsilateral side to the primary tumor. Proponents suggest that prophylactic central node dissection regularly identifies nodal disease and potentially reduces recurrence risk and need for reoperation in a scarred surgical field. Additionally, increased staging and risk stratification information is available postoperatively. However, not resecting microscopic central cervical nodal metastases that would be identified by prophylactic central node dissection does not appear to influence the prognosis of low-risk papillary cancer (104,105), and the only randomized controlled trial evidence available (albeit in a small study) does not show an effect on recurrence risk (106). Increased staging information for clinicians also risks prompting excessive postoperative treatment (e.g., radioiodine) from up-staging patients' disease (107). Finally, while the risks of permanent surgical morbidity such as recurrent laryngeal nerve injury and hypoparathyroidism are low some series, increased rates of these complications in have been reported in other settings (108). On balancing these issues, the ATA concludes that not performing prophylactic central node dissection is appropriate for patients with smaller, lower risk papillary cancers (i.e., intrathyroidal T1 and T2 tumors) (1).

There is clear consensus for compartmental neck dissection of involved neck areas (as opposed to simply 'berry picking' clinically abnormal nodes). If the central neck (level VI) is

the only area clinically involved, targeting this compartment is likely sufficient; however, more extensive lateral neck dissection is required for lateral (N1b) nodal disease. Uncertainty exists in the decision to include level V dissection in modified the lateral neck dissection for N1b papillary cancer patients, balancing the potential benefit of reducing persistence/recurrence risk and preserving of the function of the spinal accessory nerve remains controversial (109).

Postoperative radioiodine therapy

There are perhaps few controversies more heated in the thyroid cancer field than whether radioiodine should be used routinely following total thyroidectomy for patients with low-risk papillary thyroid cancer. Part of the difficulty is perhaps the failure to distinguish between remnant ablation and adjuvant therapy, which are both under the rubric of "postoperative radioactive iodine therapy". In low-risk patients, radioiodine is used in two contexts: [i] "remnant ablation" to destroy remnant tissue remaining after surgery, which may improve staging based on a posttreatment scan, and which theoretically will allow more specific follow-up with diagnostic radioiodine scanning and serum thyroglobulin measurements; and [ii] adjuvant therapy, given to destroy "occult" disease in those low-risk patients who may be at higher risk for recurrence, but which will not improve disease specific survival. In addition to the semantic problem, the lack of prospective randomized controlled trials showing benefit from radioiodine therapy, particularly in low-risk patients, is an additional difficulty leading to disagreements among various professional groups (1,110,111).

The ambiguity between "remnant ablation" and "adjuvant therapy" is illustrated by two randomized controlled trials showing that "high dose" (100 mCi) and low dose (30 mCi) radioiodine therapy using either withdrawal or recombinant human thyrotropin (TSH) were equivalent in achieving remnant ablation (112,113). One might ask whether the administration of 100 mCi of radioactive iodine constitutes remnant ablation or adjuvant therapy. In any event, although neither trial was designed to assess long-term outcomes in thyroid cancer patients, both trials have reported on rates of residual/recurrent disease after long-term follow-up. Neither showed a difference among any of the treatment arms: for the HiLo study, recurrence rates were: 1.5% vs 2.1% at 3 years; , 2.1% vs 2.7% at 5 years; and 5.9% vs 7.3% at 7 years (HR 1.10; 95% CI 0.47 to 2.59 p=0.83), for low and high dose groups, respectively (114). For the second study (ESTIMABL1), the recurrence rate was 2% at a median follow-up time of 5.4 years, again with no difference between the high and low dose radioiodine groups (115). There are two randomized controlled trials, IoN (NCT01398085) and ESTIMABL2 (NCT01837745), which will provide vital information, since both trials have a "no therapy" arm. These studies are ongoing and should provide the needed information about the usefulness of postoperative radioiodine therapy.

While there is evidence from retrospective studies of improved outcomes possibly in older patients and those with intermediate risk disease (116,117), the overwhelming majority of patients have low-risk disease. In such patients, there are currently no data to support the use of radioactive iodine therapy for remnant ablation or for adjuvant therapy (118,119). The ATA guidelines stress that "RAI [radioiodine] remnant ablation is not routinely recommended after thyroidectomy for ATA low-risk DTC [differentiated thyroid cancer] patients. Consideration of specific features of the individual patient that could modulate recurrence risk, disease follow-up implications, and patient preferences are relevant to RAI decision-making." (1). Unfortunately, recent data show that the decision to administer radioiodine therapy in low-risk patients in the United States is often driven by nonclinical factors, such as geography, ethnicity, and insurance status (120). In order to bridge some of the gaps in practice between endocrinologists and nuclear medicine physicians, leaders from the American Thyroid Association, the European Association of Nuclear Medicine, the Society of Nuclear Medicine and Molecular Imaging, and the European Thyroid Association

recently published a set of "guiding principles" related to radioiodine therapy for differentiated thyroid cancer that will hopefully lead to less variation in practice (121).

Given modern highly sensitive serum thyroglobulin assays, as well as high-resolution ultrasound, some have argued that the need for remnant ablation in low-risk patients is no longer necessary (92). Indeed, if the goal of remnant ablation is to achieve an undetectable serum thyroglobulin, some have wondered whether remnant ablation is even ethical in patients who already have very low or undetectable postoperative serum thyroglobulin levels (122). There is little evidence to support routine remnant ablation in such patients (123-125). Even in patients not receiving remnant ablation who do not have undetectable postoperative serum thyroglobulin levels, these levels tend to decrease substantially over time, often becoming undetectable (126). Further, there is also a decrease in thyroglobulin autoantibody titers over time in low-risk patients not undergoing postoperative radioiodine therapy (127).

In addition to the controversy about the true efficacy of radioiodine therapy, its role has become less relevant in 2019, since lobectomy, with its advantages of safety and potential preservation of thyroid function, is becoming an ever more popular surgical approach to the management of low-risk thyroid cancer (1,128). In patients undergoing lobectomy, completion thyroidectomy would only be considered in "patients for whom a bilateral thyroidectomy would have been recommended had the diagnosis been available before the initial surgery" (1), and mainly done to facilitate radioiodine therapy. In patients with intermediate risk disease with lower risk features (e.g., small central neck lymph nodes), who have undergone total thyroidectomy (either at the outset or after completion thyroidectomy), the ATA recommends low dose radioiodine therapy (30 mCi; recommendation 55A) (1). In contrast, activities up to 150 mCi are recommended for those patients with large remnants or who have suspected residual disease for whom adjuvant therapy is indicated (recommendation 55B) (1). However, whether radioiodine will improve outcomes in such patients will not be known until the results of IoN and ESTIMABL2 are published. With that, there hopefully will be broader agreement on the use of postoperative radioiodine in low-risk disease, which accounts for the vast majority of thyroid cancer patients (129).

Thyroid hormone suppression therapy: is it necessary?

Since TSH is a growth factor for thyroid tissue and thyroid cancer, the idea that maintaining a low serum TSH would benefit patients with thyroid cancer has been a cornerstone of thyroid cancer treatment for over half a century (130,131). However, older studies often did not distinguish between replacement and suppression therapy, and they lacked the ability to detect low volume recurrences using thyroglobulin measurements and high-resolution ultrasound. More recent studies have not shown a benefit from aggressive suppression therapy (undetectable serum TSH in a third generation TSH assay) or even less severe degrees of TSH suppression (i.e., serum TSH <0.1 mU/L) in patients with low risk disease (118,132-134). In contrast, one retrospective study noted a strong survival benefit of maintaining serum TSH levels below 0.1 mU/L in patients with advanced disease (134). There has been only one randomized controlled trial in which patients' serum TSH levels were adjusted to remain within the reference range versus levels <0.01 mU/L (135). In this study, no difference in disease-free survival was noted after almost 7 years of follow-up, including in a separate analysis of high-risk patients.

One major benefit of thyroid lobectomy versus total thyroidectomy in low-risk disease is the possibility that patients may not need postoperative thyroid hormone therapy. Recent studies have shown that a preoperative serum TSH >1.7 mU/L (136) or 2.5 mU/L (137) is a predictor of postoperative hypothyroidism, especially if anti-TPO antibodies are positive (137). A retrospective study showed that patients whose serum TSH levels were maintained below 2.0 mU/L with levothyroxine after lobectomy fared no better than patients whose serum TSH levels were allowed to remain between 2.0 and 4.5 mU/L (138). However, there

was a difference in the frequency of incomplete biochemical responses between the two groups, with patients not receiving levothyroxine having a higher rate compare to patients who serum TSH levels were maintained <2.0 mU/l (17.2% vs 9.4%). It should be noted that patients in this study who underwent lobectomy also had an ipsilateral prophylactic central neck dissection, making comparisons with patients who have only undergone a lobectomy difficult.

In addition to dubious benefits in low risk patients, long-term suppression of serum TSH can result in a number of adverse consequences, including cardiovascular disease (139), atrial fibrillation (140-142), osteoporosis (143), and risk of fractures (140). These negative effects of iatrogenic exogenous subclinical hyperthyroidism on the heart and skeleton are most striking in older individuals and in postmenopausal women, respectively.

Current ATA guidelines recommend no TSH suppression in low and intermediate risk patients who have had an excellent response to treatment (serum TSH levels of 0.5-2.0 mU/L), but recommend mild TSH suppression (serum TSH levels 0.1-0.5 mU/L), in high-risk patients who have had an excellent response to therapy (1). Mild TSH suppression is also recommended for patients who have an incomplete biochemical response to therapy. More aggressive suppression (serum TSH <0.1 mU/L) is recommended for those patients with residual structural disease or a biochemically incomplete response if the patient is young, premenopausal, or is at low risk for developing cardiovascular complications. The guidelines also emphasize ongoing risk assessment of the patient's thyroid cancer status, as well as the patient's potential comorbidities, older age, menopausal status, and the interim development of cardiovascular disease. Other clinical guidelines suggest similar schemas (2-5).

Key decisions in follow-up

Tailoring follow-up strategies to the extent of initial treatment

With practice guidelines (1-5) recommending risk-adapted management of papillary thyroid cancers, defining follow-up strategies tailored to initial treatment is mandatory. This is especially critical as the adoption of these guidelines will lead to an increase in conservative surgeries (144). However, while current guidelines clearly outline the follow-up protocols to be applied to patients who have had a total thyroidectomy (with or without radioiodine remnant ablation), there are no clear, straightforward recommendations on the assessment schedule that should be adopted in patients with papillary thyroid cancer who have undergone lobectomy. This is mainly because the majority of evidence comes from patient cohorts who have undergone the traditional extensive therapeutic approach.

In patients who have had a total thyroidectomy (with or without radioiodine), a disease-free status (also known as excellent response) comprises undetectable serum thyroglobulin levels (basal or TSH-stimulated), in the absence of interfering antibodies, and no clinical and imaging evidence of tumor (1,145,146). Thyroglobulin has a central place in this definition of "cure", because when structural recurrence occurs, a positive thyroglobulin result is usually identified before abnormal imaging. A new generation of highly sensitive thyroglobulin assays, characterized by a much improved analytical sensitivity, have been endorsed by current international guidelines (1) and are becoming more common in clinical practice. By applying these methods, serum thyroglobulin levels <0.2 ng/mL during TSH suppression or <1 ng/mL after TSH stimulation reliably identify those patients who remain disease-free over time; the negative predictive value is close to 100% (147-149). Since sensitive measurements of basal thyroglobulin provide similar information on disease status as stimulated thyroglobulin determinations, TSH stimulation may be avoided if sensitive assays are available. Regardless of the method used, thyroglobulin levels should always be interpreted in light of the pretest probability of clinically significant residual tumor. In low to intermediate risk patients who have undetectable serum thyroglobulin and no structural

evidence of disease on neck ultrasound at initial assessment (excellent response to therapy), the future recurrence risk is <2% (145,146). These patients can be safely followed with periodic (every 12-24 months) serum thyroglobulin and thyroglobulin antibodies assays and neck palpation, without routine use of ultrasonography. Repeated neck ultrasound assessment in these patients may lead to more false positive findings (up to 67%) than true disease (<1.2%) (150,151). Undetectable thyroglobulin levels in patients with initially high-risk cancers may require additional, second-line diagnostic procedures to rule-out disease (see following section), as the absence of the circulating tumor marker may simply reflect the dedifferentiation of the residual neoplastic foci and their loss of ability to synthesize or secrete thyroglobulin. On the other hand, minimally detectable thyroglobulin values in individuals at low to intermediate risk carry a very low positive predictive value (147), and a significant proportion of patients with a biochemically indeterminate response (basal thyroglobulin 0.2-0.99 ng/mL) or a biochemically incomplete response (basal thyroglobulin ≥1 ng/mL) to therapy remain free of structural disease during prolonged follow-up (152-154). In these patients, the thyroglobulin trend may be helpful in correctly classifying them, in that declining values predict a disease-free status, whereas rising levels suggest the presence of growing neoplastic foci (126,155). The presence of thyroglobulin autoantibodies can falsely lower immunometrically determined thyroglobulin levels (156). Alternative biochemical approaches to follow thyroglobulin autoantibody positive patients include: [i] using radioimmunoassay or liquid chromatography-tandem mass spectrometry for thyroglobulin measurements (156), as they resist thyroglobulin autoantibody interference (however, the functional sensitivity is much lower, being 0.5-1 ng/mL); [ii] using highly sensitive thyroglobulin assay and applying lower thyroglobulin thresholds than in patients without thyroglobulin antibodies (157); and [iii] assessing the temporal trend in thyroglobulin autoantibody titers (158,159).

However, for post-lobectomy patients, a thyroglobulin-centered definition of disease status is problematic and is supported by much less evidence. Here, thyroglobulin assay results cannot discriminate between a “benign” thyroglobulin from the residual thyroid lobe, and a “malignant” thyroglobulin from small volume residual disease. Reliable thyroglobulin cutoffs for distinguishing these two states have not been established, and the role of serum thyroglobulin assay trends has to be determined. A cut-off of 30 ng/mL has been proposed to discriminate between patients having or having not an excellent response to therapy (93-96). While this value has yet to be validated, many conditions are expected to introduce wide variability in thyroglobulin levels among subjects with a residual thyroid lobe. These include the volume of the residual thyroid tissue, the TSH levels, and the iodine supply. Based on all these considerations, neck ultrasound is universally regarded as the essential tool for assessing the response to initial treatment in patients treated with lobectomy (1-5). Since a conservative management approach is reserved for low-risk patients, in the few cases that recur after lobectomy, disease is almost always localized to the neck (84,160). These recurrences may involve the ipsilateral thyroid bed and lymph nodes, and the contralateral lobe, which can all be sonographically identified using well-established criteria (161-163). Similar to thyroglobulin assays, neck ultrasound has a high sensitivity, but the specificity may be lowered by false-positive findings (150,164-166). Watchful waiting is thus appropriate for low-volume lesions, while fine-needle aspiration cytology or thyroglobulin/molecular assay of needle washout fluid (167,168) may be warranted to confirm malignancy in those lesions with documented structural disease progression and who will undergo further treatment if recurrent disease is confirmed (1). The ATA guidelines set the short-axis nodal diameter cut-off for when to biopsy at 8 mm for central neck nodes, and 10 mm for lateral neck nodes (1). However, many other additional factors should be taken into account when considering surgical options. These include the risk of revision surgery

(e.g., proximity of the nodal lesions to vital structures, functional status of the vocal cords), primary tumor factors (e.g., histology or molecular patterns associated with aggressive behavior), and patient factors (e.g., age, comorbidities, patient preference).

What to do with rising thyroglobulin levels

Among patients who have had complete thyroid gland removal, with or without postoperative radioiodine therapy, the proportion of patients with serum thyroglobulin levels above the disease-free (excellent response) cut-off value range from 20 to 40% (169). While patients with low but detectable serum thyroglobulin levels (<5 ng/mL) and no structurally identifiable neck lesions at ultrasound are expected to remain disease-free during prolonged follow-up (170,171), individuals with higher values or rapidly increasing values (i.e., doubling time <1 year) are more prone to have or to develop a structural recurrence (155,172,173). In these cases, second-line imaging studies may be warranted to detect persistent tumor foci (Figure 2). The diagnostic work-up may include functional (whole-body radioiodine scanning and ^{18}F-FDG-PET scanning) and cross-sectional (computed tomography or magnetic resonance imaging) studies (1,162). It is noteworthy that ^{18}F-FDG-PET has a much higher sensitivity than the post-therapeutic whole body scan (97% vs 22%), and it can also provide prognostic information (174,175). Avidity with ^{18}F-FDG is most commonly seen in the more aggressive histological papillary thyroid cancer variants (175), radioiodine-refractory disease (176), patients with thyroglobulin levels exceeding 5 ng/mL or rapidly increasing (i.e., doubling time <1 year) (173), and after TSH stimulation (177) (although conflicting results have been reported on this issue; thus TSH stimulated ^{18}F-FDG not routinely recommended in the clinical practice (162)). The option of the empiric radioiodine treatment may be considered in patients in whom cross-sectional studies or ^{18}F-FDG-PET have failed to reveal a tumor source (1). However, there is no evidence that such an approach improves survival, and watchful waiting until disease is detected on anatomic imaging remains an option.

Advanced papillary thyroid cancer management

Current management with multikinase inhibitor therapy

While one third of the papillary thyroid cancer patients with radioiodine-avid metastatic disease can be successfully treated with therapeutic radioiodine activities, the remaining patients do not benefit from repeated radioiodine administrations. The overall 10-year survival rate drops from 92% in the first group to 19% in the second (178). The latter group may be eligible to move from a radionuclide-targeted cancer therapy to a kinase-targeted therapy.

Proposed characteristics for a patient having radioiodine-refractory thyroid cancer include: target lesions that do not take-up radioactive iodine either on a diagnostic or posttreatment radioiodine scanning (even if accompanied by radioiodine-avid lesions); or progression despite a substantial radioiodine uptake or a cumulative radioiodine activity of >22.2 GBq (600 mCi) (1,121). These features can be of help in identifying patients who may qualify for systemic treatment, in the presence of symptomatic or significantly progressive metastatic disease (Figure 3). Before considering a patient as eligible for systemic therapies, a thorough assessment should be performed to assess whether one or more lesions are amenable for localized treatments. This applies especially to those individuals with one or few areas of metastatic spread (oligometastases), or multiple lesions with an isolated area of progression (oligoprogression). A variety of approaches are available, including surgery, radiotherapy or percutaneous minimally invasive techniques (e.g., ablation of metastatic lesions with laser, radiofrequency energy, microwaves, cryotherapy, radio or chemoembolization) (182,183) Additionally for skeletal metastases, low level-of-evidence data support a benefit of bone resorption inhibitors (bisphosphonates and denosumab) in

potentially decreasing the skeletal related events (e.g., pathological fractures, spinal-cord compression) and improving pain (184,185).

For radioiodine-refractory papillary thyroid cancer patients eligible for systemic therapy, two options are approved by the European Medicines Agency and Food and Drug Administration: sorafenib and lenvatinib. Both are oral multikinase inhibitors with antiangiogenic activity and both have been investigated in large, randomized phase III trials: DECISION (186) and SELECT (187), respectively. Both studies showed a statistically significant improvement in progression-free survival (the primary endpoint) compared with placebo. For sorafenib, the median progression-free survival was 10.8 months vs 5.8 months for placebo (HR, 0.59; 95%CI, 0.45 to 0.76; p<0.0001), while for lenvatinib, the median progression-free survival was 18.3 vs 3.6 months for placebo (HR, 0.21; 99% CI, 0.14 to 0.31; p<0.001). No significant difference in overall survival was observed in the either trial, possibly related to the fact the patients in the placebo groups were allowed to "cross over" to active therapy at the end of the trials. However, in a prespecified subgroup analysis of the lenvatinib trial, a significant improvement in overall survival emerged in patients aged >65 years (188). Both multikinase inhibitors can cause important adverse events and require close monitoring; specific management strategies may minimize their incidence and severity (189). Although the main goal of cancer therapies is improving the quantity and quality of patients' lives, whether these drugs are able to improve the quality of life has not been characterized.

Beyond these two agents (i.e., sorafenib and lenvatinib), no additional therapies are currently approved for treating patients with advanced, radioiodine-refractory papillary thyroid cancer. When disease progression occurs for patients treated with multikinase inhibitors, clinicians have several options. For oligoprogression, patients may benefit from combining a localized treatment with the ongoing therapy (albeit after a short treatment break from the multkinase inhibitor to ensure wound healing and/or recovery from any toxicity). For patients experiencing generalized treatment failure on one agent, data from the SELECT study support switching multikinase inhibitor, since patients experiencing treatment failure with one prior multikinase inhibitor had a clinical benefit from subsequent lenvatinib treatment (187). For generalized failure after using both agents, patients may be assessed for suitability for clinical trial recruitment, if any are available (see following section). In the absence of ongoing and recruiting clinical trials, the National Comprehensive Cancer Network guidelines suggest additional kinase inhibitor alternatives that have been approved by the Food and Drug Administration for other cancers, and for which evidence for treatment efficacy in thyroid cancer may be derived from phase 1 or phase 2 studies (including axitinib, cabozantinib, dabrafenib, everolimus, pazopanib, sunitinib, vandetanib, and vemurafenib) (4). Of note, access to these drugs may not be available in all countries.

Future targeted therapies

Other classes of drugs are being studied in papillary thyroid cancer patients and hold promise for treating patients with advanced, radioiodine-refractory disease. An exciting area of research that may lead to new drug treatments involves the modulation of thyroid cancer differentiation, aimed at restoring radioiodine uptake in cancer cells that are unable or have lost the ability to take up the radioiodine (so-called redifferentiation). Several unsuccessful attempts have been made in past years from this perspective (190). However, recently, two kinase inhibitors (selumetinib [a selective MEK inhibitor] and dabrafenib [a selective BRAF inhibitor]), targeting the mitogen-activated protein kinase pathway have been used to re-induce radioiodine uptake in radioiodine-refractory thyroid cancer patients (191-193). Almost two thirds of patients exhibited new or increased radioiodine uptake, with a partial radiologic and clinical response being observed in 30 to 60% of the cases. These experiences should be considered "proof-of-concept" studies, involving a small proportion of patients. Larger prospective studies are needed to confirm these results, to determine the duration of response,

the impact on survival, the characteristics of patients who are most likely to benefit from therapy.

Other exploratory, promising approaches include the use of agents targeting "druggable" mutations, like *BRAF* or *TRK*. BRAF inhibitors (i.e., vemurafenib and dabrafenib) showed antitumor activity (partial response) in almost one third of the patients with progressive, radioiodine-refractory, $BRAF^{V600E}$-mutant papillary cancer (194-196). Co-targeting the downstream MEK protein with a MEK inhibitor (i.e., trametinib) plus BRAF inhibitor (i.e., dabrafenib) has been shown to be effective in treating $BRAF^{V600E}$-mutant undifferentiated thyroid carcinoma (197), which likely arose from papillary cancer. This has led the Food and Drug Administration to approve trametinib/dabrafenib combination for treating anaplastic thyroid carcinoma harboring this genotype. In a phase I study enrolling patients with TRK-fusion-positive cancers, the novel TRK-directed agent larotrectinib was reported to yield a partial response rate of 87% in the subgroup of cases with TRK-rearranged papillary thyroid cancer (n=15) (198). It is likely that additional targeted approaches for advanced papillary thyroid cancers, including targeted immunotherapy, will be developed in the future (199).

Although all these approaches hold promise as being effective in treating advanced, radioiodine-refractory papillary thyroid cancers, the indications for each, and their long-term efficacy and safety profile remain to be clarified.

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Figure 1. Framework for planning extent of thyroidectomy for pre-operatively diagnosed papillary thyroid cancer

Figure 2. Management of patients with serum thyroglobulin levels above the disease-free (excellent response) cut-off value and negative neck ultrasound. Abbreviations: TT, total thyroidectomy; RAI, radioactive iodine; 18-FDG-PET, 18-fluoro-2-deoxyglucose positron emission tomography.

Figure 3. Management of patients with advanced papillary thyroid cancer. [a] Patients with metastatic disease that does not take up radioactive iodine at the time of initial treatment, or that loses the ability to take up RAI after previous evidence of ^{131}I uptake, or with RAI uptake in some lesions but not in others, or with metastatic disease that progress despite substantial uptake of RAI. [b] Patients who received RAI cumulative activities >22.2 GBq (600 mCi) are

less likely to benefit from further ^{131}I administrations. [c] Single organ or single/few lesions should be considered for localized treatments. [d] The size and location(s) should be considered in determining if asymptomatic disease at potentially critical sites (cerebral, peritracheal, perivascular, bony, paraspinal etc.) require earlier treatment. [e] Disease progression should be evaluated through serial imaging at 3-6 month intervals. Significant disease progression includes an increase in tumor size between two time points of at least 20% according the Response Evaluation Criteria In Solid Tumors (RECIST) system, and/or a tumor doubling time (the time after which the diameter/volume of the lesions has doubled) <1 year (179-181). Abbreviations: RAI, radioactive iodine.

Table 1. Modified Haddon's matrix for preventing overdiagnosis harm in papillary thyroid cancer

Time-point	Patient factors	Diagnostic technology and definitions	Healthcare providers and environment
Pre-diagnosis	Educate the community on overdiagnosis concepts (e.g., individual patient consultations, media campaigns, education of journalists on overdiagnosis concepts)	Better define high-risk vs low-risk incidental imaging findings	Regular training for healthcare providers on overdiagnosis concepts
	Understand patients' knowledge, values, and decision-making heuristics to better consider trade-offs in early diagnosis vs potential over-diagnosis	Standardize imaging reporting to clearly state incidental findings vs symptomatic disease, features of identified lesions that allow improved clinical risk stratification (e.g., size, location, presence or absence of invasion into or through the capsule, or small lymph node metastases)	Reduce ordering of unnecessary ultrasound investigations (e.g., Choosing Wisely program)
		Change focus of research efforts from pathologic diagnosis of thyroid cancer to biologic behavior	Reduce unnecessary diagnostic fine needle aspiration/biopsy (e.g., guidelines)
			Consider reimbursement models for investigation of incidentally found nodules/lesions
Diagnostic events (FNA, surgery)	Educate patients on possibility of incidental diagnosis when performing surgery for apparent benign disease (e.g., compressive nodular goiter or Graves' disease)	Re-classify variants of disease with lowest risk as non-cancers (e.g., non-invasive follicular neoplasm with papillary like features)	Diagnostic procedures by high volume providers
		Investigate markers to predict outcome (somatic, gene expression, miRNA, etc.)	Encourage use of conservative procedures (e.g. lobectomy)
Post-diagnosis	Develop formal decision aids for patients to consider less invasive treatment options (e.g., active surveillance, lobectomy, withholding radioiodine), and be aware of success of treatment options in unlikely event of recurrence	Refine post-diagnosis risk stratification	Monitor and publish outcomes for less invasive treatment approaches in incidentally or potentially overdiagnosed disease

Table 2. Potential risk factors for papillary thyroid cancer

Exposures studied	Evidence summary
Extrinsic	
Radiation	The best-defined risk factor for papillary thyroid cancer, although the increased risk is only established following exposure in childhood and adolescence (35). Radiation exposure has increased in the USA; however, most of this is due to radiation from computed tomography and nuclear medicine scans (36), which are rare before age 20. The prevalence of known radiation-induced genetic signatures is declining in new papillary cancer cases (37,38). Without new evidence, it seems unlikely that radiation is the cause of rising thyroid cancer incidence.
Smoking	Most evidence suggests a 30-40% reduced risk of thyroid cancer in active smokers (39-41). There is a reducing prevalence of smoking in most countries (42). While it is plausible that some of the incidence rise for papillary cancer could be due to declining smoking rates, this is not directly actionable for thyroid cancer prevention

	given smoking's overwhelming harms. The association is, however, worthy of future research to explore potential mechanisms of causation.
Alcohol	Most studies suggest a 20-30% reduced risk of thyroid cancer in those with moderate alcohol consumption (43). It is unlikely that alcohol consumption has significantly dropped in most countries where thyroid cancer incidence is increasing, and therefore is unlikely to be a major cause of the rising incidence.
Dietary	Iodine – iodine deficiency is associated with higher follicular and anaplastic thyroid cancer rates. Transitioning a population from iodine deficiency to sufficiency increases the proportion of papillary cancer diagnoses and high iodine intake may be associated with papillary thyroid cancer (44). However, the incidence of papillary cancer has also increased in countries where iodine status is essentially unchanged.
	Nitrates/nitrites – the relationship between exposure to nitrates and nitrites in food and water to thyroid cancer risk has been examined in several large cohort studies (45-47) (in addition, other studies have assessed nitrate-containing cruciferous vegetable intake; see below). Results are inconsistent, and it is unclear whether any real relationship exists.
	Vegetable intake – small, mostly retrospective studies suggested associations between intake of cruciferous vegetables and thyroid cancer risk, and inverse associations between non-cruciferous vegetable intake and thyroid cancer risk (48). These findings have not been confirmed by a recent large prospective cohort study (49).
Environmental toxins	Flame retardants – One small study suggests exposure to specific retardants increases thyroid cancer risk (50). Two other studies were negative for a flame retardant-thyroid cancer relationship, although assessed different flame retardants (51,52). Exposure to flame retardants has increased over time. Further research is required.
Medications, particularly hormonal	Women undergoing fertility treatments have been reported to be at increased risk of thyroid cancer diagnosis (53). Interpreting these results is very difficult, because of the heterogeneous causes of infertility, the generally short exposure to hormonal fertility treatments, the potential for incidental thyroid cancer diagnosis, and the lack of supporting evidence from other studies assessing reproductive factors (see below).
Intrinsic	
Body size	Body weight and obesity – Many, but not all, studies suggest that an increase in body mass index is associated with risk of thyroid cancer (e.g., in a pooled analysis of body mass index measured at various time points in 22 prospective studies, for each 5 kg/m^2 increase in body mass index, the risk of thyroid cancer increased by 6-13% (54)). While there is the potential for obesity to be associated with increased medical presentation and thus incidental diagnosis, obesity has been linked with more aggressive tumor features and increased risk of thyroid cancer mortality in obese patients (54). The prevalence of obesity is increasing worldwide. This association is worthy of continued attention.
	Height – increasing height is associated with increased thyroid cancer risk (similar to many other cancers) (54). This association is not actionable, although understanding the mechanism of the association could advance knowledge for numerous cancer types.
Metabolic factors	There is very little evidence for altered thyroid cancer risk in patients with diabetes, hyperlipidemia, or metabolic syndrome, despite numerous studies.
Serum TSH concentration and autoimmunity	Cross-sectional studies suggest papillary thyroid cancer diagnosis associated with higher serum TSH concentration (55) and Hashimoto's thyroiditis (56). These studies can't rule out the effect of selection bias and confounding, and prospective studies could also be prone to these biases. Indeed, two prospective studies yield contradictory findings for a serum TSH-thyroid cancer relationship (57,58). Both studies find lower serum TSH to be associated with thyroid cancer diagnosis, yet only one finds higher TSH also to be associated with risk (58). Lower serum TSH concentration is plausibly related to thyroid cancer risk via thyroid autonomy with greater TSH pathway signaling, however could also be due to incidental diagnosis in patients treated surgically for thyrotoxicosis. Further research is needed. Future studies assessing Hashimoto's thyroiditis as a risk factor for thyroid cancer should demonstrate prospective ascertainment of thyroid autoimmunity and employ methods of assessing for potential ascertainment.
Estrogen and reproductive factors	The female preponderance for thyroid cancer remains unexplained. Reproductive and hormonal factors have been extensively investigated with mostly negative results (or very weak and inconsistent associations if positive) (48). Autoimmunity is more common in women, although autoimmunity has not been proven to cause thyroid cancer (as above).

Abbreviations: TSH, thyrotropin