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Review

Advancements in the treatment of differentiated thyroid cancer

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***Abstract*:** Derived from follicular epithelial cells, differentiated thyroid cancer (DTC) accounts for the majority of thyroid malignancies. The threefold increase in DTC incidence over the last three decades has been largely attributed to advancements in detection of papillary thyroid microcarcinomas. Efforts to address the issue of overtreatment have notably included the reclassification of encapsulated follicular variant papillary thyroid cancers (EFVPTC) to non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP). In the last 5 years, the overall management approach for this relatively indolent cancer has become less aggressive. Although surgery and radioiodine ablation remain the mainstay of DTC therapy, the role of active surveillance is being explored. Furthermore, the most recent American Thyroid Association (ATA) guidelines offer flexibility between lobectomy and total thyroidectomy for thyroid nodules between 1 cm and 4 cm in the absence of extrathyroidal extension or nodal disease. As our understanding of the natural history and molecular underpinnings of DTC evolves, so might our approach to managing low-risk patients, obviating the need for invasive intervention. Simultaneously, advances in interventional and systemic therapies have greatly expanded treatment options for high-risk surgical candidates and patients with widespread disease, and continue to be areas of active investigation. Continued research efforts are essential to improve our ability to offer effective individualized therapy to patients at all disease stages and to reduce the incidence of recurrent and progressive disease.

Keywords: differentiated thyroid cancer, DTC, management, therapy, thyroid carcinoma, treatment options

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Background

Thyroid cancer is the most common endocrine malignancy, accounting for 2.9% of all new cancers in the United States (US).[1] It is approximately three times more common in females than males (age-adjusted incidence: 23.1 *versus* 8.1 per 100,000, respectively), and has an excellent prognosis with a 5-year relative survival rate of 98.3%.[1] Differentiated thyroid cancer (DTC) is derived from follicular epithelial cells and accounts for over 90% of all thyroid malignancies.[2] DTC can be subdivided into papillary thyroid cancer (PTC; 85–90%), follicular thyroid cancer (FTC; 5–10%), and the rare subtype Hürthle (oncocytic) cell thyroid cancer (2–5%).[3–8] Exposure to ionizing radiation, particularly during childhood, age at diagnosis, and family history of thyroid cancer are known risk factors for DTC,[3,9–11] but genetic and environmental factors are being increasingly recognized.[12–17]

In the last 5 years, we have seen the overall management approach for this relatively indolent cancer become less aggressive. This is mainly because of the observation that the threefold increase in DTC incidence over the last three decades has been largely attributed to papillary thyroid microcarcinoma (PTMC; <1 cm) as a result of advances in ultrasonography and cytological analysis.[10,18,19] In an effort to address the issue of overtreatment arising from a diagnosis of cancer, encapsulated follicular variant papillary

Table 1. Potential candidates for active surveillance.

Suspicious for PTC (Bethesda category V) with suspicious ultrasonographic characteristics (irregular margins, taller than wide shape, hypoechoic, microcalcifications)
PTC (Bethesda category VI)
Tumor size ⩽ 1 cm
No clinical or radiographic evidence of local or distant spread
Tumor location not adjacent to the recurrent laryngeal nerve or trachea
High risk surgical candidate
Relatively short life expectancy
Urgent concurrent medical or surgical issues

PTC, papillary thyroid cancer.

thyroid cancers (EFVPTC) were renamed non-invasive follicular thyroid neoplasms with papillary-like nuclear features (NIFTP) in 2016.[20–22] Though questions regarding appropriate monitoring and follow-up for patients with NIFTP remain, the indolent nature of these neoplasms no longer mandate completion thyroidectomy or radioiodine ablation therapy.[23] Moreover, the US Preventive Services Task Force (USPSTF) currently advises against thyroid cancer screening in asymptomatic adults in the absence of known risk factors for thyroid cancer due to the limited benefit of screening and the potential harms of treatment.[22] However, it is important to note that, over the same time period, advanced stage PTC has also increased.[14,17,24]

For a known or suspected thyroid nodule, thyroid ultrasound with a survey of the cervical lymph nodes is the test of choice. The American Thyroid Association (ATA) recommends fine needle aspiration (FNA) biopsy for nodules ⩾ 1 cm in diameter with a high or intermediate sonographically suspicious pattern. Features of a highly suspicious nodule include microcalcifications, hypoechogenicity, irregular margins, taller than wide shape, and extrathyroidal extension, correlating with an estimated 70–90% risk of malignancy.[25] Results should be reported based on the six diagnostic categories outlined in the Bethesda System for Reporting Thyroid Cytopathology, which now takes into consideration the NIFTP reclassification, and the FNA biopsy repeated if the report reveals a nondiagnostic or unsatisfactory specimen.[25,26] Surgical resection, radioiodine ablation, and thyroid stimulating hormone (TSH) suppression remain the mainstay of DTC therapy but the benefit of active surveillance, and interventional and systemic therapies has also been increasingly acknowledged in more recent years for select cases.[8,25]

Active surveillance

Active surveillance can be an alternative to immediate surgery in patients with very low risk tumors such as papillary microcarcinomas showing no cytologic evidence of aggressive disease, in high-risk surgical candidates, those with concurrent comorbidities requiring urgent intervention, or patients with a relatively short life expectancy (Table 1).[25,27] The landmark Japanese studies investigating observation without immediate surgery in patients with low risk PTMC have provided compelling evidence for adopting active surveillance as a safe and effective management approach for certain patients.[25,28,29] In their 2014 analysis, Ito *et al.* excluded patients with regional lymph node or distant metastases, signs or symptoms of recurrent laryngeal nerve or tracheal invasion or tumors adjacent to these structures, and FNA biopsy findings suggestive of high grade malignancy.[28] Of 1235 patients diagnosed with PTMC between 1993 and 2011, 8% showed tumor enlargement by 3 mm or more after 10 years of observation. In addition, 3.8% developed lymph node metastasis, and 6.8% progressed to clinical disease at 10 years. They noticed that a higher proportion of patients who progressed were younger than 40 years, suggesting older patients with PTMC may be better candidates for observation, though younger patients may still have surgery as an option after progression.[29]

A 2017 study by Tuttle *et al.* also demonstrated low rates of tumor growth in their cohort of 291 patients with PTC ⩽ 1.5 cm over a median follow-up period of 25 months at a US institution.[30] They observed tumor growth of 3 mm or more in 3.8% of patients and showed that younger age at diagnosis and risk category at presentation were associated with a likelihood of tumor growth.[30] They also noted a classic exponential growth pattern with a median doubling time of 2.2 years in tumors that increased in volume by over 50%, highlighting the potential role of serial tumor volume measurements in defining the threshold for intervention in patients undergoing active surveillance.[30]

Further research on the frequency of imaging, TSH goals, thyroglobulin (Tg) monitoring, and timing of surgery is required in order to reliably differentiate patients with indolent disease who are unlikely to develop significant disease.[25,31] Randomized [ClinicalTrials.gov identifier: NCT04129281] and non-randomized [ClinicalTrials.gov identifier: NCT02609685] interventional clinical trials investigating the role active surveillance in PTMC are actively recruiting patients in Italy and the US, respectively. Patients should be carefully counseled on the risks and benefits of this approach, and there should be regular communication among members of the care team. Patient anxiety should also be considered and addressed.[32]

Extent of surgery

Surgical planning is a multifaceted process, involving consideration of extent of surgery, lymph node management, adjunctive therapy, and patient preference.[33,34] The ATA provides clear guidelines for tumors <1 cm and for those >4 cm. For PTMC, the ATA strongly recommends lobectomy over thyroidectomy as the initial surgical approach in the absence of prior head and neck radiation, family history of thyroid cancer, or nodal metastasis, unless there are clear indications to remove the contralateral lobe.[25] However, despite the fact that lobectomy has been a treatment option for small low risk cancers since 2006, a study analyzing Surveillance, Epidemiology, and End Results (SEER) data showed that the proportion of total thyroidectomies performed as initial surgical management for patients with tumors <1 cm remained unchanged or increased between 2006 and 2014.[35–37] The authors attributed this finding to the lag that comes with changes in practice, but noted that other patient and provider factors may be contributory, thus highlighting the need for similar studies in this area.[35] For tumors >4 cm or those with extrathyroidal spread/metastasis, the ATA recommends thyroidectomy and gross removal of all primary tumor tissue, which may be accompanied by lymph node dissection in the presence of nodal disease.[25]

There is no clear consensus as to whether there is a survival benefit to performing a total thyroidectomy over lobectomy in patients with nodules between 1 cm and 4 cm without extrathyroidal extension or evidence of metastasis.[38] For this reason, the most recent ATA guidelines offer flexibility between lobectomy and total thyroidectomy.[25,31] This represents a significant departure from the 2009 version of the ATA guidelines, which recommended thyroidectomy for patients with thyroid cancer >1 cm.[31] A lobectomy might be considered to avoid the need for hormone replacement and to decrease the risk of surgical complications. However, a completion thyroidectomy might be required based on histopathology results, as a final diagnosis of the tall cell, columnar cell, or hobnail variant of PTC, widely invasive FTC, or poorly differentiated carcinoma portends a more unfavorable outcome.[25] Conversely, thyroidectomy might be preferred in patients expected to receive radioiodine ablation postoperatively, and complications might be minimized if the procedure is performed by high-volume surgeons.[38] In either case, patient preference should be considered.[38]

Surgical complications

Intraoperatively, the recurrent laryngeal nerve should be visualized during dissection, and the parathyroid glands with their blood supply preserved to avoid complications such as recurrent laryngeal nerve damage, and transient/permanent hypoparathyroidism, which can significantly impair quality of life.[25] Other important complications include hematoma formation, wound infection, and lifelong thyroid hormone therapy and monitoring (Table 2).[8,19] The risk of these complications is higher for total thyroidectomy and for low-volume surgeons who perform less than 25 thyroid cases each year.[8,24,35,39,40] Although traditionally an inpatient procedure, advantages of thyroid surgery in the outpatient setting include reduced exposure to nosocomial infections, improved patient comfort, and reduced healthcare costs.[24,41] This is carefully balanced against the immediate risks of symptomatic hypocalcemia, airway obstruction, and cervical hematoma

Table 2. Common complications of thyroid surgery.

Wound infection
Transient/permanent hypoparathyroidism
Transient/permanent recurrent laryngeal nerve damage
Cervical hematoma
Requirement for thyroid hormone replacement

formation.[24,41,42] Neck swelling, dysphagia, stridor, paresthesias, and fever, are common early signs and symptoms of postoperative complications.[42] Relative contraindications to outpatient thyroidectomy include anticoagulant or antiplatelet therapy, excessive distance from a skilled facility, and locally advanced cancer.[42] Appropriate precautionary measures and monitoring should be implemented to preserve patient safety and enhance the overall patient experience.

Postoperative course

Serum Tg measurements, ultrasonography, and iodine radioisotope scanning are typically used to evaluate postoperative disease status.[25] Initial TSH suppression to <0.1 mU/l in high risk DTC patients is recommended to decrease the risk of cancer growth stimulation by TSH.[25,43] Calcium and vitamin D supplementation can be useful with TSH suppression because long-term side effects of thyroid hormone therapy include cardiac arrhythmias, angina, decreased bone density, and psychiatric abnormalities.[5,44] The ATA only provides weak recommendations for TSH suppression in intermediate and low risk patients based on low-quality evidence.[25] A study by Lee *et al.* showed that preoperative TSH (>2.5 mIU/l) and the presence of microsomal antibodies were significant predictors of levothyroxine use after lobectomy.[45] In their cohort of 276 patients, 23.6% required levothyroxine an average of 3.2 months after surgery, but 26.2% of these were able to discontinue after an average of 16.4 months.[45] Moreover, while serum Tg values are expected to reach their nadir 3–4 weeks after surgery, there is no target cutoff for serum Tg measurements.[25] It is also important to note that 25% of DTC patients develop antibodies to Tg. In addition, Tg production varies based on tumor subtype and assays differ among laboratories. These factors limit the efficacy of Tg as a marker for disease recurrence.[44,46]

Molecular classification

The most recent edition of the Bethesda System for Reporting Thyroid Cytopathology incorporates the option of molecular testing as an adjunct to cytopathologic evaluation.[26] The National Comprehensive Cancer Network (NCCN) guidelines Version 2.2018 further specified that, while the use of molecular testing is an appropriate intervention, it is not standard of care for atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS) or follicular neoplasms. However, they added that molecular testing might be useful in identifying actionable mutations for advanced DTC.[47] Molecular profiling is commonly performed using commercially available testing services such as the ThyroSeq v3 Genomic Classifier, a DNA/RNA next generation sequencing assay evaluating 112 candidate genes providing information on >12,000 mutation hotspots and >150 gene fusion types (CBLPath, Inc., Rye Brook, NY, USA), Afirma Genomic Sequencing Classifier (GSC), designed based on the RNA expression profiles of 1115 core genes, with the Xpression Atlas extension measuring variants and fusions in 593 genes (Veracyte, Inc., South San Francisco, CA, USA), and ThyGeNEXT® + ThyraMIR®, a multiplatform test comprised of the ThyGeNEXT® mutation panel and ThyraMIR® microRNA risk classifier (Interpace Biosciences, Inc., Parsippany-Troy Hills, NJ, USA).[48–52] The MAPK and PI3K-AKT molecular pathways have been implicated in the pathogenesis of DTC, and may provide useful information for risk stratification in DTC.[25] In 2014, The Cancer Genome Atlas (TCGA) project recognized *BRAF*^{V600E}-like PTCs (BVL-PTCs) and *RAS*-like PTCs (RL-PTCs) as distinct entities based on their genetic, epigenetic, and protein expression profiles.[53] The *BRAF*^{V600E} mutation acts in the MAPK pathway promoting PTC aggressiveness, and is found in approximately 40% of primary PTCs and 70% of recurrent PTCs,[12] but there is currently not enough evidence to support completion thyroidectomy based on this feature alone.[2,25] It is also important to acknowledge TERT promotor mutations given their known synergy with *BRAF*^{V600E} mutations in PTC.[54] *TERT* promoter mutations are thought to coexist with *BRAF*^{V600E} mutations in 7.7% of PTCs.[2] Several studies suggest that this combination enhances PTC aggressiveness, but the long-term clinical implications require further investigation.[55–57] Gene rearrangements activating the MAPK pathway include *RET-PTC3*, which is associated with radiation exposure,[58] and *NTRK*.[2,59] *RAS* point mutations can activate either pathway,[60] and have been reported in 10–20% of PTCs, and 40–50% of FTCs.[2,9,12] Furthermore, aberrant *PTEN* methylation or *PIK3CA* kinase mutations may activate the PI3K-AKT pathway in FTC.[2,27,60] As the practice of molecular profiling evolves, so might its utility in guiding clinical management.

Table 3. Potential candidates for radioiodine ablation after total thyroidectomy (adapted from the 2015 ATA guidelines).

ATA high risk with distant metastases
ATA high risk of any size with gross ETE
ATA low/intermediate risk[a] with lateral neck or mediastinal lymph node metastases
ATA low/intermediate risk[a] with >5 microscopic central compartment neck lymph node metastases
ATA low/intermediate risk[a] greater than 4 cm with adverse features such as advanced age or microscopic ETE
ATA low/intermediate risk[a] greater than 1–4 cm with aggressive histology or vascular invasion

[a]Positive postoperative disease status (on thyroid hormone therapy or after TSH stimulation), surgeon experience, and other clinical factors should also be considered.
ATA, American Thyroid Association; ETE, extrathyroidal extension; TSH, thyroid stimulating hormone.

Radioiodine ablation

The ATA recommends radioiodine (RAI) adjuvant therapy for high risk DTC patients after total thyroidectomy (Table 3). Prior to RAI therapy, serum TSH, Tg, and anti-Tg antibody measurements should be obtained.[25] Patients should be instructed to maintain a low iodine diet (50 mg/day) for 1–2 weeks, and undergo thyroid hormone withdrawal.[5,25,61] Levothyroxine (LT4) should be discontinued 3–4 weeks prior, and liothyronine (LT3) discontinued 2 weeks prior to therapy. ATA low and intermediate risk DTC patients and patients with contraindications to a hypothyroid state may undergo recombinant human TSH stimulation instead of thyroid hormone withdrawal.[10,25,27,61] The 5-year follow-up results of the ESTIMABL1 trial [ClinicalTrials.gov identifier: NCT00435851], a randomized control trial investigating rhTSH *versus* thyroid hormone withdrawal and low activity (1.1 GBq) *versus* high activity (3.7 GBq) RAI in patients with low-risk DTC, showed no evidence of disease regardless of preparation method or radioiodine dose used, providing further support for the use of rhTSH and 1.1 GBq radioactive iodine in these patients.[62] For advanced DTC, dosimetry might be appropriate to quantify RAI uptake and determine dosing given the variability from person to person, and within cells of the same tissue.[27,63,64]

The goals of RAI therapy include destroying occult disease foci, eliminating residual healthy tissue that may serve as a locus for neoplastic transformation, and improving the specificity of Tg as a tumor marker, and of whole body RAI scans during long-term surveillance.[5,10,61] A dose of 30 mCi is recommended over higher doses in lower-risk patients,[25] but high-risk patients may require 100–200 mCi.[5,64] During RAI ablation, ^{131}I is taken up by follicular thyroid cells, where the molecules accumulate and undergo beta decay.[10,12] This process is optimized by functional sodium iodide symporter expression (NIS).[12] Dedifferentiating tumors lose NIS expression and become fluorodeoxyglucose (FDG) avid as they lose RAI avidity. For this reason, FDG-PET (positron emission tomography) positive tumors tend to be more aggressive and unlikely to respond to RAI.[65] Age greater than 40 years, large tumor burden, and Hürthle cell histology are also indicators of poor response.[12,61] MAPK and PI3K/AKT activation is thought to decrease NIS activity,[64,66] and tumors with *RAS* mutations may be more likely to be RAI avid than those with *BRAF* and *TERT* mutations.[67]

Side effects of RAI therapy include nausea, temporary or permanent salivary gland and lacrimal duct dysfunction, sialadenitis, parotitis, thyroiditis, and bone marrow and gonadal dysfunction.[5,18,63] Adequate hydration might help alleviate symptoms.[5] There is also a risk of second primary cancer of soft tissue, salivary gland, colon, and blood, associated with higher cumulative doses.[2,10,27] Less than 10% of DTC patients will develop metastatic disease. Of these, approximately one in three experience complete remission after RAI therapy.[10,64] The ATA recommends a whole body scan with or without single photon emission computed tomography (SPECT)/computed tomography (CT) to determine RAI avidity for residual structural disease after therapy.[25]

Response is most commonly determined using Response Evaluation Criteria in Solid Tumors (RECIST).[68] For patients with structural progression within 12–16 months after adequate therapy, subsequent treatment with RAI is unlikely to be effective.[43,69] A 2018 retrospective study showed no clear benefit of a second round of RAI treatment in DTC patients with biochemically or structurally incomplete response.[70] More studies are needed to explore other potential indications for RAI therapy. The ESTIMABL2 [ClinicalTrials.gov identifier: NCT01837745] and IoN [ClinicalTrials.gov identifier: NCT01398085] randomized clinical trials investigating the role of RAI ablation *versus* no RAI ablation in low risk DTC are currently ongoing.

Postoperative risk stratification

There are many prognostic classification systems for DTC, but the American Joint Committee on Cancer/Union for International Cancer Control/tumor, node, and metastasis (AJCC/UICC TMN) staging is most widely used.[25] While these systems are useful for predicting risk of death from thyroid cancer, they are less suitable for predicting risk of recurrence, which has been reported to be as high as 20–30%.[3–5,32,71–73] Risk stratification is a dynamic process that should be repeated throughout the follow-up period to determine whether additional intervention is required.[25,32,72,74,75] ATA guidelines for response to therapy reclassification after initial risk stratification has been validated for DTC patients treated with total thyroidectomy and RAI remnant ablation.[25,76] Studies report a proportion of variance explained (PVE), which measures the performance of a predictive model, for dynamic risk stratification of 60–80% compared with 20–30% reported for static predictive models.[71,75] In 2014, Momesso and Tuttle[71] proposed a modified dynamic risk stratification system for patients treated with lobectomy or total thyroidectomy without RAI therapy. This was validated in a retrospective review of 507 patient records over a median follow-up period of 100.5 months, where excellent response was defined as nonstimulated Tg < 0.2 ng/ml for total thyroidectomy and stable nonstimulated Tg < 30 ng/ml for lobectomy, with undetectable Tg antibodies and negative imaging in both cases. They observed recurrent/persistent structural evidence of disease (SED) based on imaging/pathology in 0% ($n = 326$) of patients with excellent response, 1.3% ($n = 152$) with indeterminate response, 31.6% ($n = 19$) with biochemical incomplete response, and ($n = 10$) 100% with structural incomplete response. The authors determined they were able to identify patients with increased recurrence risk/persistent (SED) providing evidence for the use of dynamic risk stratification in these treatment groups.[77] However, the utility of these thresholds in appropriately stratifying patients after lobectomy has been challenged.[78,79] Further investigation is therefore needed to better define response criteria for patients treated with lobectomy.

Advanced DTC

The pattern of lymphatic spread for DTC is unique, occurring in order from level VI to levels III, IV, and II.[80] DTC often metastasizes to the lung, bone, and, in some cases, the liver, brain, or skin.[9,10] PTC spreads primarily by lymphatic spread and FTC by hematogenous spread.[3] Furthermore, lung metastases are typically seen in younger patients or those with PTC while bone metastases are often seen in older patients or those with FTC.[10] In patients with unresectable local or metastatic disease, refractory to RAI, interventional therapy such as external beam radiation therapy (EBRT), radiofrequency ablation (RFA), ethanol ablation (EA), and laser ablation should be considered.[2,9,12,66,81] Treatment planning should evaluate prior therapy, disease location, rate of progression, extent of spread, life expectancy, technical feasibility, and potential impact on quality of life.[66,82] For slowly spreading symptomatic disease, local therapy may delay the need for systemic treatment.[82] The overall intent of therapy may be definitive, adjuvant, or palliative, but this is not always easy to delineate in practice.[80]

External beam radiation therapy

The American Head and Neck Society recommends EBRT for residual disease with limited radioiodine avidity but not for patients under 45 years of age, and it is not offered routinely in the adjuvant setting.[80] EBRT is often used for bone metastases, but patients with symptomatic bone disease may also be treated with bisphosphonates or denosumab.[68,69,82] A retrospective study investigating adjuvant RAI +/− EBRT in 88 patients with advanced DTC over a median follow-up period of 117 months showed that older age and esophageal involvement predict worse

disease-free survival.[83] There was no significant difference in outcome between the two groups even though patients receiving RAI and EBRT had more extensive disease and invasion. Patients with tracheal/esophageal involvement receiving RAI alone had worse locoregional control than those with recurrent laryngeal nerve (RLN) invasion alone suggesting RAI therapy might be sufficient in cases of invasion into the RLN only.[83] Another retrospective study by Makita *et al.* reported a 2-year survival rate of 71% in DTC patients treated with EBRT with or without RAI therapy,[84] and demonstrated that both EBRT >50 Gy and RAI therapy after EBRT were associated with a more favorable outcome.

Adverse effects from EBRT correlates with radiotherapy volume, and the amount of radiation normal structures receive.[85] These include dermatitis, xerostomia, dysphagia, mucositis, hoarseness, dysguesia, and fatigue.[68,80] More uncommon but life-threatening effects include esophageal stricture requiring gastrostomy tube placement, tracheal stenosis, chronic laryngeal edema, and spinal necrosis.[80,81] Intensity-modulated radiotherapy (IMRT) is the preferred technique for EBRT delivery because it relies on 3D technology to precisely deliver radiation beams to the clinical target while sparing surrounding structures.[80,81,85] Intraoperative radiotherapy (IORT) permits higher radiation doses without harming healthy tissue but this has not yet been investigated in DTC.[86]

Interventional therapies

Over the past two decades, percutaneous interventional ablative techniques have gained popularity for the treatment of benign thyroid nodules, but may also have an increasing role in the management of malignant disease. Percutaneous laser ablation (PLA) is particularly effective on smaller lesions (<15 mm), but RFA and EA may be used on larger lesions (29–40 mm).[66] A 2019 retrospective study suggested that PLA therapy is safe and effective in patients with PTMC ($n=37$) who were considered high-risk surgical candidates without prior thyroid surgery or radioiodine therapy. Complications included neck discomfort (34/37), self-limited neck swelling (37/37), and TSH abnormalities (1/37), and only one patient had cervical lymph node metastasis at 24 months.[87] Another retrospective study suggested that low-power (20W) RFA is safe and effective in patients with PTMC refusing surgery ($n=37$). Over a median follow-up period of 6 months, 37/38 nodules were completely absorbed, with no recurrent nodules and no reported complications.[88] However, discomfort, cutaneous burns, voice changes, and requiring additional sessions have been noted.[25] A clinical trial [ClinicalTrials.gov identifier: NCT04129411] sponsored by the Mayo Clinic is actively recruiting to study the efficacy of RFA in PTC. EA has been used since the early 1990s in nodal disease but may require multiple doses to be effective.[66,89] In 2018, the Korean Society of Thyroid Radiology recommended EA as a secondary treatment option in recurrent thyroid carcinoma but not in primary thyroid cancer, and listed local pain or discomfort, temporary hoarseness, radiating pain to the head and chest, and tumor implantation through the tumor track as potential complications.[90] Further research is therefore required to explore the role of these interventional therapies in DTC and to establish appropriate follow-up procedures.

Systemic therapy

Systemic therapy might be considered after surgical and radiation therapy options have been exhausted.[25] Although doxorubicin and other chemotherapy agents have been used in advanced DTC, they have been largely replaced by newer kinase inhibitors.[9,68] The molecular pathways involved in DTC pathogenesis forms the basis of multikinase inhibitor therapy.[60] Sorafenib and lenvatinib are US Food and Drug Administration (FDA)-approved for locally recurrent or metastatic, progressive radioiodine refractory (RAIR) DTC.[91] Although the DECISION trial reported no significant difference in overall survival between the sorafenib treatment and placebo groups, there was an objective response rate of 12.2%, and median progression-free survival of 10.8 months in the treatment group compared with 5.8 months in the placebo group.[92] Results of the SELECT trial demonstrated a 64.8% response rate and a median progression-free survival of 18.3 months in the lenvatinib treatment group compared with 3.6 months in the placebo group.[93–95] More recently, selpercatinib was approved by the FDA for patients 12 years of age and older with advanced or metastatic *RET* fusion-positive RAIR thyroid cancer requiring systemic therapy.[91] The LIBRETTO-001 trial showed a 79% objective response rate for selpercatinib in 19 previously treated *RET*

fusion-positive thyroid cancer patients, with a 1-year progression-free survival rate of 64%.[96] Because *RET* mutations occur rarely in DTC, the majority of patients in this study ($n = 162$) had a diagnosis of medullary thyroid cancer.[96] Other agents under investigation include axitinib, pazopanib, and sunitinib.[97,98] Kinase inhibitor therapy is often limited by its side-effect profile, which includes nausea, diarrhea, fatigue, weight loss, hand-foot syndrome, hypertension, and QTc prolongation, so medical comorbidities should be assessed prior to therapy.[12,18,43,99,100] Although significant, treatment-emergent hypertension in lenvatinib therapy has been correlated with improved outcomes.[101] Moreover, tumors eventually develop resistance to kinase inhibitor therapy through an escape mechanism, reducing the efficacy of therapy.[18,97] Kinase inhibitors should therefore be discontinued once there is no longer a net benefit.[69] Immune checkpoint blockade is also being explored in advanced DTC.[97] Active interventional clinical trials investigating the role of anti-PD-1 inhibitors alone or in combination with other agents include [ClinicalTrials.gov identifier: NCT02628067]: Pembrolizumab (KEYNOTE 158), [ClinicalTrials.gov identifier: NCT03360890]: Pembrolizumab + Docetaxel (iPRIME), and [ClinicalTrials.gov identifier: NCT03914300]: Cabozantinib + Nivolumab + Ipilimumab (CaboNivoIpi).

Several interventional trials have investigated the role of various agents in restoring iodine avidity in RAIR thyroid cancer patients. MEK inhibitor selumetinib, *BRAF* inhibitors vemurafenib and dabrafenib, PPARγ agonist rosiglitazone, histone deacetylase inhibitor romidepsin, and retinoic acid have been used to induce expression of NIS, enabling thyrocyte ^{131}I uptake to deliver a therapeutic dose of radiation.[12,27,64] Of these, selumetinib, dabrafenib, and vemurafenib have demonstrated promising results. Ho *et al.*[102] reported increased uptake in 12/20 patients after 4 weeks of selumetinib therapy, including 5/5 patients with NRAS mutations, and 4/9 patients with *BRAF* mutations; 8/12 patients were treated with radioiodine, 5 of whom had a partial response, and 3 had stable disease. Rothenberg *et al.* demonstrated increased radioiodine uptake in 6/10 $BRAF^{V600E}$ DTC patients after 25 days of dabrafenib therapy who were subsequently treated with 5.5 GBq ^{131}I therapy.[59] There were two partial responses and four stable responses at 3 months. A more recent study investigating vemurafenib in DTC patients with $BRAF^{V600E}$ showed new or increased avidity in 6/10 patients after 4 weeks of therapy. Of these, four patients met the threshold for ^{131}I therapy with subsequent partial response in two patients, and stable disease in the other two patients. The authors noted pharmacologic reprogramming of *BRAF* signatures in all three patients who were biopsied before and after vemurafenib treatment, and significantly higher pretreatment serum Tg values in responders, which, in this case may serve as a marker of differentiation.[103]

The use of rosiglitazone, isotretinoin, and romidepsin in improving ^{131}I uptake has not been as successful. Kebebew *et al.* showed that 5/20 patients had a positive scan after 8 weeks of rosiglitazone therapy with no clinically significant response at 3 months follow-up,[104] and observed no treatment-related effects on PPARγ mRNA and protein expression level in an earlier study.[105] Another study reported improved radioiodine absorption in five out of nine patients after 6 months of therapy, but cited adverse interactions with long-term diabetes therapy in Europe as the reason for early study termination.[106] Short *et al.* showed increased radioiodine uptake in 1/15 patients treated with isotretinoin that was not significant enough for subsequent radioiodine therapy, and reported instances of skin and mucous membrane toxicity.[107] However, a more recent study suggested that a better response might be observed with retinoic acid in *BRAF*-positive DTC.[108] A study evaluating romidepsin was discontinued after serious adverse events possibly related to the drug were reported, namely one instance of sudden death and one pulmonary embolus.[109] Prior to that point, 13/20 patients had stable disease and 7/20 had progressive disease. Although avidity was restored in two patients, who subsequently underwent RAI treatment, the authors recommended against further investigation of romidepsin as a single agent in the treatment of RAIR DTC. Continued research on more robust differentiation strategies in RAIR DTC patients is warranted. The role of trametinib [ClinicalTrials.gov identifier: NCT02152995] in increasing tumoral iodine incorporation in RAIR thyroid cancer is currently being studied. Moreover, utilizing ^{124}I PET/CT lesional dosimetry over traditional ^{131}I scintigraphy/CT might be more advantageous in quantifying tumoral iodine uptake, and predicting the ^{131}I dose to be delivered during RAI therapy.[59,103]

Conclusion

Although surgery and radioiodine ablation remain the mainstay of DTC therapy, we have become less aggressive in our management of low-risk patients. As our understanding of the natural history and molecular underpinnings of DTC evolves, so might our approach to managing this patient subset, obviating the need for invasive intervention. At the same time, advances in interventional and systemic therapies have greatly expanded treatment options for high-risk surgical candidates and patients with widespread disease, and continue to be areas of active investigation. Continued research efforts are essential to improve our ability to offer effective individualized therapy to patients at all disease stages and to reduce the incidence of recurrent and progressive disease.

Author contributions

The original manuscript was drafted by LS under the supervision of JK. Both LS and JK contributed to the initial conceptualization, editing/revision, and approval of the final product.

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