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Novel Approaches to Thyroid Cancer Treatment and Response Assessment

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The incidence of thyroid cancer has been increasing. After total thyroidectomy of well-differentiated thyroid tumors with intermediate- or high-risk features on pathology, radioiodine remains one of the mainstays of therapy for both thyroid remnant ablation as well as for treatment of metastatic disease. SPECT/CT, a relatively new modality, has been shown to play a pivotal role predominantly in the post-therapy setting by changing the risk stratification of patients with thyroid cancer. In the case of radioiodine treatment failure, FDG-PET/CT may provide prognostic information based on extent and intensity of metabolically active metastatic sites as well as serve as an important imaging test for response assessment in patients treated with chemotherapy, targeted therapies, or radiotherapy, thereby affecting patient management in multiple ways. The role of newer redifferentiation drugs has been evaluated with the use of I-124 PET/CT.

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Differentiated thyroid cancer accounts for approximately 95% of all thyroid carcinomas; of these, approximately 85%-90% are papillary, approximately 10% are follicular, and approximately 3% are Hurthle cell carcinomas or tumors with poorly differentiated histology.[1] The most recent American Thyroid Association guidelines (ATA, 2009) recommend total thyroidectomy for tumors larger than 1 cm and possible lobectomy for tumors $\leq$1 cm.[1] However, a recent retrospective analysis of more than 3600 patients with differentiated thyroid cancer found that tumors 1-2 cm have the same disease-specific survival and recurrence-free survival compared to tumors $\leq$1 cm when omitting tumors with aggressive features such as nodal metastatic disease and extrathyroidal extension.[2] Similarly, DeGroot et al[3] reported a decreased risk of death and risk of recurrence for tumors $>$1 cm in a group of 269 patients with papillary thyroid cancer (PTC) treated with extensive initial surgery as well as postoperative I-131 ablation. The frequency of nodal metastases was the highest in PTC (61%), whereas Hurthle cell carcinomas showed a 33% incidence of distant metastases in a retrospective review of 1038 consecutive patients with differentiated thyroid cancer treated over a period of 55 years.[4] Although PTC and follicular thyroid cancer (FTC) are two distinct histologic types, they have been studied collectively under the header of "differentiated thyroid cancer." A retrospective study of 760 patients with differentiated thyroid cancer (589 PTC and 171 FTC) showed marked differences in prognostic factors in the two groups. Patients with PTC are typically younger than 50 years and have smaller tumors and a higher incidence of lymph node metastases, multicentricity, and extrathyroidal extension. Patients with FTC show a higher incidence of distant metastatic disease and more frequently receive radioiodine. The independent factors predicting poor prognosis for the PTC group were age $\geq$50 years, tumors $\geq$3.5 cm, extrathyroidal extension, and incomplete resection. In the FTC group, these factors were age $\geq$50 years and incomplete resection of distant metastatic disease.[5] Other studies have concluded that, stage for stage, the prognosis is similar for papillary and FTCs in general.[6,7] Other histologic subtypes of PTC, such as columnar cell variant, tall cell variant, and diffuse sclerosing variant; more aggressive variants of FTC; and poorly differentiated aggressive histologies have a worse prognosis—these tumors typically exhibit aggressive histologic features such as extrathyroidal extension, vascular invasion, and tumor necrosis.[8] Recent ATA guidelines propose a three-level stratification (low, intermediate, and high risk) based on the presence or absence of

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aggressive histologic features, presence of local or distant metastases, and imaging features on post-therapy scans.[1]

In recent years, it has become clear that many thyroid cancers are driven by oncogenic mutations. For instance, approximately 45% of papillary differentiated thyroid cancers harbor BRAF V600E mutations; other mutations such as RAS or RET/PTC mutations are less frequent.[9,10] RAS mutations are more common in poorly differentiated thyroid cancers.[11] Thyroid cancers bearing the BRAF V600E mutation show significantly higher FDG avidity compared with BRAF wild-type tumors.[12] These data shed interesting light on the connection between tumor biology and imaging features and may also be helpful in designing clinical trials, which would be discussed later.

Treatment Design and Role of Conventional Imaging

After surgical resection of the primary tumor, radioactive iodine (RAI, I-131) is used in most of the patients[13] for both thyroid remnant ablation and treatment of expected or proven locoregional or distant metastases.[14] Metastatic thyroid cancers of follicular cell origin retain, to varying degrees, the ability of normal thyrocytes to take up and retain iodide; this depends critically on the presence of functioning cell-membrane-based sodium-iodine symporters (NIS),[15] which are active in approximately 80% of well-differentiated thyroid cancers. Few other cell types (such as salivary glands, lactating breasts, stomach, and small intestines) possess the ability to concentrate iodide; therefore, I-131 is a selective, targeted approach for delivering tumoricidal doses of radiation to thyroid tumors. I-131 can be particularly effective for radioiodine-avid small-volume (<1 cm) micronodular lung metastases from well-differentiated thyroid cancer, as shown in a study of 444 patients.[16] The efficacy of I-131 treatment, however, is limited in patients with larger tumors, which are nevertheless often treated repeatedly with I-131.[16-20] Not all patients with thyroid cancer need to be treated with radioiodine. The recent ATA guidelines recommend radioiodine therapy only for intermediate- and high-risk patients with known distant metastases, gross extrathyroidal extension (regardless of tumor size), or primary tumors >4 cm. Radioiodine ablation is recommended for selected patients with primary tumors measuring 1-4 cm and clinicohistologic features predicting intermediate to high risk of tumor recurrence.[1]

To achieve sufficient iodine uptake into tumor cells, RAI ablation or therapy requires elevated levels of thyroid-stimulating hormone (TSH). TSH stimulation can be accomplished by thyroid hormone withdrawal or by intramuscular injection of rh-TSH (Thyrogen). Serum TSH levels >30 mU/L can be obtained in >90 patients with either method of preparation, both of which are effective.[21-23] Following appropriate stimulation, a pretherapy scan with low activities of I-123 or I-131 can be performed to quantify the percentage of neck uptake and is recommended when scan findings are expected to change management (eg, high residual uptake of iodine in the neck or visualization of unsuspected metastatic disease may prompt changes in the amount of I-131 chosen for ablation or treatment[1]). ATA guidelines recommend (based on expert opinion rather than hard data) that low activities of I-131 (1-3 mCi) or I-123 (1.5-3 mCi) be used for pretherapy scans and therapeutic I-131 activities be administered within 72 hours of this diagnostic procedure.[1] A SPECT/CT before RAI treatment remains of limited use. Occasionally, this test may detect iodine-avid neck node metastases, depending on the extent of surgical resection. However, today, many surgeons perform a preoperative neck ultrasound and then resect all nodes that appear suspicious. Any remaining (presumably small) iodine-avid neck nodes do not change management, and ablation with RAI proceeds regardless. Occasionally, a pretreatment SPECT/CT may also detect (unexpected) distant metastases, which may prompt selection of a higher treatment activity. Nevertheless, a negative-result pretreatment SPECT/CT may potentially give false comfort, as the probability for detecting distant disease is significantly limited by the low activity used for pretreatment scans. Studies such as the following should therefore be interpreted in this context. In a prospective study of 320 patients, preablation iodine SPECT/CT changed the risk stratification in 15% patients as compared with recurrence risk estimation based on histopathology alone. Regional metastases were noted in 35% and distant metastases in 8% of patients. The authors reported that this led to a change in clinical management in approximately 30% of patients.[24] However, these changes largely pertained to changes in the amount of RAI administered, and eight patients with "unexpected" bulky neck nodes were referred back to surgery. The latter should be a rather unusual occurrence when surgeons take advantage of preoperative ultrasound imaging and perform a thorough intraoperative exploration of the tracheoesophageal groove and neck.

Three approaches to determine the amount of RAI for ablation and therapy are widely practiced: administration of a fixed empirical activity, calculation of a maximum tolerated activity (MTA) (using dose constraints to blood or bone marrow and lung), and quantitative tumor lesional dosimetry.[14] In low-risk patients, activities between 30 and 100 mCi I-131 are often administered, which yield similar rates of remnant ablation.[25-28] In patients with primary tumors showing aggressive histologic features, such as tall cell, columnar, or insular carcinoma, higher activities (100-200 mCi) are recommended.[1] The maximum tolerated radiation-absorbed dose (MTRD), defined as 200 rads (cGy)[29] to blood, can be exceeded in a significant number of patients undergoing empirical treatments with arbitrary or fixed amounts of I-131. In a retrospective study of 328 patients, a fixed empirical treatment with 200 mCi I-131 would have exceeded the MTRD in 22% of patients 70-79 years old and 38% of patients aged 80 years or older.[30] In another study, empirical treatment with 100, 150, 200, 250, and 300 mCi of I-131 would have exceeded the MTRD in $<1\%$, 5%, 11%, 17%, and 22%, respectively.[31] In part, this is related to the fact that many older patients exhibit somewhat compromised renal excretory function. Lesional dosimetry, performed with diagnostic I-124 PET/CT, is the most sophisticated albeit laborious and

time-consuming approach for treatment planning; its role would be discussed later.

Following I-131 therapy, post-therapy scans are performed approximately 3-10 days after the RAI administration. These posttreatment scans may show additional metastases in 10%-26% patients when compared with pretreatment imaging,[32,33] although higher numbers were also reported in some studies. Extensive disease noted on posttreatment scans may alter the clinical stage in approximately 10%, and clinical management in 10%-15% of patients.[32-34] In contrast with the pretreatment setting, a SPECT/CT may provide meaningful and actionable information in the posttreatment setting. In a study of 148 consecutive patients (109 postsurgical and 39 with recurrent or metastatic disease), SPECT/CT provided clear classification of iodine uptake as benign or malignant, thus eliminating the need for additional cross-sectional imaging in 20% of patients. SPECT/CT better characterized clearly metastatic disease in the neck as well as distant metastases in lung, liver, and bone.[35] In another study of 57 patients, SPECT/CT of the neck determined nodal involvement more accurately than did planar imaging and altered clinical management in approximately one quarter of patients.[36] In another study of 151 patients, post-therapy SPECT/CT of the neck showed lymph node metastases in 26% of T1b cancers and 22% of the microcarcinoma group.[37] In a retrospective study of 147 patients with differentiated thyroid cancer, SPECT/CT improved detection and localization of I-131 in nodal and distant metastases as compared with whole-body planar imaging and changed clinical staging in 9 of 147 patients (6.1%) and therapy planning in 3 of 147 patients (2%).[38]

The antitumor effect of I-131 depends on the amount of RAI that can be delivered successfully to the target lesion ("lesional activity").[39-42] Without "lesional dosimetry" to quantify the amount of RAI accumulating in a given disease site (thus allowing some prediction of the efficacy of RAI treatment), the amount of I-131 administered for metastatic disease must be determined empirically or using whole-body dosimetry. The latter yields an MTA, defined as the highest activity that can be administered without toxicity to bone marrow and lungs[43] (MTA is the activity of I-131 that results in a dose of 200 rads to blood and in a retained activity of $\leq$80 mCi in the lungs at 48 hours—the latter is usually relevant only in patients with diffuse lung metastases). However, there may be considerable heterogeneity of RAI uptake among lesions. This can be addressed by lesional dosimetry only with I-124 PET/CT, which permits quantification of iodine uptake in each disease site and thus individualized, patient-specific treatment planning.[44] Maxon et al[41] determined that a dose of at least 8000 rads is needed to achieve complete destruction of thyroid cancer metastases and at least 30,000 rads for the thyroid remnant. Except for lesional dosimetry, no other techniques exist to predict which patient with metastatic thyroid cancer would respond to RAI therapy. Therefore, in practice, many patients would be treated repeatedly with RAI, using "empirical" activities; however, this may well be ineffective and could cause potential morbidity.[45,46]

External-beam radiotherapy (EBRT) is rarely employed in the management of differentiated thyroid cancer. However, it is a meaningful adjuvant modality in patients >45 years of age with gross unresectable tumor or significant extrathyroidal extension in whom further surgery or RAI would not be effective.[1] In an earlier study from our institution, EBRT provided effective locoregional control in a select group of locally advanced or recurrent nonanaplastic thyroid cancers, with 2- and 4-year overall locoregional control rate of 86% and 72%, respectively.[47] In a more recent study with 66 patients, these data were confirmed: EBRT alone or in conjunction with chemotherapy proved safe and effective, providing locoregional control in 90% of patients undergoing concurrent chemoradiotherapy and >85% locoregional control in patients with no metastases.[48]

PET/CT Imaging With Iodine-124 and F-18 FDG

I-124 is a positron emitter with a half-life of 4.2 days; approximately 22% of the disintegrations produce positrons of relatively high energies as well as high-energy gamma and x-rays.[49,50] Most published studies using I-124 PET or PET/CT include only small numbers of patients due to logistical challenges and expense of I-124. Therefore, conclusions remain somewhat preliminary. Nevertheless, it has been shown convincingly that I-124 PET/CT is more sensitive in detecting metastatic disease than gamma camera imaging with I-131[51-54] (Fig. 1). For instance, in a study of 25 patients, I-124 PET identified 50% more sites of disease than the pretreatment ("diagnostic") scan with I-131 dosimetry scans in 32% of patients.[52] I-124 PET/CT also enables lesional dosimetry. In a retrospective study of 34 patients, I-124 PET allowed for reliable volume estimation (>0.80 ml) in 59 lesions of 17 patients.[55] In another study, I-124 PET lesional dosimetry was used to calculate the amount of RAI needed to achieve doses of $\geq$100 Gy to all metastases without exceeding dose of 2 Gy to the blood; I-124 PET led to a change in management in 25% of patients.[56] In another study, 15 of 30 patients with known metastatic disease showed no I-124 uptake on serial scans (4, 24, 48, and 72 hours), despite sufficiently high TSH levels, suggesting that these lesions would also be refractory to I-131 treatment.[57] A smaller study in 12 patients disagreed with this conclusion and suggested that I-124 PET should not be used in isolation to prevent treatment with I-131.[58] However, it should be realized that uptake of I-131 alone on posttreatment scans is not sufficient for response, unless the local dose from accumulated iodine is tumoricidal. The probability of achieving tumoricidal doses is best predicted by I-124 PET.

An inverse relationship between FDG avidity and radioiodine uptake (originally described by Feine as the flip-flop phenomenon,[59] Fig. 2) is often seen in metastatic thyroid cancer lesions; increased FDG uptake is generally associated with decreased disease-specific survival.[60] In general, FDG avidity increases and iodine avidity decreases as tumors or metastases dedifferentiate, which is associated with increasing disease aggressiveness, refractoriness to RAI therapy, and poorer prognosis.[61] A histopathologic study also showed that most metastases in patients with radioiodine-refractory, FDG-

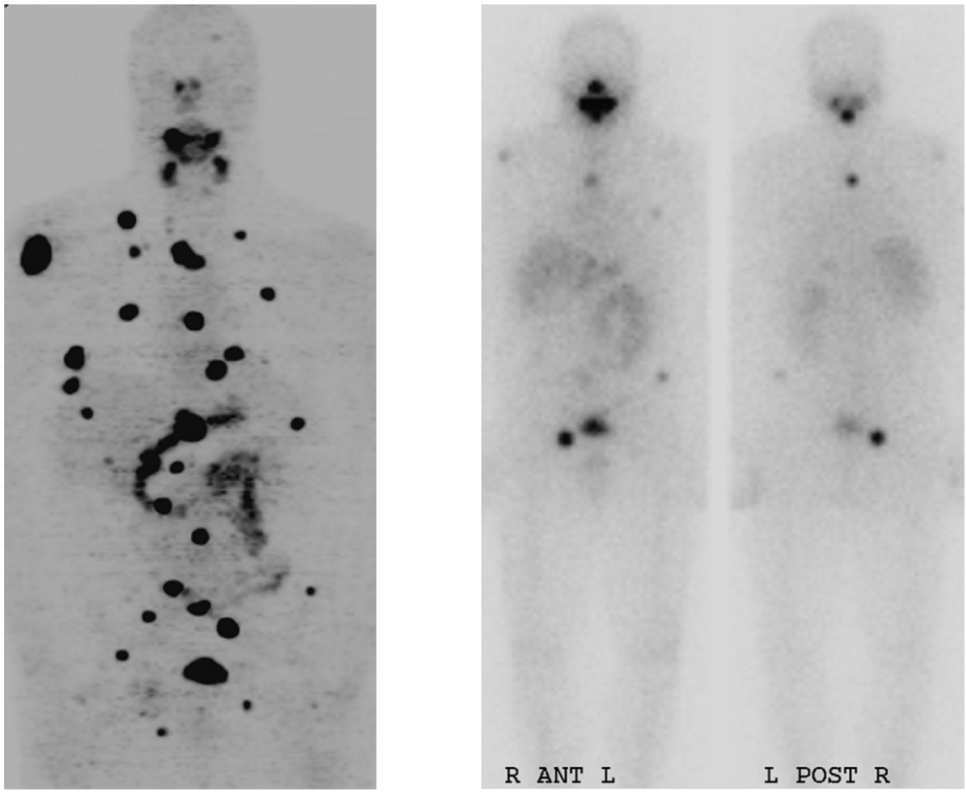

Figure 1 I-124 PET MIP scan showing uptake in multiple bone metastases. I-131 Post-therapy scan performed approximately 4 years earlier showed uptake in a few bone metastases.

positive metastases were of histologically aggressive subtypes.[62] However, the "FDG-iodine flip-flop" is not an all-or-none phenomenon. On one extreme side of this spectrum are anaplastic carcinomas, which are reliably avid to FDG and in which the intensity of FDG uptake is correlated with survival.[63] On the other end of the spectrum are metastases from well-differentiated papillary carcinomas that show intense iodine uptake, but no FDG uptake. In patients with truly advanced disease, there is usually a spectrum of metastatic lesions—some avid more or only to iodine, and some avid more or only to FDG. The presence, intensity, and extent of FDG-avid disease provides prognostic information, helps guide therapy (even high activities of RAI have little or no therapeutic effect on FDG-avid metastases[64]), and may aid in treatment monitoring (a decline in FDG uptake may indicate a response to novel targeted drugs in patients with advanced thyroid cancer). The prognostic value of FDG-PET in advanced thyroid cancer was well documented in a classic study with 125 patients in whom survival was lower among patients with FDG-positive disease as compared with patients without FDG-avid lesions: patients with a volume of FDG-avid disease >125 ml had a significantly shorter survival.[65] FDG-PET may also help in the management of patients with differentiated thyroid cancer presenting with elevated Tg levels but a negative I-131 scan; in this setting, FDG-PET may be most useful when Tg levels are greater than 10 mcg/ml.[66-69] Beyond the volume of FDG-avid disease, the intensity of FDG uptake in metastatic lesions, measured as standardized uptake value, further refines the prognostic information of this test. In a retrospective study of 400 patients with thyroid cancer, FDG standardized uptake value and number of FDG-avid lesions were correlated with poor survival. Among all patients, those with local neck disease had the best survival, those with regional metastases (eg, in supraclavicular or mediastinal nodes) fared slightly worse, and patients with distant metastases had the lowest overall survival[67] (Fig. 3). For all of these aforementioned reasons, postoperative FDG-PET is recommended to be performed routinely in patients with thyroid cancer and aggressive histologies to establish a reference stage for future follow-up. In this retrospective study of 20 patients with a total of 86 lesions, FDG-PET was more sensitive than postablation radioiodine scan for detection of lesions (69% vs 59%).[70]

Discoveries in Thyroid Cancer Biology Provide a Rationale for Novel Targeted Therapies

Oncogenic Signaling Diminishes Iodide Avidity in RAI-Refractory Thyroid Cancer

Recent advances in targeted molecular therapies have helped us in better understanding those patients who may benefit from I-131 therapy and identify other patients who may benefit from new therapeutic approaches.[71] Patients with RAI-refractory (RAIR) metastatic tumors that either lack or lose the ability to trap iodide possess a worse prognosis: the 10-year survival of patients with metastatic lesions retaining RAI avidity

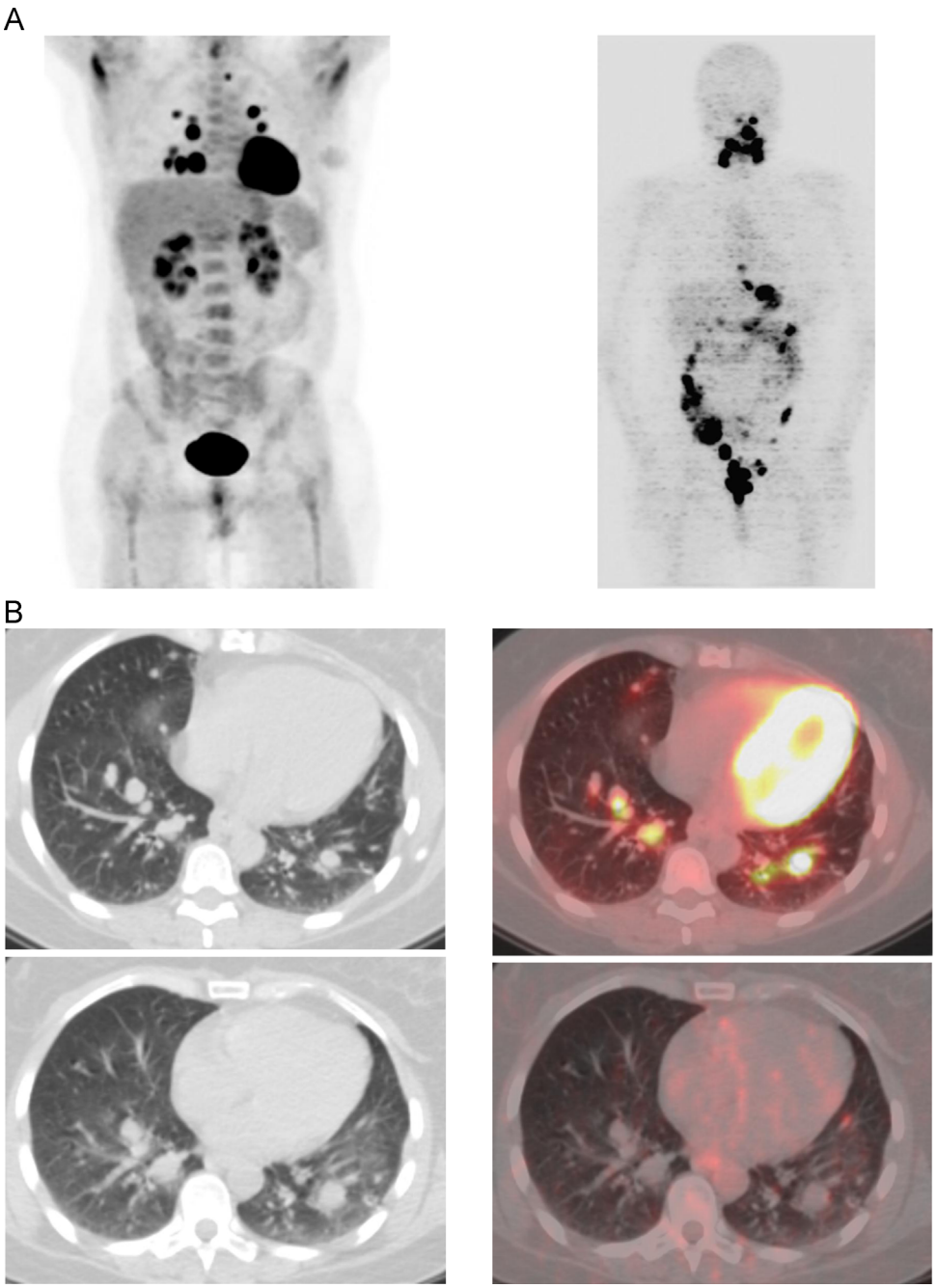

Figure 2 (A) Flip-flop phenomenon showing multiple FDG-avid lung metastases, which are not iodine avid on I-124 PET scan. (B) Flip-flop phenomenon showing multiple FDG-avid lung metastases, which are not iodine avid. Top row transaxial images are FDG-PET and bottom row transaxial images are I-124 PET.

is approximately 60%, but only 10% for patients with RAIR disease.[16] Over the past decade, multitargeted tyrosine kinase inhibitors, which are thought to block tumor angiogenesis by inhibiting multiple receptor tyrosine kinases (eg, vascular endothelial growth factor receptor and platelet-derived growth factor receptor), have emerged as new treatment modalities for metastatic thyroid cancer. Based on these data, the Food and Drug Administration approved the tyrosine kinase inhibitors sorafenib and lenvatinib for the treatment of RAIR thyroid cancer[72,73] (Fig. 4). The challenge of these therapies is the need to maintain continuous drug dosing and manage the accompanying drug toxicities to realize clinical benefit. In a multicenter, randomized, double-blind, placebo-controlled phase 3 trial with sorafenib in progressive RAIR differentiated thyroid cancer, sorafenib improved progression-free survival compared with placebo (10.8 months with sorafenib vs 5.8 months with placebo).[72] In another multicenter phase 3 randomized, double-blind study of patients with progressive thyroid cancer comparing lenvatinib vs placebo, the median progression-free survival was 18.3 months in the lenvatinib group vs 3.6 months in the placebo group. There were four complete responses (64.8%) in the lenvatinib group and 1.5%

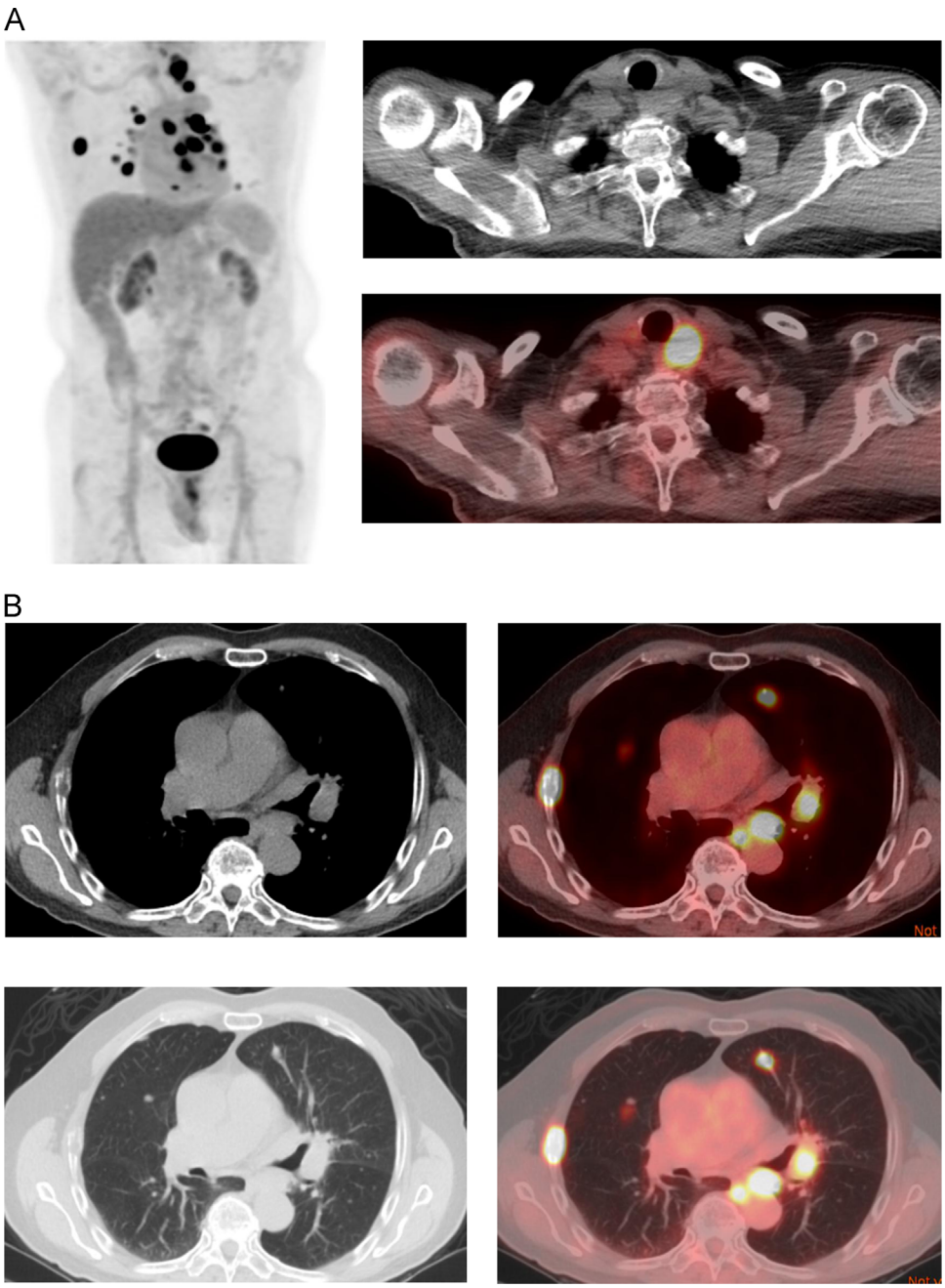

Figure 3 (A) FDG-PET MIP scan shows uptake in left tracheoesophageal groove mass, lung, thoracic nodal, and osseous metastases. (B) FDG-PET shows uptake in lung, thoracic nodal, and osseous metastases. MIP, maximum intensity projection.

in the placebo group.[73] Of note, in the phase 3 trials, the rate of dose interruption, reduction, and discontinuation was significant for both sorafenib and lenvatinib, which may undermine the benefits of these therapies.[72,73] For these patients, developing a novel strategy of restoring the efficacy of I-131 would provide a therapeutic alternative for managing metastatic disease with a discrete period of treatment, and potentially delay the need to initiate continuous drug therapy.

Current experimental strategies aim to target oncogenic signaling pathways that diminish iodide avidity in thyroid cancer. For instance, activation of the mitogen-activated protein kinase (MAPK) signaling pathway (RET-RAS-RAF-MEK-ERK) is a central oncogenic event for the development of most thyroid malignancies. The pathway is aberrantly activated primarily through mutually exclusive genetic alterations in the growth factor receptor RET, the three isoforms of RAS (N, H, and K), and BRAF, one of which is present in ~70% of papillary thyroid carcinomas (PTCs).[10,74-76] The $BRAF^{V600E}$ mutation is the most common genetic alteration in PTC.[10,77]

Beyond promoting cellular proliferation and survival, oncogenic activation of MAPK signaling suppresses the expression of follicular cell-specific genes that are responsible for iodide uptake (eg, NIS) and metabolism.[78-80] Additionally, each

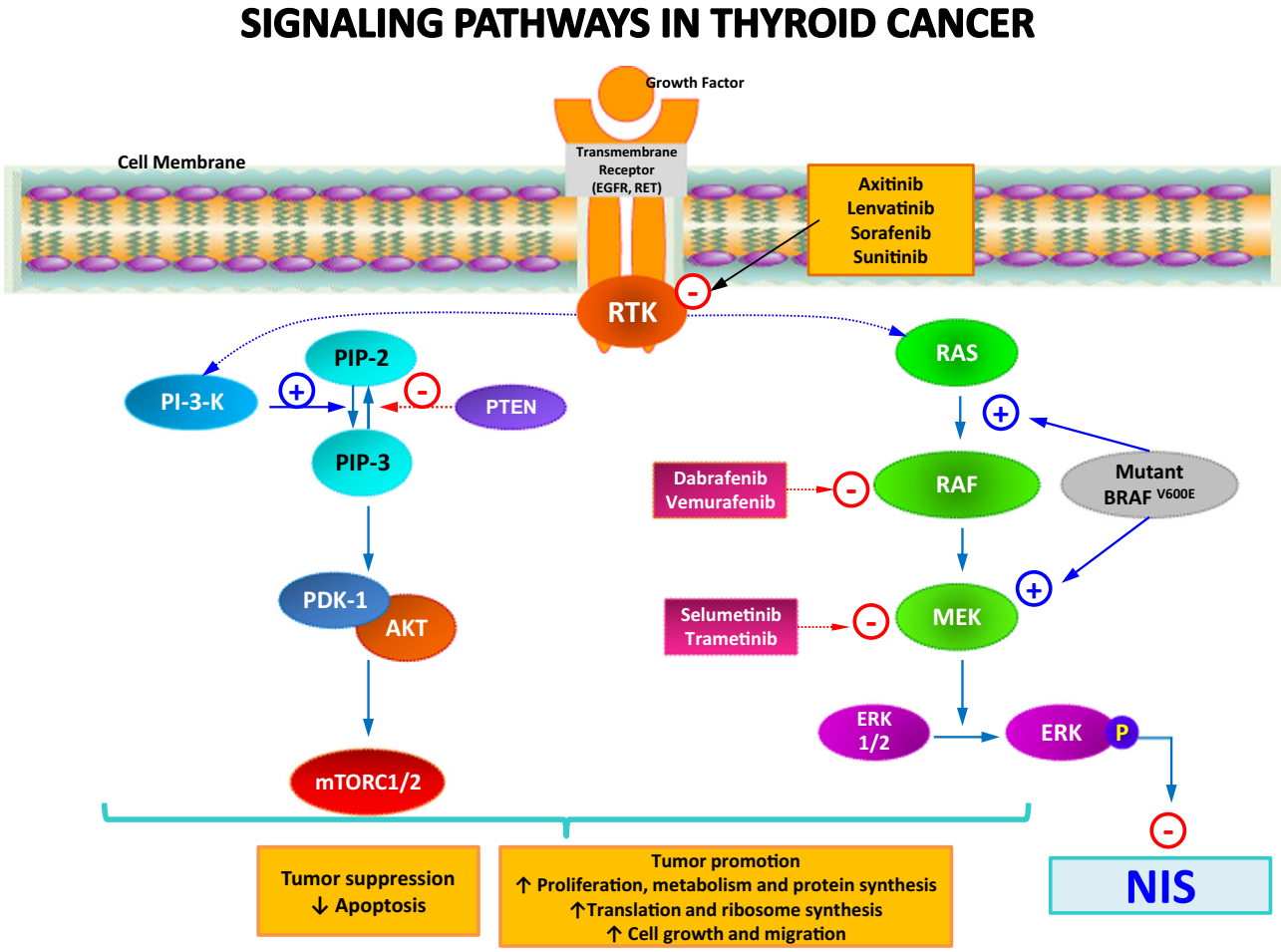

Figure 4 Signaling pathways in thyroid cancer.

MAPK pathway alteration is also associated with different degrees of MAPK signaling output: BRAF-driven cancers possess higher MAPK output relative to RAS-driven cancers.[81] The differential effect on MAPK signaling output also translates to differences in suppression of thyroid differentiation. The Cancer Genome Atlas genomic analysis of almost 500 PTCs demonstrated that higher MAPK output tumors (eg, "BRAF mutant cancer—like") exhibit greater suppression of thyroid differentiation than other tumors (eg, "RAS mutant cancer—like").[82] This biology provides the mechanistic basis of the well-established clinical observation that BRAF mutant tumors have a more aggressive clinical behavior and are more often refractory to RAI.[83-85] In aggregate, these observations suggest that oncogenic MAPK pathway activation in thyroid malignancies diminishes iodide avidity by suppressing components of thyrocyte-specific gene expression; the extent to which this is achieved is determined by the specific MAPK pathway alteration.

MAPK Pathway Inhibition to Enhance RAI Avidity and Efficacy

Experiments in cell line and animal models provided proof-of-principle data that pharmacologic manipulation of the MAPK pathway with small molecule inhibitors may be a novel approach for enhancing iodide avidity. In a mouse model of poorly differentiated thyroid cancer driven by inducible thyroid-specific expression of $BRAF^{V600E}$, treatment with downstream MAPK pathway inhibitors targeting either BRAF or MEK partially restored expression of *NIS* and iodine avidity.[86] These preclinical data led to a pilot clinical trial evaluating the effect of the MEK inhibitor Selumetinib on iodide uptake in patients with RAI-refractory thyroid cancers.[87] In this study, recombinant human TSH (rh-TSH) I-124 PET/CT lesional dosimetry was used to quantify drug-induced changes in iodide incorporation within specific lesions. Of the 20 evaluable patients, 12 (60%) had new or increased I-124 incorporation with Selumetinib. For eight (40%) patients, the I-124 uptake predicted that $\geq$2000 cGy of I-131 could be delivered; these patients were treated with Selumetinib in combination with therapeutic I-131. These changes in iodide incorporation translated to clinical benefit, as all eight patients treated with I-131 experienced reductions in tumor size. In total, there were five confirmed partial responses and three patients had stable disease. Substantial decreases in serum Tg level were also achieved in all patients. This approach appeared to be particularly effective for patients harboring the *NRAS* mutation, as all five enrolled on the study qualified for treatment with I-131. By contrast, only one patient with *BRAF* mutation received I-131 treatment. This pilot study provided a

critical proof-of-concept that MAPK pathway inhibition can enhance RAI incorporation and efficacy in a subset of RAIR patients. Much remains to be investigated in clinical trials before this approach can be introduced into regular clinical practice. The differences in efficacy observed within different genetic subsets of disease and the heterogeneity in the degrees of enhancement in iodide avidity achieved in the pilot study suggest that there is still opportunity to optimize pathway inhibition and restoration of thyrocyte-specific gene expression with alternative MAPK pathway inhibitors alone or in drug combinations. For patients with BRAF mutation, treatment with a BRAF inhibitor may be a more promising approach: a recent pilot trial showed that dabrafenib increased iodide incorporation in six of ten patients with BRAF mutation, resulting in tumor shrinkage after subsequent treatment with I-131 in five of the six patients (two partial responses and four patients with stable disease).[88]

Other Targeted Drugs

Romidepsin (a histone deacetylase inhibitor) has been studied in a group of 20 patients with RAIR thyroid cancer. Restoration of radioiodine avidity was documented in two patients. No major response evaluation criteria in solid tumors (RECIST) responses were documented; stable disease was seen in 13 and progressive disease in seven patients. This study had poor accrual after a grade five adverse event.[89] Another drug, axitinib (a selective inhibitor of vascular endothelial growth factor receptors 1, 2, and 3), was studied in 60 patients with advanced thyroid cancers in a multi-institutional phase 2 trial; partial responses were seen in 18 patients (30% objective response rate), and 38% patients showed stable disease at ≥ 16 weeks.[90]

In summary, although some of the data discussed in this section appear promising, optimizing and defining the efficacy and safety of various novel drugs would be accomplished only through larger prospective clinical trials. Imaging, including PET/CT with I-124 and FDG, as well as SPECT/CT with I-123 and I-131, would be a critical part of clinical trials and would be essential to guide and monitor novel targeted therapies. We expect that these therapies would ultimately translate into improved outcomes for patients with advanced thyroid cancer over the next decade.

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