A New Theranostic Paradigm for Advanced Thyroid Cancer

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The successful use of $^{131}$I as a systemic treatment of a patient with metastatic thyroid cancer was first reported in 1948 1. This agent has subsequently become firmly established as part of the treatment of high-risk thyroid cancer and especially for metastatic disease. There has been an evolution in the quality of assessment of the distribution of radioactive iodine (RAI) within the body, progressing from Geiger-Muller counting to imaging; first with the rectilinear scanning and then with the gamma camera. The physical characteristics of $^{123}$I as a diagnostic tracer compared with $^{131}$I, further improved imaging by facilitating higher quality SPECT and SPECT/CT. More recently, use of $^{124}$I PET/CT has further increased the sensitivity for detection of differentiated thyroid cancer and offers the promise of prospective dosimetry estimation 2. Uptake of all these forms of RAI relies on the presence of functional sodium-iodide (NaI) symporters, which are required for efficacious treatment with $^{131}$I.

Augmenting thyroid stimulating hormone (TSH) levels by combined use of thyroid resection and either withholding thyroid hormone or use of recombinant human [rh]-TSH to stimulate RAI uptake has further improved the diagnostic paradigm of DTC as has preparation of patients using a low iodine diet and avoidance of iodine-containing radiographic contrast agents or drugs, e.g. amiodarone. Consequently the proportion of truly non-RAI avid disease has diminished. The role of $^{18}$F-fluorodeoxyglucose (FDG) PET/CT is now well established for detection and staging of disease in the context of abnormal structural imaging or elevated serum thyroglobulin (Tg generally > 10ng/ml) but negative radioiodine imaging 3. The
combined use $^{18}$FDG PET/CT in appropriate cases has reduced the role of empiric $^{131}$I therapy, particularly by localizing regional disease amenable to salvage surgery or radiotherapy. In some cases of metastatic disease, disease heterogeneity can be demonstrated with lesions with the highest FDG uptake tending to be poorly differentiated as evidenced by loss of avidity on iodine imaging. Better localization and characterization of disease sites using these complementary techniques allows more rational selection and monitoring of patients with metastatic disease.

Differentiation status and metabolic reprogramming are increasingly being recognized as determinants of imaging phenotype. In contrast to well-differentiated tumours, which are reliant on mitochondrial oxidative phosphorylation to generate the energy needed for cellular processes, poorly differentiated cancer cells depend on the inefficient mechanism of aerobic glycolysis—the Warburg effect. Notably, Hurthle cell (or oncocytic) tumours, both benign and malignant, are generally characterised by very intense FDG-avidity representing inherent constitutive activation of glycolytic pathways. Loss of the mitochondrial respiratory chain complex I has been shown to be a marker of this oncocytic phenotype. Further phenotypic differences are reflective of genomic changes associated with neoplastic transformation, particularly including mutations involving the mitogen-activated protein kinase (MAPK) pathway. These provide potential therapeutic targets for non-iodine-avid thyroid cancer. The multikinase inhibitors lenvatanib and sorafenib have recently demonstrated significant improvement in progression-free survival in phase III trials of progressive radiiodine refractory disease, albeit with significant toxicities. Ho et al. pioneered re-differentiation therapy in advanced thyroid cancer using a four-week course of the MEK-inhibitor selumetenib to restore expression of Nal Symporter, allowing I-131 therapy, particularly in patients with NRAS mutations. There is favourable early data from patients with advanced thyroid cancer and BRAF<sup>V600E</sup> mutations treated with BRAF-inhibitors such as Vemurafenib. The Cancer Genome Atlas Research Network’s reclassification of papillary thyroid cancer into BRAF<sup>V600E</sup>-like or RAS-like molecular subtypes may potentially be used to stratify management of advanced thyroid cancer in the future.

This “dual tracer” approach seems to address most cases of differentiated thyroid cancer. However, the paper by Binse et al in this issue of the *Journal of Nuclear Medicine*...
reference when available) addresses a small subgroup where this paradigm still fails to identify a reason for persisting Tg elevation. In such cases it might be assumed that the volume of disease is below the limits of imaging detection. However, the current paper challenges this idea by demonstrating the utility of somatostatin receptor (SSTR) imaging to detect previously occult disease. Their small consecutive series identified that uptake of 68Ga-DOTATOC, which targets SSTR subtypes 2 and 5, was most prevalent in patients with poorly differentiated or oncocytic carcinomas (4/4), compared to papillary (1/5) or follicular (0/6) thyroid cancers. Notwithstanding the limitations inherent in a retrospective study, including inconsistent RAI imaging methodology and timing, these findings are intriguing since poorly differentiated gastro-entero-pancreatic neuroendocrine tumours (GEP-NET) typically lose SSTR expression\(^\text{13}\). The exception to this rule is insulinoma, where a significant proportion of benign insulinoma (approximately one third) lack SSTR\(^\text{14}\), whilst it is maintained in the vast majority of malignant lesions making it a suitable target for peptide receptor radionuclide therapy\(^\text{15}\,\text{16}\). Unlike in most GEP-NET, a prior immunohistochemical study in thyroid malignancy demonstrated predominant expression of SSTR-5 rather than SSTR-2\(^\text{17}\), favouring radioligands with affinity SSTR-5 (e.g. 68Ga-DOTANOC or 68Ga-DOTATOC) over SSTR-2 ligands (e.g. 68Ga-DOTATATE) in this disease. Hurthle cell carcinoma has been previously reported as having increased SSTR expression, comprising the majority of cases in a previous small series treated with peptide receptor radionuclide therapy (PRRT)\(^\text{18}\). While localisation of disease in 33% of cases in the current study provides the opportunity for additional local therapy, the relatively modest intensity of uptake identified within this small series (mean SUV\text{max} 4.8, range 3.0-10.1) suggests that only a minority of cases will demonstrate sufficient uptake to enable PRRT.

Whilst it is not uncommon for poorly differentiated or oncocytic thyroid cancer to be non-RAI avid, these subtypes typically demonstrate the greatest 18FDG avidity. For example, a previously reported comparison of 18FDG and 68Ga-DOTATOC in 17 patients with 104 lesions demonstrated that loss of SSTR expression coincided with a loss of iodine uptake\(^\text{19}\). Whilst there was a similar incidence of 18FDG and 68Ga-DOTATOC uptake in iodine avid lesions, as expected, 18FDG performed significantly better than 68Ga-DOTATOC in the 73 non-iodine avid cohort. This makes the findings of the current study even more unusual.
In addition to a need to verify these findings in larger prospective studies, it will be important to better understand the biological basis for SSTR expression in the thyroid and its role in cell signalling. This study certainly broadens the potential role of \textsuperscript{68}Ga-DOTATOC PET/CT to include cases of thyroid cancer with elevated Tg despite negative RAI and FDG PET/CT. It also provides a unique opportunity to review the current role of molecular imaging in advanced thyroid cancer, and outline a new theranostic paradigm incorporating SSTR imaging for this heterogeneous disease (Figure 1).
REFERENCES:


Figure 1: Proposed theranostic paradigm for advanced thyroid cancer utilising dual tracer imaging with TSH stimulated $^{124}$I and $^{18}$FDG PET/CT to direct subsequent management, including $^{68}$Ga-DOTATOC PET/CT in those cases with non-localised disease despite elevated thyroglobulin. TSH, thyroid stimulating hormone; MEK-i, MEK inhibitor; BRAF-i, BRAF-inhibitor; EBRT, external beam radiotherapy; PRRT, peptide receptor radionuclide therapy.
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