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Functional Imaging In Carcinoma Thyroid

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ABSTRACT:

Thyroid imaging is a rapidly evolving field that has received numerous addendum. In current scenario thyroid imaging is not limited to structural imaging but it has included numerous functional imaging modalities ranging from years old Iodine based imaging to PET and SPECT-CT. Of these functional imaging modalities FDG-PET has generated greatest interest with perhaps the greatest utility being the potential localization of tumor in differentiated thyroid cancer(DTC) patients who are radioiodine whole body scan (WBS) negative and thyroglobulin (Tg) positive. It is also useful in identification of patients unlikely to benefit from additional 131I therapy and in identification of patients at highest risk of disease-specific mortality, which may prompt more aggressive therapy or enrollment in clinical trials. Emerging data suggest that PET/CT fusion studies provide increased accuracy and modify the treatment plan in a significant number of DTC cases whereas studies documenting it's utility in Medullary&Anaplastic thyroid cancer are scarce. Another potential utility of FDG-PET is in guided surgery to assist in tumor localization in radio-iodine negative, FDG-PET positive DTC patients. Currently studies documenting improvements in survival and tumor recurrence attributable to FDG-PET imaging in thyroid cancer patients are lacking.Diffusion MRI is being studied in predicting the malignant potential of thyroid nodules.Studies documenting the utility of SPECT-CT fusion

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imaging are limited to identification of residual foci in neck and systemic metastasis. This article reviews the utility and limitations of functional imaging modalities in thyroid cancer management, and offers practical recommendations

1. INTRODUCTION:

Thyroid cancer is most common endocrine malignancy, accounting for 94.6% of the total new endocrine cancers, and 66.0% of the deaths due to endocrine cancers. The discrepancy between the total number of cases of all endocrine cancers arising in the thyroid (94.6%) and the total proportion of endocrine cancer deaths (66.0%) reflects the relatively indolent nature and long-term survival associated with thyroid malignancies.

In recent years thyroid imaging has made exponential progress, considerably changing the approach to diagnosis, treatment, prognosis, follow-up and evaluation of thyroid cancer. Moreover this notable technical advance has proven its ability for identification of incidental thyroid nodules and the achievement of more accurate evaluation of recurrent/residual thyroid carcinoma.

Imaging technologies used to assess patients with thyroid cancer may be subdivided into structural and functional imaging categories. Structural imaging entails the assessment of morphologic features of thyroid malignancy and that of adjacent structures within which it is confined. Functional imaging is comprised of a multitude of noninvasive imaging techniques that are currently in use to probe tumor molecular processes, and to study tumor physiology, in vitro and in vivo. Functional imaging can be implemented through use of diffusion-weighted imaging (DWI), dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI), magnetic resonance spectroscopy (MRS) as well as through positron emission tomography (PET) and single-photon emission computed tomography(SPECT).

2. RATIONALE FOR FUNCTIONAL IMAGING:

Cross-sectional structural imaging by CT, MRI, and US is currently used in standard clinicalpractice on a daily basis to qualitatively or semi quantitatively detect,

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characterize, stage,assess posttherapeutic response, and determine recurrence of malignant tumors. Theseimaging techniques are based on structural features such as tumor shape, size, margins, location, spatial extent, attenuation (on CT), signal intensity (on MRI), echogenicity (on US), or gross degree of enhancement afterintravenous contrast administration. Despite its many contributions to the management of patients with cancer, structural imaging alone suffers from many shortcomings in such settings.

The first is that alteration in tumor tissue at the molecular, sub-cellular, or cellular levels proceed in time to gross macroscopic changes in tissues or organs due to cancer [1], [2].This has significantimplications with regard to early detectionof cancer for screening purposes, as well as formonitoring response to therapeutic intervention. The second is that macroscopic abnormalitiesare often nonspecific and often seenin nonneoplastic conditions. For example,enlarged lymph nodes in the setting of known malignancy may be either be due to metastaticdisease or due to reactive hyperplasia in inflammatory disease [3]. The third is thatdata regarding molecular characteristics, biological processes and physiology of tumors are notobtained. As such, structural imaging at a singletime point may not provide adequate informationregarding patient prognosis, probabilityof tumor response to therapeutic intervention,and new drug development.

2.1 Radio-iodine and Non radio-iodine based Thyroid Scintigraphy:

It is a planar imaging technique using gamma camera using various radiopharmaceuticals, most commonly 99mTcO4, Iodine-123-iodide (123I) and Iodine-131-iodide (131I). Use of 123-I and 131-I is more physiological as Iodine is trapped and metabolized by thyroid follicular cells whereas 99mTcO4 undergoes no further alteration in thyroid cells. Routine use of 131-I and 123-I in clinical thyroid scintigraphy is somewhat unpractical due to their logistic and physical limitations. 123I is a cyclotron product and therefore not universally available and relatively expensive moreover it has pure gamma emission of 159 KeV and is ideal for in vivo gamma camera imaging with a reasonable half-life of 13 hours.

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Radioiodine 131-I has been superseded by 99mTcO4 for thyroid imaging due to its higher gamma emission of 364 KeV and long half-life of 8 days leading to noisy images and un-necessary high radiation burden. In addition to its therapeutic function that stems from its beta emissions, it has retained its imaging function in post-surgical follow-up of differentiated thyroid carcinoma.

Other radiopharmaceuticals, with different mechanism of uptake, include 201Tl or 99mTc-MIBI [4], [5] which is used in the assessment of cold nodules and post-surgical follow-up especially in noniodine avid thyroid carcinoma.

2.2 Positron Emission Tomography Scan:

PET and now PET/CT are recent addition in thyroid cancer imaging armamentarium. The concept of fusion of anatomic and metabolic imaging as "anatometabolic" images has been present for nearly 15 years, but has been transformed into a valuable clinical practice only quite recently. PET is a type of emission computed tomography that is used to study the distribution of radiolabeled tracers within the body. PET radiotracers emit positrons that, after encountering electrons, lead to emission of 2 gamma rays directed at 180 degrees from each other. Sites of tracer accumulation in the body are thus determined by detection of these paired gamma rays, which is termed "coincidence detection."Currently,whole-body PET-CT has been approved foruse in assessing suspected recurrenceof well-differentiated thyroid cancer(WDTC) in patients with radioiodinenegativescans and detectable thyroglobulin(Tg) levels.

FDG-PET in the Assessment of Incidentalomas: Thyroid incidentaloma is defined as a newly identified thyroid lesion encountered during an imaging study for non-thyroidal disease . Due to the increasingly extensive use of ultrasound (US), computed tomography (CT), magnetic resonance (MR) and 18F-FDG PET imaging, an incidental finding of a nonpalpable thyroid nodule is a common problem. Structural imaging techniques cannot accurately differentiate between benign and malignant thyroid nodules. Most centers use fine needle-aspiration (FNA) cytology for this purpose. However, FNA has several shortcomings, such as its inability to

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provide a diagnosis due to sampling error or its inability to clearly differentiate benign follicular adenomas from welldifferentiated follicularcarcinomas [6]. The ability to better distinguish benign from malignant incidentalomascould be achieved with functional imaging and might spare patients undergoing unnecessary investigations and surgical resection.

The normal thyroid gland shows low grade FDG uptake or is usually not visualized on the whole-body 18F-FDG PET scan [7], [8]. Diffuse increased thyroid FDG uptake is usually an indicator of chronic thyroiditis [9] but has also been described in Grave's disease [10]. Several retrospective studies have assessed the incidence and causes of focal increased uptake within the thyroid gland on 18F-FDG PET. There isdisagreement on standard uptake value (SUV) which can differentiate between benign and malignant thyroid nodules. A retrospective study by Bogsrud*et al* [11]reviewed 18F-FDG PET-CT scans performed over a three-year period and measured the maximum SUV (SUVmax) of thyroid incidentalomas. They found focal incidental high uptake in79/7,347 patients (1.1%). Of these, 48 patients had adequate follow up enabling correct diagnosis. A benign etiology was determined in 31/48 (64.6%), while 17/48 patients (35.4%) had malignancy confirmed or had FNA highly suspicious of malignancy, with papillary carcinoma confirmed in 12/17 of those malignancies. Median SUVmax for the benign group was 5.6, range 2.5-53.Median SUVmax for the malignant lesions was 6.4, range 3.5-16. SUVmax between benign and malignant groups was not statistically different (p=0.12). There have been other retrospective studies using 18F-FDG PET. In patients who had adequate follow-up, Cohen *et al.* (12), Kang *et al.* (13) and Kim *et al.* (14) found malignancy in 47% (7/15), 27% (4/15) and 50% (16/32), respectively.

Despite the non-discriminatory value of SUV mentioned earlier, a significant number of studies have found it to be useful in differentiating benign from malignant focal thyroid lesions. Bloom *et al.* [15] looked at 12 patients with focal thyroid uptake. Four malignant lesions (3 papillary and 1 follicular carcinoma) all had SUVmax>8.5. The 8 benign lesions (follicular adenomas) had SUVmax<7.6. Supportive data comes from Cohen *et al.* [12] who found that seven patients with

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malignant thyroid lesions had significantly higher SUV on average (6.92±1.54, range 4.1-14.5), compared with seven patients with benign lesions(3.37±0.21, range 2.9-4.9).

PET Scan in followupof WDTC:PET-CT scan is mainly used in detection of recurrentdisease in patients with negativeradioiodine scans.[16-21]WDTCs are generallyslow-growing and retain somecapacity to concentrate iodine. However,if the cancer becomes more poorlydifferentiated, it gradually loses thiscapacity—mainly due to decreased expression of the sodium-iodine symportersand becomes undetectable by the radioiodine scan. By virtue of their increased growth rate and subsequent increased utilization of glucose, these lesions then become detectable by FDG PET-CT imaging . The radioiodine and the PET-CT scans are, therefore, complementary in this clinical scenario. [19]

In a meta-analysis of 17 studies comprising 571 patients, the pooled sensitivity and specificity of FDG PET-CT in patientswith recurrent cancer but negative radioiodine scanswere shown to be 0.835 and 0.843, respectively [22]. Detection of recurrence on the PET-CT scan has been shown to correlate positively with thyroglobulin levels,[23] suggesting that small lesion volume may be a cause of false-negative studies.

Role of rhTSH in FDG PET-CT: Several glucose transporters (Glut) have been described that move glucose into cells. Glut1 is expressed in aggressive thyroid carcinomas. TSH stimulation increases glucose metabolism in thyroid cells, and increases Glut 1 expression. Triiodothyronine and Levothyroxine may increase both Glut1 and Glut4 expression. These findings suggest that recombinant human TSH (rhTSH) may offer the unique opportunity to take advantage of both mechanisms by continuing exogenous thyroid replacement/ suppression and simultaneously providing TSH stimulation.

Petrich et al. [24] investigated 30 patients with FDG-PET during TSH suppression and again after rhTSH. During TSH suppression, PET scans were positive in 30% with identification of 22 tumor-like foci. After rhTSH, 63% had positive PET scans with 78 tumors-like foci identified (15 of these 78 foci were subsequently confirmed as tumor). Although it is logical to accept that rhTSH can be used to

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improve the sensitivity of FDG PET-CT for thyroid malignancy, more data are needed to determine the true usefulness of rhTSHin this indication.

Iodine-124 as a PET radiopharmaceutical : Because of the spatial resolution limitations of 123I or 131I and the widespread availability of PETCT imaging, interest is growing in using 124I and PET to image thyroid malignancies. 124I, a positron-emitting isotope with a half-life of 4.2 days, combines the resolution and localization advantages of PET-CT with the specificity of an iodine-based tracer in imaging the thyroid.

Freudenberg et al[25]compared 124I PET-CT with FDG PET-CT in patients with elevated thyroglobulin but negative ultrasonography and found the sensitivities forWDTC detection to be 80% and 70%, respectively. Other recent articles have also pointed out therole of 124I in recurrence detection, as well as in quantifying patient-specific radioiodine therapydosimetry prior to ablation [26], [27].

Medullary thyroid cancer: Currently, FDG PET-CT in medullary thyroid cancer is most commonly used in cases where conventional imaging modalities are negative or inconclusive in the presence of raised tumor markers such as calcitonin and carcinoembryonic antigen (CEA). Some studies show that FDG PET-CT is superior to conventional modalities, such as ultrasound, contrast enhanced CT, and 111In octreotide scans in the detection of recurrent MTC.[28,29] However, the diagnostic accuracy of FDG PET-CT for MTC is limited compared with its use in WDTC. Overall sensitivity has been reported to range from 47.4%[30] to 80%;[31] however, detection rates seem to improve in patients with higherserumcalcitonin levels.

18F-dihydroxyphenylalanine(18F DOPA) and 68Ga-DOTA peptides that bind to somatostatin receptors, such asDOTA-TOC and DOTA-NOC, are also being evaluated for this indication.

Anaplastic thyroid cancer: Due to its aggressive growth andsubsequent significantly elevated glucoseutilization, FDG PET-CT can be utilized to detectboth primary and metastatic anaplasticthyroid cancer. Astudy by Nguyenet al[32] foundthat PET-CT imagingwith FDGdetectedall primary tumor and nodalmetastases,as well as 5 out of 8 lung

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metastases.However, for better characterization of FDGPET-CT's diagnostic accuracy,morestudies are needed.

Impact of FDG-PET Imaging on outcome of Thyroid Cancer Patient: Studies documenting impact of FDG-PET imaging on patient survival are lacking. Initial studiesin small series of patients showed PET/CT to be superior to either PET or CT alone for approximately 25% of patients by identifying recurrent tumors or metastatic lymphadenopathy before surgery [33]. PET/CT had a reported sensitivity of 66% and a specificity and a positive predictive value of 100% for the diagnosis of recurrent thyroid cancer.Despite a lower negative predictive value, PET/CT provided additional, previously unknown information that altered further management in 40% of patients [34]. An-other study reported similar results for patients with iodine-negative suspected recurrence of thyroid cancer, with an improved diagnostic accuracy of PET/CT of 93%, compared with an accuracy of PET of 78%. In addition, fused images led to a change in management in 48% of patients[35].

Pitfalls of PET Imaging: One intrinsic limitation of PET derives from the nature of positron decay and the principle of coincidence detection. A positron generally must travel a certain distance in tissues before colliding with an electron. Annihilation occurs approximately 1 to 2 mm away from the positron's origin. This phenomenon places a theoretical limit on PET's achievable spatial resolution, which is estimated at 2 to 3 mm. False-negative results are encountered with very smalllesions (<4 mm) or in well-differentiated lesions. False-positive results are due to uptake in normal brown fat and inflammatory lesions but these can easily be ruled out through careful review of the clinical history and other imaging.It has been noted that sites of metastasis visualized better with 18F-FDG include cervical and mediastinal lymph nodes, whereas lung and bone lesions showed less uptake compared to 131I scan and 99mTc-MIBI .

2.3 Functional Magnetic Resonance Imaging :

The role of MRI in the evaluation of thyroid lesions has become more important in recent years because of the development

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of surface coils and functional MRI such as perfusion imaging and Diffusion Weighted MR imaging (DWI). DWI is a non-invasive diagnostic method which evaluates the mobility of water in different tissues to generate diffusion weighted images and Apparent Diffusion Coefficient (ADC) maps.

Schueller et al [36] performed a prospective study on 31 patients during 18 months period , who were posted for total thyroidectomy . MRI including DWI was performed day before surgery.Six patients were excluded from the study due to motion artifacts and poor image quality in 3 patients and a solitary nodule with a size <8 mm in 3 patients. At surgery, 5 patients had adenoma, 10 had papillary thyroid carcinoma (PTC), 6 had medullary thyroid carcinoma (MTC), and 4 had follicular thyroid carcinoma (FTC).The ADC values for thyroid cancer differed significantly from the ADC values of adenomas (P = .004) . There were no significant differences between the ADC values for the 3 types of carcinoma (P > .05).

2.4 ^{131}I-Iodide SPECT/CT:

SPECT involves the use of radioisotopes that emit single gamma rays in arbitrary directions, thus requiring the presence of a metallic collimator to determine sites of tracer accumulation in the body. While the collimators provide directionality, they screen out most of the emitted photons. SPECT/CT is new addition in thyroid imaging. Most of the literature showing utility of SPECT/CT in thyroid imaging is limited to single institution case series. In a study by Angela Spanu et al.[37] based on 117 consecutive thyroidectomized DTC patients SPECT/CT was compared with traditional planar imaging technique , 131I scintigraphy. Planar 131I imaging showed 116 foci of uptake in 52 of 117 patients. SPECT/CT showed 158 foci in 59 of 117 patients, confirming all 116foci seen on planar imaging in 52 of the patients. In the neck, planar imaging and SPECT/CT showed 67and 81 foci, respectively. Outside the neck, planar imaging showed 49 foci in 16 patients and SPECT/CT showed 77 foci in 18 patients.In this study both SPECT/CT and planar imaging were concordantly negative in 49.6% and concordantly positive in 44.4% and discordant (planar imaging negative and SPECT/CT positive) in 6%. In

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35.6% of patients with positive findings, more appropriate decision about therapeutic management was made. All lesions determined to be a presumptive tumor on SPECT/CT were confirmed to be malignant.

In another study by Ka Kit Wong et al[38] SPECT/CT was used for post thyroidectomy staging before giving ablative dose of 131I in forty-eight patients.SPECT/CT changed the planar scan interpretation for 19 (40%) of 48 patients, detecting regional nodal metastases in four patients and clarifying equivocal focal neck uptake in 15 patients. Daniela Schmidt et al[39] studied the diagnostic value of 131I SPECT/CT on nodal staging of fifty seven patients with thyroid carcinoma at the first ablative radioiodine therapy.SPECT/CT led to a revision of the original diagnosis in28 of 143 cervical foci of radioiodine uptake seen on planar imaging.

These pilot studies suggest that diagnostic improvements brought about by SPECT/CT in patients with thyroid carcinoma are considerable. However, considering the variable clinical presentations of differentiated thyroid cancer, validity of the above conclusion should be based on large-scale multi-centre prospective studies enabling stratification of patients into statistically meaningful homogeneous subgroups.

2.5. FDG RADIO-GUIDED SURGERY:

Kraeber-Bodere et al. have reported FDG radio-guided surgery to assist in tumor localization in radio-iodine negative, FDG-PET positive DTC patients [40]. All FDG-PET visually identified lesions were detected with the gamma probe, and the mean tumor activity was 40% higher than the surrounding neck tissue. Additional studies will be necessary to clarify the ability of radio-guided surgery to render patients free of disease, or reduce local tumor recurrence.

3. CONCLUSIONS:

Imaging remains an integral tool for clinical detection,staging, and management of thyroid cancer. While significantimprovements in anatomic resolution havebeen achieved, (131)I thyroid scan continues toyield significant numbers of false negativestudies. Furthermore, traditional anatomic thyroid cancerimaging (ie, size and morphology)

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provides limited information about the underlying tumor biology. A clear challenge for thyroid cancer imaging is to movebeyond anatomic techniques to find new directionsthat not only improve detection, but also provide guidancefor therapeutic strategies and accurate, rapid evaluationof response to treatment.New strategies using targeted molecular agents andadvanced imaging technology are rapidly emerging. These techniques increasingly allow reproducible clinicalimaging of the molecular components of tumor and/ or normal tissue in the thyroid. While these are excitingand potentially important advances, much work will be required to identify the technologies that truly increasediagnostic accuracy and improve patient outcomes.

In conclusion, despite the fact that PET/CT has been shown to be an indispensible tool in the management of thyroid carcinoma, both utility and limitations need to be completely explored. During practice, we should select appropriate candidates and optimize the condition, so that PET/CT imaging can be used more effectively in both diagnosis and treatment of thyroid cancer.

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