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EDITORIAL

Current role of radionuclide imaging in differentiated thyroid cancer

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Abstract

Nuclear medicine plays an integral role in the management of differentiated thyroid cancer. This editorial aims to provide a summary of the current role of radionuclide imaging, including whole body iodine scan and fluorodeoxy-glucose (FDG)-positron emission tomography (PET), in the diagnostic work-up and follow-up of patients with thyroid cancer.

Keywords: *Nuclear medicine; thyroid cancer.*

Thyroid nodules are a common clinical dilemma. The prevalence of a palpable thyroid nodule is approximately 5% in women and 1% in men in iodine-sufficient parts of the world[1,2]. The main aim in evaluating thyroid nodules is to detect thyroid cancer that occurs in 5−10% depending on age, gender, history of radiation exposure, family history and other factors[3,4]. More than 90% of thyroid cancers are differentiated, comprising papillary and follicular carcinoma[5].

High resolution ultrasound is the most common and ideal initial imaging investigation for thyroid nodules[6,7]. Combining ultrasound with guided fine needle aspiration cytology (FNAC) markedly improves its specificity and diagnostic accuracy. In particular the positive predictive value of FNAC is very high and this plays a major role in the management of thyroid cancer[8−10]. Conventional radionuclide thyroid scanning using [99mTc]pertechnetate or ^{123}I can determine whether a nodule is hyperfunctioning ('hot'), isofunctioning ('warm') or hypo/non-functioning ('cold') when the serum thyrotropin (TSH) level is subnormal or FNAC is indeterminate. A hot nodule is almost always benign and does not require further diagnostic evaluation[11]. Other radiotracers with

affinity for neoplastic lesions, such as ^{201}Tl, [99mTc]sestamibi, [99mTc]tetrofosmin, can be employed to characterize suspicious nodules[12−17], but are being increasingly supplanted by [^{18}F]fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) in recent years[18−24]. There is no clear-cut differentiation between malignant and benign thyroid nodules by these radiotracers. However, FDG-PET and [99mTc]sestamibi scintigraphy (because of their high negative predictive values) may help to reduce unnecessary thyroidectomies for cytologically indeterminate thyroid nodules[17,22,23].

With the exception of low-risk unifocal microcarcinoma, total thyroidectomy followed by radioiodine ablation and TSH-suppressive thyroid hormone therapy is the standard treatment for differentiated thyroid cancers[25−27]. The benefits of prophylactic 'en bloc' central node dissection in the absence of pre- and intra-operative evidence for nodal disease remain controversial. Sentinel lymph node (SLN) biopsy has been advocated to avoid the morbidity of routine nodal dissection but allow the identification of draining nodes from the tumour and detection of micrometastases. These nodes can be located with preoperative lymphoscintigraphy

followed by intraoperative hand-held gamma probe[28]. SLN biopsy may play a role in early small thyroid cancers and larger clinical trials are awaited.

TSH-stimulated thyroglobulin, measured by sensitive immunoradiometric assays, provides one of the most sensitive means for detection of persistent disease in the absence of interfering anti-thyroglobulin antibodies[29]. For follow-up after standard treatment, a combination of TSH-stimulated thyroglobulin and ultrasound of the neck +/− FNAC are often sufficient in low-risk patients[30]. For high-risk patients or in cases of increasing TSH-stimulated thyroglobulin, radioiodine whole body scan (WBS) or FDG-PET is recommended for detection of persistent or metastatic disease.

Post-therapy WBS, performed 3−10 days after a therapeutic dose (30−100 mCi or more) of ^{131}I, helps to determine the extent of disease, predict prognosis and identify patients requiring additional workup. Post-therapy WBS has a higher diagnostic yield than pre-therapy diagnostic WBS in 10−50% of patients[31−35], the latter being acquired with a low radioiodine dose (1−5 mCi, typically less than 3 mCi) in order to minimize 'stunning' of thyroid cancer from responding to ensuing ^{131}I therapy[36−38]. Such concern about ^{131}I-induced stunning has led to an increasing trend of avoiding pre-therapy diagnostic ^{131}I WBS altogether, or considering the use of ^{123}I instead of ^{131}I for diagnostic WBS[39−41]. Iodine-123 has no beta (β) emission hence lesser thyroid stunning and no therapeutic value, yet it emits gamma (γ) energy with better imaging characteristics. It is, however, more expensive and not universally available.

Diagnostic radioiodine WBS during follow-up can help to assess the effectiveness of previous radioiodine ablation or treatment, and the requirement of further ^{131}I therapy for residual iodine-avid lesions in the thyroid bed or metastatic sites[42]. Diagnostic radioiodine WBS must be performed under endogenous or exogenous TSH stimulation (by 4-week withdrawal of levothyroxine or 2-day intramuscular administration of recombinant human thyrotropin). Its diagnostic sensitivity is relatively low (compared with post-therapy WBS), depending on the radioiodine dose and histological type, ranging from 45 to 75%, whereas the specificity is generally above 95%[43−46].

Radioiodine WBS, albeit with high diagnostic specificity, offers limited anatomical details with myriad pitfalls, such as physiologic uptake or secretion in various organs (salivary gland, nose, stomach, liver, breast, etc.), gastro-intestinal and urinary excretion, serous cavities or cysts, inflammation or infection, and non-thyroidal neoplasms[47]. To circumvent these problems, it is useful to perform single photon emission computed tomography (SPECT) to supplement planar scintigraphy. Precise anatomical localization of radioiodine uptake can further be achieved by co-registration with transmission CT images, which can readily be obtained with hybrid SPECT/CT imaging system available nowadays[48].

The incremental value of SPECT/CT was found to have therapeutic impact on 25−41% of patients with thyroid cancer[49−51]. Caution should be taken against the use of iodinated CT contrast that affects subsequent diagnostic or therapeutic application of radioiodine.

In less or de-differentiated thyroid cancer, recurrent or metastatic tumour cells may lose the expression of sodium iodide symporter and decreased ability to concentrate radioiodine[52]. In these circumstances, FDG-PET becomes a valuable investigation, especially in cases of elevated thyroglobulin and negative diagnostic or even post-therapy radioiodine WBS[53−56]. A multicentre series by Grünwald et al. found a higher sensitivity by FDG-PET (75%) than ^{131}I WBS (50%) and [^{99m}Tc]sestamibi/^{201}Tl WBS (53%) with comparable specificities[57]. The sensitivity of FDG-PET increased to 85% in the subgroup of patients with negative ^{131}I WBS. Robbins et al. documented significant inverse relationship between survival and both the FDG avidity of the most active lesion and the number of FDG-avid lesions[58].

Although FDG-PET serves an important role in the follow-up of patients with thyroid cancer, accurate localization of FDG-positive lesions is often difficult. Like SPECT/CT, the advent of hybrid PET/CT scanners has increased diagnostic confidence and reduced equivocal results in either PET or CT alone. Pitfalls of PET such as uptake in normal structures, bowel activity, urinary excretion of tracers, presence of brown fat are reduced[59]. Several recent studies have confirmed the value of PET/CT in differentiated thyroid cancer, especially those thyroglobulin-positive but iodine-negative cases, altering clinical management in 23−51% of cases[60−65].

For decades, nuclear medicine has had a major role in the management of differentiated thyroid cancer. The increasing availability of FDG-PET or PET/CT has expanded the armamentarium of the radionuclide imaging modality, complementing the well-established radioiodine scans towards the diagnosis, staging and follow-up of thyroid cancers. With advancement of hardware and development of radiopharmaceuticals or molecular probes, the potential scope of nuclear medicine in oncology continues to expand, further enhancing its role in the management of thyroid cancer.

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