



Review Article

Usefulness of PET-CT scan in recurrent thyroid cancer

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Abstract The aim of this paper is to discuss the risk of recurrence in patients with differentiated thyroid cancer and emphasize the importance of risk-group stratification, early recurrence identification and application of new imaging modalities, what is the PET-CT. Moreover, follow-up of patients with thyroid carcinoma should be carried out by specialized teams throughout life. Therefore, interdisciplinary case discussions in tumor conferences may improve the use of multimodal therapy especially in patients with poorly differentiated thyroid carcinomas. After baseline follow-up, if there is a suspicion of thyroid carcinoma, early PET-CT should be used for early detection and appropriate planning. Fortunately, due to the good localization possibility, the PET-CT enables a focused surgical procedure with avoidance of an unnecessary tumor search and thereby a reduction of the risk of injury of neighboring structures which is a concern with reoperative neck surgery.

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Introduction

Thyroid cancers are the most common tumors of the endocrine system, although overall are placed at the last positions among the other human malignancies. Follicular epithelial neoplasms account for more than 90% of these tumors with a favorable prognosis. On the contrary, remaining tumors (medullary, anaplastic, lymphoma, sarcoma, etc.) are more aggressive, with a rapidly progressive behavior and a low survival rate.¹

Nevertheless, proper surgical intervention is associated with better outcomes especially in differentiated thyroid carcinoma (DTC). Therefore, the operative management of local recurrences is pivotal for a local control of the tumor and a better quality of life.²

Accordingly, early identification of patients with a suspicious recurrence is essential to develop appropriate therapeutic strategies and to improve the results of the follow-up period. At the same time, increasing the awareness of clinicians, endocrinologists, surgeons, pathologists, nuclear medicine specialists and radiologists about recurrences could contribute to an early diagnosis and intervention.

Absence of tissue differentiation in recurrent thyroid carcinoma however causes lack of radio-iodine uptake from thyrocytes. Thus, new diagnostic methods such as positron emission tomography (PET), play an important role in their detection in order to define the operative strategy.³ PET is a nuclear medicine functional imaging technique employed to observe metabolic processes in the body. The technique is based on the detection of the two 511-keV gamma-ray photons generated by the conversion of a positron-emitted radionuclide. The latter is introduced into the body on a radio labeled biologically active molecule to generate three-dimensional images showing the concentration of the tracer in the body.

Currently, because PET is integrated with computed tomography (CT) scan, the three-dimensional imaging is obtained by a simultaneous CT X-ray scan performed during the same session with the same machine. For instance, if the biologically active molecule chosen for PET is fludeoxyglucose (FDG), an analogue of glucose, concentrations of tracer in the image indicate tissue metabolic activity as it corresponds to the regional glucose uptake.^{1–5}

Histological subtype, tumor stage, male sex, age more than 50 years, primary tumor larger than 1 cm, poor dedifferentiation of the primary tumor, regional lymph node metastasis, and multifocality are related to a [Table 1](#) shows factors associated with increased risk of thyroid cancer recurrence in patients who underwent total thyroidectomy. Consequently, it is recommended to adopt an aggressive surgical approach and a strict post-operative monitoring.^{1,3}

The incidence of differentiated thyroid carcinomas recurrence accounts for 8–23% while that of medullary tumors can reach up to 50%.^{4,5} Subsequently, the aggressiveness of anaplastic thyroid carcinomas is reflected by a median survival of 5 months after diagnosis and 20% one-year survival rate. Further, these tumors have a locally invasive growth in 90% of patients and accompanying metastasis in up to 50% of patients at the first diagnosis.⁶

Despite, surgery still remains the cornerstone for management of recurrent thyroid cancers.

The good results of surgical procedure in patients with recurrent thyroid cancer depend, in particular, on the precise preoperative tumor localization. Hence, PET-CT has a high value in the follow-up of differentiated thyroid malignancies, especially when tumor detection by ¹³¹I whole body scintigraphy (WBS) is not possible. The exact determination of the tumor recurrence offers an optimal surgical planning and thus better outcomes.⁶ Various markers however are examined for their sensitivity in the detection of recurrence of different subtypes of thyroid carcinoma but this is difficult, especially in the case of poorly differentiated ones.^{4,7}

The presence of detectable levels of thyroglobulin after total thyroidectomy implies the presence of a differentiated thyroid carcinoma recurrence, with the indication for radioiodine scintigraphy; however, the condition for its detection is the iodine uptake capacity of the tumor cells. In rare tumor variants such as the oncocytic thyroid carcinoma, a proof of recurrence by means of a radio-iodine uptake is not possible. In these cases, the sensitivity of ¹³¹I-WBS is only 60% unsatisfactory.^{6,8} Since the recurrence detection associated with a tailored operative therapy, has an impact on the survival of patients, alternative imaging techniques need.

PET-CT in differentiated thyroid carcinoma

The lack of ¹³¹I trapping by metastatic tissue in patients with DTC does not allow the detection and treatment of metastatic spread by ¹³¹I-WBS. Hence, the prognosis of ¹³¹I-iodine-negative DTC metastasis is significantly worse. Moreover, early diagnosis of non-iodine avid metastases with complete surgical excision remains the optimal therapeutic approach in these patients. In this view, a highly sensitive localizing imaging different from ¹³¹I-WBS is required.

Ultrasonography (US) is characterized by a relatively high sensitivity in these patients, but it is operator-dependent and it is limited to neck exploration only. Also, CT scan and magnetic resonance imaging (MRI) are characterized by a relatively low sensitivity even if surgeons utilize them to identify surgical anatomy perioperatively.

Table 1 Factors associated with increased risk of thyroid cancer recurrence.

Histological subtype
Tumor stage
Male sex
Age more than 50 years
Primary tumor larger than 1 cm
Poor dedifferentiation of the primary tumor
Regional lymph node metastasis

The integrated PET-CT fusion imaging systems provide additional advantages related to a better anatomical localization of the hyper metabolic metastatic lesions. It also enables optimal anatomic delineation of PET findings as well as identification of 2-deoxy-2-(¹⁸F)-fluoro-D-glucose (FDG) or ¹⁸F-FDG-negative lesions on CT images which might improve preoperative staging.

Therefore, the typical indication of ¹⁸F-FDG PET-CT is patients with DTC previously treated by total thyroidectomy and ¹³¹Iodine ablative therapy in addition to increased serum thyroglobulin (Tg) or anti-thyroglobulin antibodies (TgAb) during the follow-up but with a negative ¹³¹I-WBS that was obtained either after diagnostic or therapeutic procedure.

A study demonstrated a significant positive correlation between the increase in thyroglobulin and a metastasis detected by ¹⁸F-FDG PET-CT.⁹

Further, several prospective and retrospective studies explored the role of ¹⁸F-FDG-PET-CT in the assessment of the recurrent DTC with elevated Tg and negative ¹³¹I-WBS.

The observed range of specificity, sensitivity, PPV and NPV have been reported as 68.4%–100%, 66.7%–98.5%, 69.1%–92%, and 61.3%–95.6%, respectively.^{10–15}

Other studies indicate that ¹⁸F-FDG-PET-CT is also a useful diagnostic tool in patients with recurrent DTC and progressively increased TgAb level as well as negative Tg and ¹³¹I-WBS.

Nonetheless, the highest diagnostic value is reached when the study is performed for patients with elevated Tg levels or in those with negative Tg serum level and rising TgAb titer.^{16–18}

A change in the management of DTC patients affected by non-iodine avid metastatic spread not visualized by other imaging techniques has been reported in 30% of patients.¹⁰

Moreover, although current clinical PET-CT scans are performed almost exclusively with ¹⁸F-FDG, recent advances in targeted molecular imaging are bringing new possibilities to the thyroid cancer imaging.^{19,20}

The development of a human recombinant thyroid stimulating hormone (rhTSH), for example, is making imaging under thyroid hormonal stimulation more feasible. Likewise, novel PET radiotracers such as ¹⁸F-DOPA, and ⁶⁸Ga-DOTATOC promise to change the way thyroid malignancies are imaged. Studies evaluating the administration of rhTSH prior to ¹⁸F-FDG PET-CT revealed an increase in sensitivity in identifying tumor recurrence of up to 95% compared to 81% without stimulation.^{19,20} However, a lower sensitivity in the diagnostic accuracy of ¹⁸F-FDG-

PET/PET-CT imaging after rhTSH stimulation was observed in the suspected recurrent thyroid cancer patients with low titer of thyroglobulin.²⁰

In this set of patients, the utility of rhTSH stimulation procedure could lie in the identification of patients with low stimulated Tg serum levels: consequently, the assessment of Tg serum level after rhTSH stimulation is potentially useful in identifying patients unlikely to benefit from an ¹⁸F-FDG-PET-CT.²¹

Finally, there are other interesting points that emerge from analyzed literature. First, a previously good quality conventional imaging raised the sensitivity in the detection of recurrent thyroid cancer of ¹⁸F-FDG-PET-CT. Second, a direct correlation between SUV (standardized uptake value) max and cervical lymph-nodes size was observed. It was also observed that the patients with SUV max lesion higher than 10 carried the worst prognosis.^{18,22,23}

PET-CT in medullary thyroid carcinoma

Evidence is emerging on the advantages of PET-CT imaging in other histological subtypes of thyroid malignancy, such as Hürthle cell, medullary, and the anaplastic variants.²⁴

Concerning the medullary thyroid carcinoma (MTC), early detection of recurrence is very difficult. Diagnostic imaging consists of cervical US for the detection of lymph node metastases as well as contrast-enhanced CT to detect thoracic and lung metastases. In addition, MRI for the detection of liver metastases and bone scintigraphy for the exclusion of bone metastases can be performed.²⁴ However, overall, imaging diagnostics only covers 40% of a laboratory-suspected relapse.⁴ The recognition of a tumor recurrence depends in particular on the level of calcitonin. The likelihood of recurrence detection increases with the increase in calcitonin or carcinoembryonic antigen (CEA).² Accordingly, with a calcitonin value < 150 pg/ml conventional detection tools (US, CT, MRI) often fail to detect metastasis. Initial studies were reported by Musholt et al²⁵ and Gasparoni et al²⁶ published in 1997 for the use of FDG-PET in medullary thyroid carcinoma recurrence. De Luca et al colleagues also explored the diagnostic value of ¹⁸F-FDG-PET-CT in detecting metastatic neck lymph-nodes. The observed sensitivity of ¹⁸F-FDG-PET-CT in this prominent district was 74.6%.²⁷

A meta-analysis by Cheng et al²⁸ showed that the sensitivities in identifying a recurrence for FDG-PET and PET-CT in medullary thyroid carcinoma averaged 68% and 69%, respectively.

Furthermore, several authors demonstrate that the ¹⁸F-FDG-PET-CT appears a valuable diagnostic instrument in detecting recurrent MTC in patients with calcitonin value higher than 1000 pg/ml: the obtained specificity and sensitivity reached an excellent value.^{29–31}

The literature data had also underlined that the sensitivity of ¹⁸F-FDG-PET-CT seems better in sporadic or familial MTC with respect to MEN related MTC.^{29,30}

Finally, a higher SUV maxi metastatic disease indicates an aggressive disease and it is significantly a worse predictor for overall survival in metastatic MTC disease.^{4,32,33}

Other imaging techniques as well as tracers to increase sensitivity were tested. In the studies by Treglia et al⁴ and

Ozkan et al³³ it has been shown that ¹⁸F-DOPA is superior to ¹⁸F-FDG, which is frequently used for tumor detection in recurrent medullary thyroid carcinoma. Lymph node recurrences are statistically significantly more frequently detected by ¹⁸F-DOPA, whereupon the diagnostic and therapeutic approach changed in 44% of the patients.

The American Thyroid Association (ATA) recommends a US and optional ¹⁸F-DOPA-PET-CT in the follow-up of medullary thyroid carcinoma with a calcitonin <150 pg/ml.³⁴

In a study by Treglia et al,⁴ in a patient with a calcitonin score of 66.7 pg/ml, ¹⁸F-DOPA-PET-CT was able to demonstrate the presence of lymph node metastasis that could not be detected by US. Increased ¹⁸F-DOPA accumulation indicates a higher degree of differentiation of the cells and may explain why the sensitivity in identifying recurrences is so high especially in small lymph node lesions.⁴ Therefore, the use of PET-CT in the follow-up with increased calcitonin or unclear/ambiguous US findings is recommended. Also, compared to other markers, ¹⁸F-DOPA was found to be superior in sensitivity.^{4,33,35} This can be explained by the metabolic mechanism of medullary thyroid carcinoma, which is similar to neuroendocrine tumors.³⁶ Some authors however described that the combined use of ¹⁸F-DOPA-PET-CT and ¹⁸F-FDG-PET-CT as complementary imaging tools, especially in patients with recurrent MTC.

The dual PET-CT approach represents a fundamental factor for tailoring further treatment (surgery, receptors targeted radiotherapy, or multi-kinase inhibitor treatment).^{32,37}

Finally, ⁶⁸Ga-DOTATOC PET-CT seems to have a relevant role on the identification of patients who would benefit from the Peptide Receptor Radionuclide Therapy (PRRT) with ¹⁷⁷Lu-DOTATATE/TOC.^{4,33,34}

PET-CT in anaplastic/undifferentiated thyroid carcinoma

The rapid and fatal progression of anaplastic thyroid carcinoma and its early metastasis require careful post-operative follow-up for early detection of relapses to improve the likelihood of survival.⁷

In 2012, the American Thyroid Society published a guideline for the diagnosis and multimodal treatment of anaplastic thyroid carcinoma. It recommends utilizing US for evaluation of the thyroid gland as well as for detection of cervical lymph node metastases, which should be supplemented by further imaging procedures.³⁸ Immediate diagnosis is necessary in suspected cases to initiate multimodal therapy.

In the natural history of anaplastic thyroid cancer, the loss of differentiation of the neoplasm determines the up regulation of GLUT-1 transporter, allowing the cancer cell to meet their excess glucose demand to the proliferation.

This phenomenon underlies the utility of ¹⁸F-FDG-PET-CT as it detects the extent of the tumor and the presence of metastases with high sensitivity.^{9,39}

To our knowledge, Borsgurd and colleagues were the first to evaluate the potential role of ¹⁸F-FDG in the assessment and management of anaplastic thyroid cancer patients. In their experience, the Mayo Clinic' group registered that a negative PET-CT scan after treatment (a

combination of radiotherapy, chemotherapies, and surgery) may be indicative of better prognosis. Furthermore, ¹⁸F-FDG-PET-CT findings had an impact on the management of patients in 50% of cases. Finally, Borsgurd compared ¹⁸F-FDG-PET-CT with other imaging modalities and registered that the molecular imaging had better diagnostic value in the assessment of ATC patients.⁴⁰

In a study on 18 patients, 265 lesions in 63 organs could be detected by ¹⁸F-FDG-PET-CT. 35% of these metastases could only be identified by ¹⁸F-FDG PET-CT [41]. In 25% of patients, this led to a change in the treatment regimen (radio/chemotherapy). A high ¹⁸F-FDG uptake of (≥ 300 ml) and a SUV max ≥ 18 were found to be a significant prognostic factor for patient survival. Accordingly, PET-CT should be part of the follow-up as a sensitive imaging modality.⁴¹

Despite the comprehensive diagnosis, the prognosis of these patients remains inadequate. As a result, palliative therapy should be taken into consideration to prevent catastrophic event including respiratory distress.

Importance of PET-CT in surgical planning

In the case of recurrence of thyroid carcinoma, the question of the resectability of the tumor always arises first. Fortunately, the answer can be determined preoperatively due to the high-resolution diagnostic imaging. The fusion of the metabolically active tracer (represented as an increase in metabolism of the tumor) and the detailed morphology of the tumor by the CT makes preoperative planning for a focused surgical intervention possible.

Tumor size, location (one-sided, two-sided) as well as the invasion into neighboring organs can be determined preoperatively. This results in a focused operation, whereby the risk, in particular of a lesion of the recurrent laryngeal nerve can be avoided by unnecessary manipulation. Likewise, the risk of postoperative hypocalcemia can be avoided as well. In addition, imaging diagnostics make it possible to estimate the risk of the operation and to provide the patient with more precise information regarding the operation and possible complications. In any case, the aim of surgery is complete tumor removal to achieve local control.

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Ethical approval

The Institution's Ethical Board Committee approved the review.

Declaration of Competing Interest

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