[Frontiers in Bioscience, Landmark, 21, 1187-1193, June 1, 2016]

Radionuclide imaging and treatment of thyroid cancer

Xiu Juan Wang[1], Xian Feng Li[2], Yuan Ren[1]

[1]Department of Nuclear Medicine, Shan Xi Tumor Hospital, Shan Xi, 030013, China, [2]Department of Nuclear Medicine, The First Hospital of Shan Xi Medical University, Shan Xi, 030012, China

TABLE OF CONTENTS

1. ABSTRACT

Over the past decades, the diagnostic methods and therapeutic tools for thyroid cancer (TC) have been greatly improved. In addition to the classical method of ingestion of radioactive iodine-131 (I^{131}) and subsequent I^{123} and I^{124} positron emission tomography (PET) in therapy and examination, I^{124} PET-based 3-dimensional imaging, Ga^{68}-labeled [1, 4, 7, 10-tetraazacyclododecane-1, 4, 7, 10-tetraacetic acid]-1-NaI(3)-octreotide (DOTANOC) PET/computed tomography (CT), Tc^{99m} tetrofosmin, pre-targeted radioimmunotherapy, and peptide receptor radionuclide therapy have all been used clinically. These novel methods are useful in diagnosis and therapy of TC, but also have unavoidable adverse effects. In this review, we will discuss the development of nuclear medicine in TC examination and treatment.

2. INTRODUCTION

Thyroid cancer (TC) is the most common endocrine malignancy and the seventh most commonly diagnosed cancer in women (1). The incidence of TC has continuously and sharply increased worldwide in the last three decades (1). Patients with symptom-free thyroid cancers are diagnosed when small thyroid nodules are discovered as incidental findings during imaging performed for another purpose (2). European statistics show that TC is three times more common in women than in men (3), but the overall relative 5-year survival rate for thyroid cancer is 85% for women and 74% for men (4). Although TC patients have a high overall survival rate, TC recurrence is as high as 10–30%, and some patients with recurrence eventually fail to respond to radioiodine treatment and subsequently experience metastasis (5).

TC originates from follicular or parafollicular thyroid cells. Epithelial cell-derived differentiated thyroid cancer (DTC) accounts for over 90% of all TC, including papillary thyroid carcinoma (80%), follicular thyroid carcinoma (11%), and other less frequent histologic subtypes. Other TC types derive from the calcitonin-producing parafollicular cells of the thyroid gland and include medullary carcinoma (5–10% of all TC) (6). DTC has a superior prognosis, whereas medullary thyroid cancer (MTC) displays only modest cure rates.

Although various methods of diagnosis and non-operative treatment of TC have been developed recently (7-10), nuclear medicine still plays an important role. As early as the 1980s, a clinico-radionuclide examination was used to accurately diagnose TC, helping guide decisions regarding operative intervention (11). Radionuclide scanning is usually used in detecting metastases and postoperative residual or recurrent tumors (12,13), especially in postoperative monitoring of patients with DTC (14). On the other hand, radionuclide therapy, such as I^{131}, is used for the treatment of papillary or follicular TC after surgery, and has served as a classical method of diagnostic detection. Therefore, although several methods have been used in TC diagnosis and surgery has been a major method in TC treatment, radionuclide imaging and therapy still hold an irreplaceable status in TC examination and treatment. In this review, we will discuss the development of nuclear medicine in TC examination and treatment.

3. RADIONUCLIDE IMAGING IN THYROID CANCER

Iodine is the rate-limiting substrate for thyroid hormone synthesis. As the thyroid gland has the ability to concentrate iodide, iodine has been widely used in TC diagnosis and treatment. Ingestion of I^{131} in combination with I^{123} and I^{124} positron emission tomography (PET) has

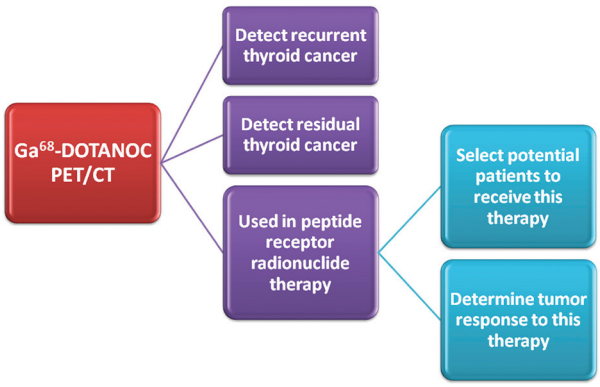

Figure 1. The Ga^{68}-DOTANOC PET/CT in thyroid cancer. The Ga68-DOTANOC PET/CT can be used to scan differentiated thyroid cancer patients that are negative in I^{131}-whole body scan for detecting recurrent or residual disease, selecting potential candidates for peptide receptor radionuclide therapy, and determine tumor response to peptide receptor radionuclide therapy.

become the classical method for diagnosis. I^{124} PET-based 3-dimensional (3D) dosimetry in multiple PET images defines the spatial distribution of radioactivity at different times after administration of the radiopharmaceutical. I^{124} PET-based 3D dosimetry can also be used in I^{131} therapy of TC. Moreover, it can be also be used to estimate the spatial distribution of cumulated activity and reveal substantial variability in intra- and inter-tumorally absorbed doses in individual patients (15). Furthermore, I^{124} PET used for scanning DTC patients before I^{131} therapy can be utilized to establish individual values for determining absolute recovery based on the particular PET scanner and radionuclide to be used (16). De Geus-Oei and colleagues (17) thought that, in addition to the thyroglobulin level after thyroid htimulating hormone (TSH)-suppressing L-thyroxin therapy, I^{123} whole-body scanning failed to improve the diagnostic sensitivity in the detection of metastases or recurrent DTC. Nevertheless, I^{131} single photon emission computed tomography (SPECT)/computed tomography (CT) is still an important tool for gaining precise anatomical localization of the radionuclide activity foci in TC metastases, thus helping to convey information needed for adequate treatment (18).

When DTC patients are negative in the I^{131}-whole body scan, those with a raised thyroglobulin level can choose Ga^{68}-DOTANOC PET/CT, which may be a better choice than 18-fluorine fluorodeoxyglucose (F^{18}-FDG) PET/CT based on the lesion. Moreover, it can be used to help select potential candidates for peptide receptor radionuclide therapy. However, this is not an appropriate choice for patients for detecting recurrent or residual disease (19). Moreover, Ga^{68}-DOTANOC PET/CT is also a reliable tool for evaluating the treatment response, and the functional volume over time obtained by PET/CT may be a reliable parameter to determine tumor response to peptide receptor radionuclide therapy (20) (Figure 1). Candidate TC patients for peptide receptor radionuclide therapy can be selected after considering the expression of somatostatin receptors in thyroid cells. In^{111}-pentetreotide, a radionuclide-labeled somatostatin analogue, is a valuable tool in the diagnosis of patients with progressive, somatostatin-receptor-positive non-MTC, particularly in patients with Hürthle cell cancer, especially if $2\text{-}F^{18}$-FDG PET is not available (21).

Pertechnetate ($TcO4^{-}$), an isotope with no β emission and a short half-life, is transported by the sodium-iodide symporter, $TcO4^{-99m}$, and it can be used to image thyroid tissue (22-24). Tc^{99m} tetrofosmin is useful to detect malignant recurrence and distant metastases in the follow up of DTC without the necessity of thyroid hormone withdrawal, especially in patients with elevated thyroglobulin level and no iodine uptake (25); in addition, Tc^{99m} MINI can be used to detect patients with recurrent MTC, particularly in cases using non-diagnostic conventional imaging techniques (26). Tc^{99m} tetrofosmin has advantages regarding the background clearance, detection rate, and dosimetry compared with Ti^{201} and Tc^{99m}sestamibi (25).

4. RADIONUCLIDE THERAPY IN THYROID CANCER

Iodine radioisotope therapy is usually used in metastatic TC (27). However, de Geus-Oei and colleagues (17) have proposed that I^{131} treatment should be considered in DTC patients with negative whole-body I^{123} scanning but an increased thyroglobulin level. Increasing radioactive iodine uptake is a key in DTC treatment. The sodium iodide symporter (NIS), a transmembrane glycoprotein, transports two sodium cations (Na^{+}) for each iodide anion (I^{-}) into the cell, thus mediating iodide uptake into the follicular cells of the thyroid gland; this is the first and key step in thyroid hormone synthesis (28) (Figure 2). In DTC, even though the expression of NIS in the primary tumor has been found to be positively associated with its expression in metastatic tissue, no significant association has been shown between the expression of NIS and radioiodine uptake in metastases (29). However, *in vivo* and *in vitro* studies using a murine anaplastic TC model showed that NIS gene transfection into a human anaplastic tumor could induce accumulation of β-emitter radionuclides, and moreover, wild-type *p53* gene expression increased the cytotoxic effect of radionuclide gene therapy with NIS (30). Thus, the influence of NIS in TC treatment may be associated with the tumor type and may be influenced by the genetic factors.

In addition to radioactive iodine therapy for TC, several novel methods have been developed and have become widely used in TC patients not indicated for traditional iodine therapy. For example, distal iodine-negative metastases could be treated with

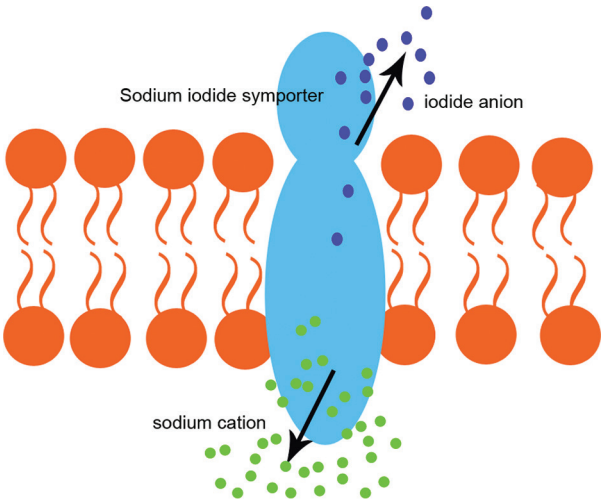

Figure 2. Sodium iodide symporter. The sodium iodide symporter (NIS) is a transmembrane glycoprotein that transports two sodium cations (Na^+) for each iodide anion (I^-) into the cell, mediating uptake iodide into follicular cells of the thyroid gland.

P^{32} (31). Moreover, pre-targeted radio-immunotherapy (PRIT) is a recent novel technique that decouples the pharmacokinetics of antibody targeting and radionuclide delivery and is able to increase the therapeutic index and the absorbed dose delivered to tumor cells through directly labeled antibodies (32). PRIT is beneficial to patients with rapidly progressing metastatic disease, including MTC patients (33). In the treatment of MTC, PRIT is the only convincing modality to increase survival compared with a control group receiving conventional treatment (34). Even in progressive metastatic MTC, the anti-carcinoembryonic antigen PRIT still has antitumor activity with manageable hematologic toxicity, as observed in a prospective phase II multicenter trial (35). In post-PRIT patients with progressive metastatic MTC, survival can be predicted using F^{18}-FDG PET (36). On the other hand, the efficacy of PRIT can be increased with paclitaxel without increasing toxicity in MTC xenografts (37). In recent years, a new PRIT compound, histamine-succinyl-glutamine peptide, has been more easily and stably labeled with radiometals such as Lu^{177} and Y^{99}beta that are feasible for PRIT, thus allowing the development of PRIT for MTC treatment (38). In addition to PRIT, the somatostatin analogue DOTA-(Tyr)-octreotate labeled with gallium (Ga-DOTATATE) may also have a potential theranostic use in MTC (39). Moreover, Lu-DOTATATE has demonstrated quality-of-life improvements and very mild adverse effects in somatostatin receptor-positive MTC, at least during a short-term period (40).

Radioactive iodine therapy is a cornerstone treatment for DTC after surgery, based on thyroid gland absorption of iodine following concentration in the tumor. However, 5–15% of patients become refractory to radioactive iodine: the 5-year survival rate in these refractory patients is 66%, and the 10-year survival rate is only 10% (41-44). Peptide receptor radionuclide therapy (PRRT) has been suggested for use in the treatment of patients with radioiodine-refractory DTC owing to its good response and minor and transient hematological toxicity 45). Even in the treatment of metastatic TC, which is radioiodine-refractory, PRRT is also a promising choice for its minimal toxicity, efficacy, and survival benefits (46). In the future, large clinical trials are needed to further confirm the efficacy and safety of PRRT in TC therapy.

5. SIDE EFFECTS AFTER RADIATION EXPOSURE

In both I^{131} imaging and treatment, the active accumulation and excretion of I^{131} in the body through the gastrointestinal tract is mainly via the gastric mucosa during gastric emptying, directly determining the I^{131} concentration (47). A study in which SPECT imaging was used in the 17-allyamino-17-demothoxygeldanamycin-treated TC mouse model also showed an increasing thyroidal radioiodine accumulation, and the duration of elevated serum TSH level is important to maximize this accumulation (48). Therefore, although radionuclide imaging and therapy are increasingly improving efficacy and safety, some side effects from radiation exposure are still unavoidable, particularly those originating from radionuclide accumulation after radioiodine exposure.

Among patients treated with radionuclide, pregnant women usually have a more severe response to radiation exposure, as high therapeutic doses of I^{131} in pregnant patients with DTC have side effects on both the pregnant woman and her unborn child, including spontaneous abortions. Side effects observed in the children include Fallot's tetralogy and low birth weight, suggesting that women should avoid pregnancy after I^{131} therapy for at least one year to ensure complete elimination of the radionuclide and to permit confirmation of complete disease remission (49).

In addition to patients, doctors or staffs carrying out radionuclide therapy also are faced with radiation exposure. However, a pilot study of three patients with non-iodine avid TC undergoing F^{18}-FDG-guided surgery showed that radiation exposure to the surgeon and staff members of an operating room is limited and safe, thus intraoperative use of this radiopharmaceutical should not be limited (50).

At the cellular level, I^{131} can induce clastogenic and age-dependent aneugenic effects in lymphocytes of TC patients, particularly those with spontaneous proneness to chromosome loss (51). Furthermore, radioiodine therapy in DTC could induce gamma-H2AX and 53BP1 DNA repair foci in blood cells even at a low dose less 20 mGy (52). Thus, we suppose

that radiation exposure may ultimately act on the DNA. However, knowledge about the mechanism by which radiation exposure damages the chromosome or DNA is still lacking. Future study on this may provide useful information regarding how to avoid or treat those side effects.

As most side effects are due to intracorporeal accumulation following radionuclide exposure, several methods to detect the absorption or clearance of radiation have been studied. Willegaignon and colleagues (53) have compared different dosimetric methods that require collecting patients' blood samples versus those involving OLINDA/EXM software; they found that the OLINDA/EXM software may be the most efficient method and could diminish the required amount of data collection, thus helping to avoid additional patient discomfort (53). On the other hand, the radioiodine clearance 5 days after I^{131} therapy of DTC patients can be assessed using a biphasic model (54).

6. CONCLUSIONS

Over the last decades, nuclear medicine in TC examination and treatment has been developed to be more efficacious and safe. In addition to classical radioactive iodine examination and therapy, novel methods have also been widely used. However, most findings are from studies with small samples. Thus, future studies with a large sample or a long follow-up may provide more convincible information concerning the efficacy and safety of nuclear medicine in TC examination and treatment. Furthermore, the side effects unavoidable in TC radionuclide imaging and treatment should also be examined extensively, as this is an important aspect regarding the clinical use of radionuclides. In addition, studies regarding the mechanism underlying how radiation exposure damage occurs may provide increased understanding that may help to avoid or treat side effects; this may be help to eliminate the bottleneck in the use of radionuclide medicine in TC or even other diseases.

7. ACKNOWLEDGEMENTS

I would like to express my gratitude to all those who have helped me during the writing of this thesis. I gratefully acknowledge the help of my supervisor professor Li Xian Feng. I do appreciate her patience, encouragement, and professional instructions in writing my thesis. Also, I would like to thank Miss Ren Ruan, who kindly gave me considerable help by means of suggestion and comments and constructive criticism. Last, but not the least, my gratitude is also extended to my family who have been assisting, supporting and caring for me throughout my life.

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Abbreviations: TC: thyroid cancer; PET: positron emission tomography; CT: computed tomography; differentiated thyroid cancer (DTC:); MTC: medullary thyroid cancer; I^{131}: iodine-131; 3D: 3-dimensional; SPECT: single photon emission computed tomography; F^{18}-FDG: 18 fluorine-fluorodeoxyglucose; FDG-PET: 2-F^{18}-fluorodeoxyglucose-positronemission tomography; NIS: sodium iodide symporter; Na^+: sodium cations; I^-: iodide anion; PRIT: pretargeted radioimmuno-therapy; Ga-DOTATATE: DOTA-(Tyr)-octreotate labeled with gallium; PRRT: peptide receptor radionuclide therapy; TSH: thyroid htimulating hormone

Key Words: Thyroid Cancer, Radionuclide Imaging, Therapy, Review

Send correspondence to: XiuJuan Wang, Department of Nuclear Medicine, ShanXi Tumor Hospital, Shan Xi, 030013, China, Tel: 86-13934130970, Fax: 86-029-85276000, E-mail: wangxiujuan_xj@126.com