Review Article

Internal radiation therapy: a neglected aspect of nuclear medicine in the molecular era

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Abstract

With increasing evidence, internal radiation therapy, also known as brachytherapy, has become a neglected aspect of nuclear medicine in the molecular era. In this paper, recent developments regarding internal radiation therapy, including developments in radioiodine-131 (^{131}I) and thyroid, radioimmunotherapy (RIT) for non-Hodgkin lymphoma (NHL), and radiopharmaceuticals for bone metastases. Relevant differences and status of their applications in China were mentioned as well. These molecular mediated internal radiation therapies are gaining increasing importance by providing palliative and curative treatments for an increasing number of diseases and becoming one of the important parts of molecular nuclear medicine.

Keywords: brachytherapy, radioisotope, neoplasm, radioiodine, hyperthyroidism

Introduction

Internal radiation therapy, also known as brachytherapy, is a form of treatment where a source of radiation is introduced inside the body. Most radionuclides used in brachytherapy emit beta particles which have a low range of tissue penetration. A few emit auger electrons and alpha particles, and several also emit gamma rays and X-rays during their decay. The radiation only travels a short distance so there is less risk of damaging nearby normal tissues. Most internal radiation therapies locate to tissues or a certain lesion by specifically binding through molecular targets such as metabolic pathways, a ligand-receptor or a specific antibody for its target antigen. The most successful application of metabolic pathway is the use of radionuclide iodine-131 (^{131}I) for the treatment of thyroid diseases, including benign hyperthyroid conditions and thyroid carcinoma. Although sodium iodide symporter (NIS), the specific target of radioiodine, was cloned in 1996, it is amazing that radioiodine therapy had set up a paradigm of molecular medicine more than half a century earlier when radioiodine was first clinically used in 1946.

In this review, ^{131}I treatment of benign and malignant disorders of the thyroid is reviewed first and then other representative targeted radiotherapies are reviewed as well.

Radioiodine–131(^{131}I) and thyroid

^{131}I decays at a physical half-life of 8.1 days with both beta and gamma emissions. The principal γ-ray of 364 keV enables thyroid function imaging or post-^{131}I therapy imaging to see the distribution of ^{131}I with a gamma camera. A principal β-particle has a maximum energy of 0.61 MeV, an average energy of 0.192 MeV, a mean range in tissue of 0.4 mm, and is the radiation effector which has a potential role in

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internal radiation therapy of [131]I. The particular target of radioiodine in thyroid disease is sodium iodide symporter (NIS), which is an intrinsic plasma membrane protein that mediates active iodide transport into the thyroid gland. NIS is modulated by many factors; thyrotropin (TSH) activates NIS via the cAMP pathway in a protein synthesis dependent manner[1], while iodide[2], thyroglobulin (Tg)[3], estradiol[4] and cytokines[5], such as tumor necrosis factor (TNF)-α, TNF-β, interferon (IFN)-γ, interleukin (IL)-1α, IL-1β, and IL-6 inhibit NIS by decreasing its expression at the mRNA or protein level. NIS can be expressed up to 140x in Graves' hyperthyroid tissue than that in normal thyroid gland[6]. While NIS is expressed in differentiated thyroid cancer (DTC), which is primarily comprised of papillary, follicular thyroid cancer and Hurthle cell carcinomas, it can also be expressed at a low level or even overexpressed as non-targeted NIS. Thus, ^{131}I therapy could be used to ablate residual thyroid to prevent recurrence and to destroy recurrent or metastatic foci of DTC. Common indications for therapy of thyroid diseases with ^{131}I primarily include, but are not limited to, benign diseases such as certain types of Graves' hyperthyroidism and toxic nodular hyperthyroidism[7], thyroid remnant ablation, and recurrent or metastatic disease treatment for DTC after near-total thyroidectomy.

Patients who are candidates for ^{131}I treatment should have a special preparation before therapy, such as discontinuation of iodide containing medications and preparations which could potentially affect the ability of thyroid tissue to accumulate iodide. The nuclear physician who performs this treatment must explain the procedure, treatment, complications, side effects, therapeutic alternatives, and radiation protection to patients.

Radioiodine treatment in Graves' hyperthyroidism

Graves' disease (GD) hyperthyroidism is caused by thyrotropin receptor antibody (TRAb), a thyroid-stimulating antibody which binds to and activates the thyrotropin receptor on thyroid cells. TRAb not only causes thyroid hypersecretion but also hypertrophy and hyperplasia of the thyroid follicles. In addition to hyperthyroidism, GD may affect the eyes (Graves' ophthalmopathy, GO) and the skin (localized dermopathy or myxedema) as a result of autoimmune reaction. So far the ideal treatment for GD, which would correct the autoimmune responses in the thyroid and orbits, thereby restoring thyroid function and resulting in the disappearance of ophthalmopathy, is not available. Once GD hyperthyroid has been identified,

the patient and physician must choose among three effective and relatively safe initial treatment options to restore the thyroid function: [131]I therapy (radioactive iodine), antithyroid drugs (ATD), or thyroidectomy. In the United States, ^{131}I had been the therapy most preferred by physicians. However, according to a recent survey which compared findings from a 1991 survey, fewer U. S. (59.7 vs. 69%) and European (13.3% vs. 25%) clinicians would use RAI therapy, with a mild shift away from RAI and toward ATDs in patients with uncomplicated GD[8]. This may be due to the concern of causing new or worsening of GO after ^{131}I therapy[9]. In China, the preferred mode of therapy in uncomplicated Graves' hyperthyroidism is ATDs, ^{131}I and surgery, according to recent questionnaire survey conducted by Chinese Nuclear Medicine Society, and only 32% of clinicians prefer choosing ^{131}I as an initial therapy; among the worries of ^{131}I therapy, 78 % of clinicians worried about hypothyroidism and 14% worried about infertility while 8% worried about carcinogenesis[10].

Among factors that may impact patient preference, choosing ^{131}I therapy for GD hyperthyroidism means that the patient would likely place a higher value on definitive control of hyperthyroidism, the avoidance of traumatic surgery, and the potential side effects (including agranulocytosis, thrombocytopenia, acute hepatic necrosis, cholestatic hepatitis, etc.) of antithyroid medications, while placing a lower value on the need for lifelong thyroid hormone replacement, rapid resolution of hyperthyroidism, and potential worsening or development of GO[9]. [131]I contraindications include pregnancy, lactation, co-existing thyroid cancer, inability to comply with radiation safety guidelines, and females planning a pregnancy within 4-6 months. It might be the first choice for individuals with comorbidities that may increase surgical risk, patients with previously operated or externally irradiated necks, or patients who lack access to a skilled thyroid surgeon or have contraindications to ATD use.

[131]I is administered orally in solution or as a capsule. It is rapidly incorporated into the thyroid, produces thyroiditis and fibrosis via its β emissions, and results in euthyroidism or hypothyroidism within 6-18 weeks. The long-term quality of life (QOL) following ^{131}I treatment for GD was found to be the same as that of the other two options in a randomized clinical study.

In the United States and European countries, the goal of ^{131}I is to control hyperthyroidism by rendering the patient with either euthyroid or hypothyroid with sufficient radiation deposited in the thyroid. In China, the goal of ^{131}I treatment is to strive for rendering euthyroid state or, the least severe extent of

hypothyroidism as possible. This may be due to the fact that most Chinese patients are afraid of hypothyroidism with lifelong levothyroxine replacement therapy. Hence, a calculated dose regime is the choice for most Chinese nuclear medicine physicians and the dose of ^{131}I administered is less than the American Thyroid Association (ATA) guideline recommendation (70-120 μCi $vs.$ 150-300 μCi per gram of thyroid estimated from either ultrasound or gamma camera imaging) accordingly. In a randomized prospective study from China[11], researchers tried to find an optimal dosing strategy for ^{131}I treatment of Graves' hyperthyroidism and attempted to achieve euthyroidism. Individual ^{131}I activity was modulated according to a clinical scoring system, including age, duration of disease, complications, severity of hyperthyroidism, use of ATDs, and gland characteristics. After a 12-year follow-up, one group of patients who received 50-110 μCi per gram of thyroid tissue was identified as the study arm that received the optimum ^{131}I dose, with 71. 8% of the patients maintaining a euthyroid status, 5.8% remaining hyperthyroid, and 22.3% becoming hypothyroid by the end of the study; the recurrence rate was 13.6%. These results are convincing that hypothyroidism could be reduced to some extent after an individualized dose modulated with the particular patient clinical score.

^{131}I has been used to treat hyperthyroidism for six decades and is well-tolerated with rare complications, except for those related to ophthalmopathy[9]. Little evidence can be observed regarding the association of ^{131}I with birth defects, infertility or overall cancer incidence. Thyroid storm occurs only rarely following the administration of radioactive iodine. Compared with the other two methods, ^{131}I therapy of Graves' hyperthyroidism proves to be more cost-effective with an 80% single remission rate and an overall effective rate above 95%, a 1%-4% recurrence rate, and the inefficacy rate of about 2%-4%[12]. So far, there is still an

uncertainty and controversy about the optimal dose, required follow-up, and radiation safety of ^{131}I therapy on Graves' hyperthyroidism, owing to the lack of well-organized multicenter randomized studies.

The role of radioactive iodine–131 (RAI) treatment in differentiated thyroid cancer (DTC)

Postsurgical re–evaluation of risk of recurrence in DTC

An escalating incidence of thyroid cancer worldwide during the last three decades has been reported[13]. As one of the major adjuvant post-surgery treatments, ablation of the small amount of normal thyroid remaining after total thyroidectomy may facilitate both initial staging, by identifying previously undiagnosed disease in post RAI whole body scan (-WBS), and surveillance for early recurrence based on serum Tg measurement and/or RAI WBS. Meanwhile, the potential tumoricidal effect of RAI on persistent thyroid cancer cells in patients at risk of recurrence or disease specific mortality cannot be neglected. Moreover, ^{131}I therapy remains an effective modality for RAI-avid metastatic DTC. Before RAI treatment, a postsurgical assessment should be done.

The AJCC/International Union against Cancer (AJCC/UICC) classification system, based on pTNM parameters and age in DTC, allows accurate identification of the majority of patients at low-risk of mortality (T1-3, M0 patients) and the higher-risk minority (T4 and M1patients) to determine the appropriate intensity of management strategy and follow-up. For the assessment of DTC recurrence risk, a three level stratification has been formulated by American Thyroid Association (ATA) guidelines (***Table 1***). However, controversy remains in the definition of "high risk" mentioned in this table, as "thyroiglobulinemia is out of proportion to what is seen on Rx-WBS". This means

Table 1 **There–level stratification of recurrence risk by ATA guideline (2009)**

| Low risk (with all of the following)	Intermediate risk (with any of the following)	High risk (with any of the following)
No local or distant metastases All macroscopic tumor has been resected	Microscopic invasion of tumor into perithyroidal soft tissue at initial surgery	Macroscopic tumor invasion Incomplete tumor resection
No tumor invasion of locoregional tissues or structures	Cervical lymph node metastases or ^{131}I uptake outside the thyroid bed on the RxWBS	Distant metastases, and possibly Thyroglobulinemia out of the proportion
No aggressive histology(e.g., tall cell, insular, columnar cell carcinoma)	Aggressive histology or vascular invasion	to what is seen on the RxWBS
No ^{131}I uptake outside the thyroid bed on the first post-treatment whole-body RAI scan (Rx-WBS)		
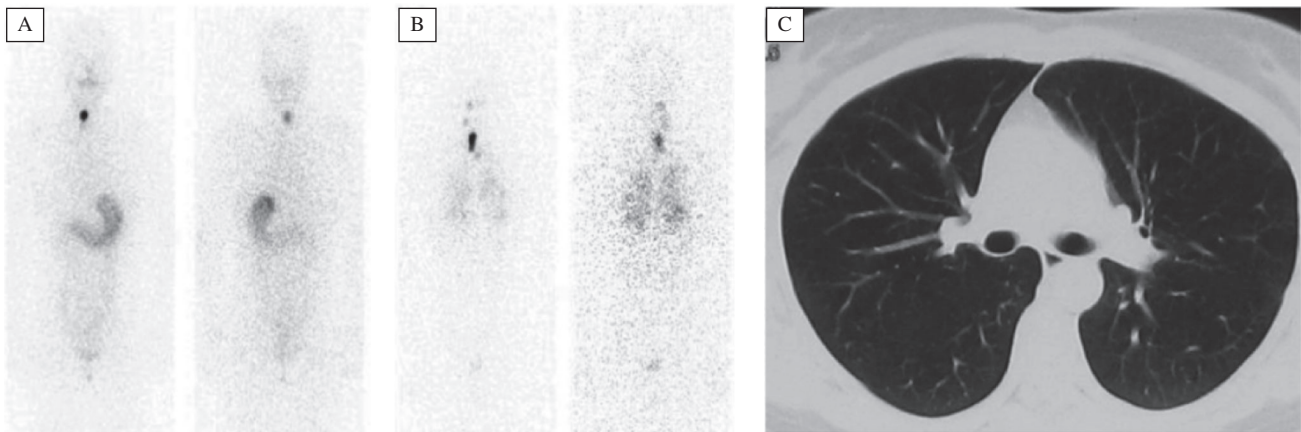
Fig. 1 **Diffuse pulmonary micrometastases (B) identified by post radioactive iodine–131 (RAI) treatment scintigraphy with normal diagnostic ^{131}I scan (A) and chest CT (C).** Cited from Lin Y et al. Clin Nucl Med, 2011; 36:1102-1105[14] with permission

that some micrometastatic patients with normal radiologic findings would be identified as high risk only after the first RAI ablation therapy, which has no impact on the dose decision to ablate (**Fig. 1**). Recent studies suggested that pre-ablative stimulated Tg (ps-Tg) might be considered as a predictive marker for distant metastasis of DTC[14-15], which implies that suspicious high ps-Tg could be regarded as one of the indices for high risk classification even without Rx-WBS (**Fig. 2**). Moreover, in accordance with the above evidence the recently published ''Chinese Management Guidelines for Patients with Thyroid Nodules and Differentiated Thyroid Cancer'' emphasized high ps-Tg level as an important pre-assessment marker and regarded it as one of the high recurrence risk indices before RAI treatment and recommendation for high dose ^{131}I.

RAI dose management in DTC

To date, the optimal ^{131}I activity for remnant thyroid ablation and metastatic disease remains controversial. Though there is a trend toward higher ablation rates with higher activities, two randomized multicenter studies indicated that low dose ^{131}I (1110 MBq, 30 mCi) provides an equally satisfactory ablative outcome, compared with high dose ($\geqslant$3700 MBq, 100 mCi), in low or intermediate risk patients for the purpose of convenient follow-up with Tg and diagnostic ^{131}I- WBS[16,17]. For patients with suspicious residual microscopic disease or more aggressive tumor histology or high recurrence risk, a high dose ($\geqslant$3700 MBq) of ^{131}I is recommended for the first RAI treatment for the purpose of reducing the risk of recurrence and/or mortality. The use of ^{123}I or ^{131}I with modern SPECT/CT or ^{124}I PET/CT-based dosimetry

may facilitate whole-body and lesional dosimetry determination, ^{131}I therapeutic dose management will eventually evolve from empiric fixed amounts to quantitative tumor dosimetry.

Low dose ^{131}I has numerous advantages, compared with high dose. It induces fewer radioiodine related adverse effects or secondary tumors, does not require hospitalization, and is low cost. Recently, Tuttle et al.[18] proposed the concept of reassessment and emphasized the evaluation of response to therapies to modify the initial risk stratification predicted by ATA staging system. Therefore, it is worth arguing the necessity of using high dose in those high risk patients with undetectable ps-Tg, which means excellent prognosis and potential to be free of ^{131}I treatment[19]. In China, fear of causing radioactive adverse effects such
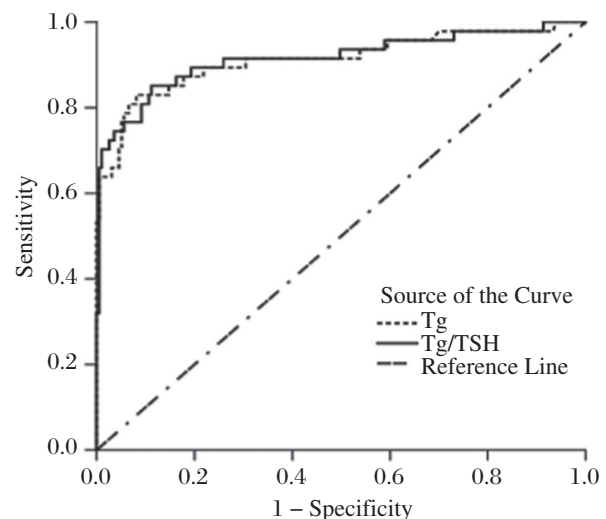

Fig. 2 **The ROC curve of accuracy of ps–Tg and Tg/TSH in distinguishing distant metastases from normal condition.** Cited from Lin Y et al. Clin Nucl Med, 2011; 36:1102-1105[14] with permission.

as secondary tumors and infertility are the major worries in using ^{131}I in DTC from the standpoint of both patients and clinicians other than nuclear medicine specialists. A countrywide, rather uneven use of ^{131}I may be due to a shortage of nuclear medicine and uneven recognition of the role of ^{131}I among surgeons and endocrinologists. Thus, appropriate use and avoiding an unnecessary dose of ^{131}I in DTC patients in China remains the primary subject of the Chinese Nuclear Medicine Society.

Cox regression revealed that ^{131}I remnant ablation in patients with uptake only in the thyroid bed and no evidence of residual tumor could decrease the risk of recurrence, distant metastases and cancer related mortality with a hazard ratio of 0.8, 0.6 and 0.5, respectively[20]. [131]I uptake in the metastatic lesions is a significant prognostic factor for survival. In a long-term retrospective study of 444 DTC patients with distant metastases, Schlumberger et al. found that ^{131}I treatment is highly effective in younger patients with ^{131}I uptake and with small metastases and patients with ^{131}I uptake in metastatic foci had a higher survival rate than those without; the survival rate was 56% *vs.* 10% in 10 years, and 45% *vs.* 6% at 15 years[21].

Dedifferentiation and re–differentiation therapy of DTC

In well-differentiated thyroid cancer (WDTC), during the natural process of the disease, 2%-5% patients lose their differentiated phenotype and dedifferentiate to a more aggressive type, which is defined as dedifferentiation. Dedifferentiated thyroid cancers (dDTC) usually present with RAI resistance and are prone to be more aggressive and more malignant, with a median survival of less than 5 years[22]. Early identification of dDTC is the key point for subsequent management. In metastatic patients with elevating Tg level and negative radioiodine uptake, dDTC should be suspected and [18]FDG PET/CT imaging should be considered for further localization. However, it is important to realize that [18]FDG trapping is not tumor-specific. Malignant thyroid tumors and some benign thyroid diseases, cervical lymph nodes with inflammation, or other inflamed tissues could show high [18]FDG uptake. At present, in China, SPECT is more widely available than PET and most patients cannot afford the expense of [18]FDG PET for diagnosis instead of treatment. A recent study indicated that dDTC lesions can be traced using angiogenesis imaging such as ^{99m}Tc-RGD imaging (***Fig. 3***), thus providing a new approach for diagnosis and localization of dDTC. Meanwhile, the highly neovascularized lesions confirmed by angiogenesis imaging may afford an alternative therapeutic target

and monitor the efficacy of certain anti-angiogenetic therapy[23].

As conventional treatment options are of very limited benefit for dDTC patients, the management of dDTC remains a significant clinical concern. Re-differentiation therapy is one of the prospects, in conjunction with the probability of re-use RAI, which is defined as a treatment to inhibit tumor growth and regain thyroid-specific functions, thus restoring radioiodine uptake and increasing the response to RAI therapy. Various agents, such as retinoid acid[24], thiazolidinedione[25], histone acetylation[26], and methylation inhibitor[27] have demonstrated a promising effect on these RAI-refractory patients.

It has been reported that approximately 39% of RAI-refractory thyroid cancers have BRAF[V600E] mutation[28], which is involved in mitogen-activated protein kinase (MAPK) signaling. The MAPK pathway is triggered by extracellular mitogenic stimuli that activate a receptor tyrosine kinase (RTK) in the cell membrane, then to RAS, RAF (such as BRAF[V600E]), MEK and ERK. ERK is activated by phosphorylation (P) and enters the nucleus where it regulates the balance between tumor-promoting genes and thyroid-specific genes. Constitutive activation by BRAF[V600E] mutation stimulates the signaling of the MAPK pathway, consequently causing the silencing of the thyroid specific gene and reducing the expression of NIS[28], while simultaneously upregulating tumor-promoting genes and leading to dedifferentiation and poor prognosis[29]. When MAPK activation was switched off or its downstream signaling was inhibited by MAPK kinase inhibitors, the tumors would regain the ability to trap radioiodine[30].

Recently, selumetinib (AZD6244, ARRY-142886), a selective MEK 1 and MEK 2 inhibitor, has shown the ability to restore radioiodine incorporation RAI-refractory thyroid cancers in several clinical trials[31]. In one well-conducted clinical trial[31], selumetinib increased the uptake of iodine-124 in 12/20 patients (4/9 patients with *BRAF* mutations and 5/5 patients with *NRAS* mutations) (***Fig. 4***). Of the 12 patients who restored uptake of RAI, 8/12 patients reached the dosimetric threshold for radioiodine therapy, including all 5 patients with *NRAS* mutations. This study provides a proof of principle that MEK inhibitors can induce iodine uptake and retention in thyroid tumors. In another phase II study of selumetinib[32], patients with BRAF[V600E] mutation (12 of 26 evaluated, 46%) had an obviously longer median progression-free survival (PFS) compared with patients with *BRAF* wildtype tumors (33 *vs.* 11 weeks, respectively). These two studies
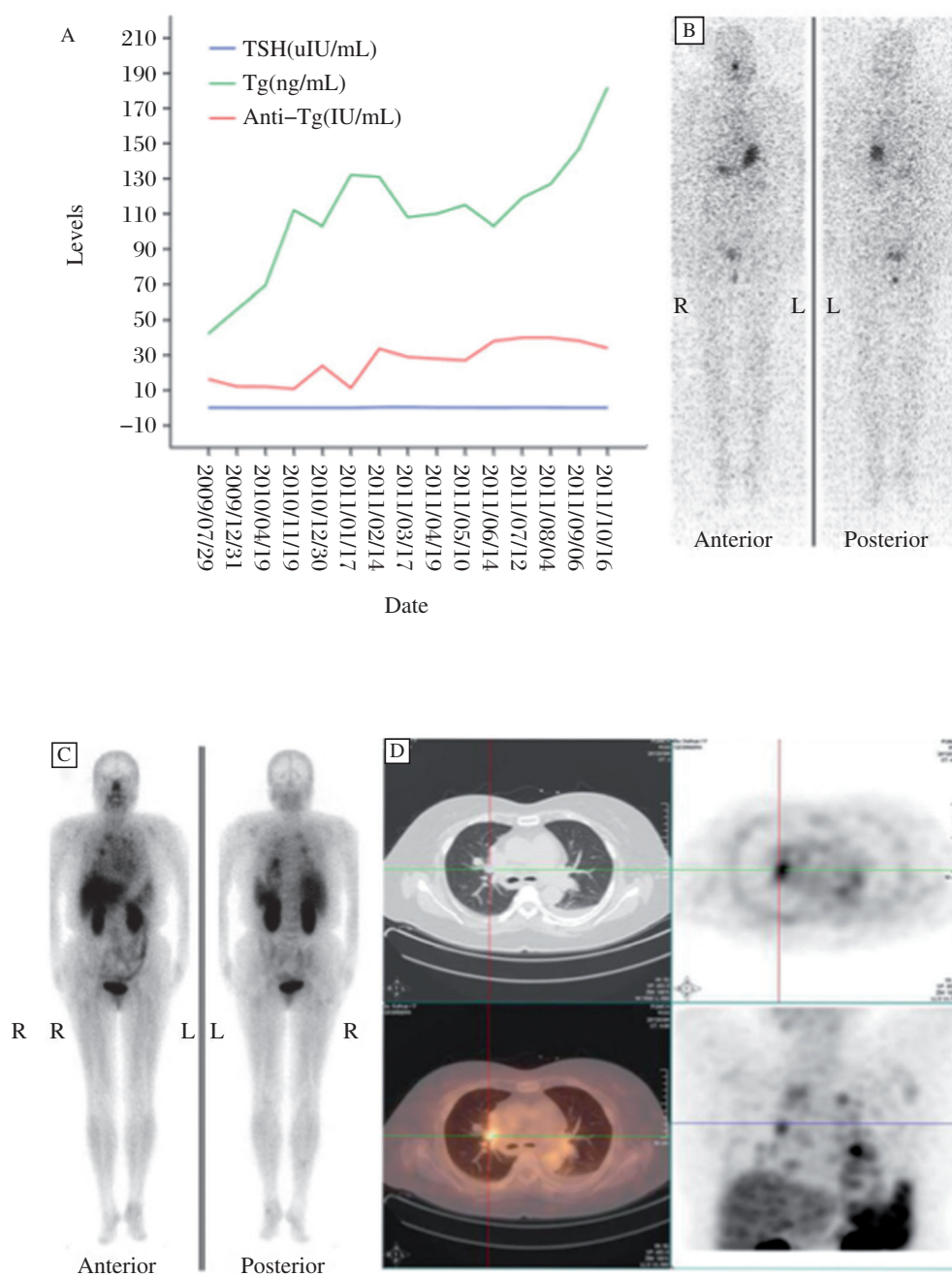
Fig. 3 Elevated levels of unstimulated Tg (ng/mL) and Tg–Ab (IU/mL) with corresponding TSH (A), ^{131}I–negative image with TSH stimulation (TSH>30 uIU/mL) (B), and ^{99m}Tc–RGD–positive planar (C) and SPECT images (D). Cited from Zhao D. et al. J Nucl Med, 2012; 53:1872-1877 with permission.

suggest that selumetinib may have more effectiveness in the case of *BRAF*[V600E] or *RAS* mutation. A randomized, double-blinded study to compare the complete remission rate following a 5-week course of selumetinib or placebo and single dose adjuvant radioactive iodine therapy is ongoing. Although it remains a challenge to manage RAI-refractory advanced or metastatic thyroid cancer, re-differentiation agents may serve as a potential regimen for such patients. We suppose that a combination regimen of MAPK kinase inhibitors and other agents on a re-differentiation therapy with RAI may achieve more promising outcomes.

Radioimmunotherapy for non–Hodgkin lymphoma

Radioimmunotherapy (RIT) refers to the therapeutic use of monoclonal antibodies conjugated via a chelator to a radioactive nuclide. The therapeutic effect is achieved through both the action of the immunoglobu-
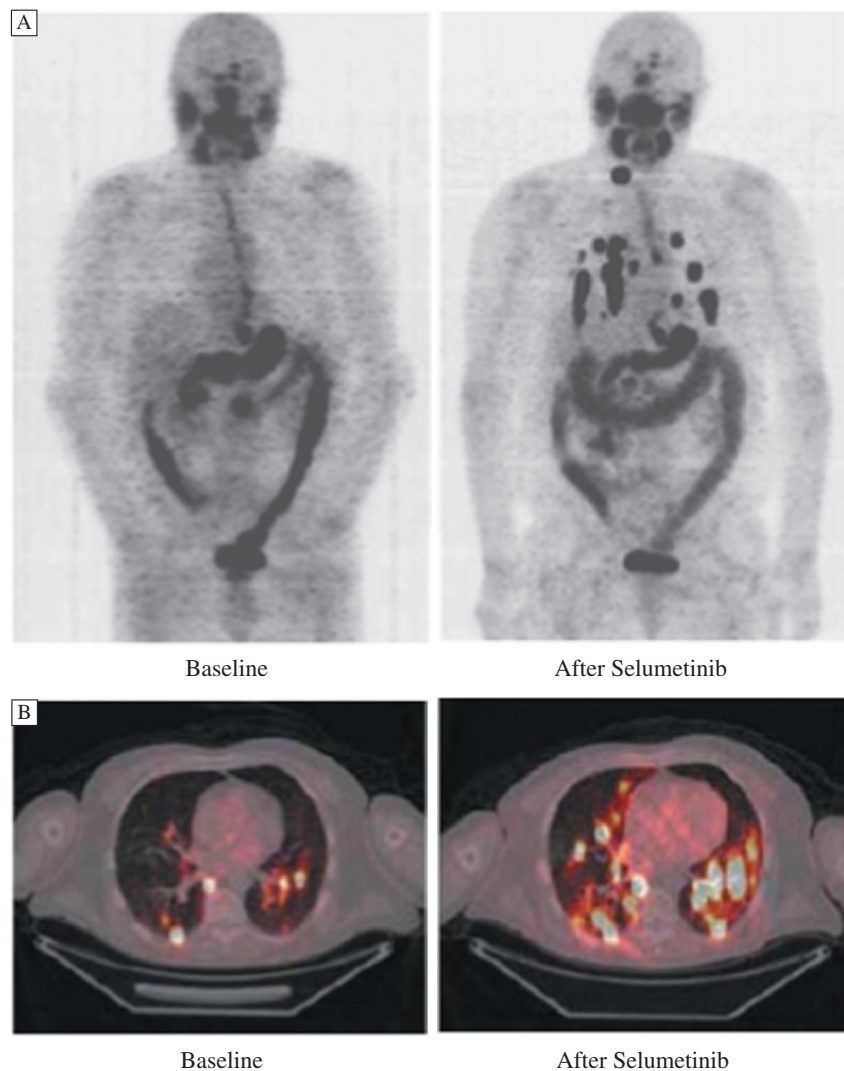
Baseline   After Selumetinib

Baseline   After Selumetinib

Fig. 4 **Whole–body maximum intensity projection images of a patient with a *BRAF* mutant papillary thyroid cancer.** New iodine uptake is shown in nearly all previously negative lung and neck metastases. Panel A shows whole-body maximum-intensity projection images of a patient with a *BRAF*-mutant papillary thyroid cancer. New iodine uptake is shown in nearly all previously negative lung and neck metastases. Panel B shows fused axial PET-CT images of a patient with an *NRAS*-mutant, poorly differentiated thyroid cancer. Both new and significantly increased iodine uptake in lung metastases is shown. Cited from Ho AL et al. N Engl J Med, 2013, 368(7):623-632 with permission.

lin as well as the radiotherapeutic effect of the attached radioisotope. RIT has been shown in clinical trials to be an effective treatment for refractory/relapsed non-Hodgkin lymphoma (NHL). The available agents are Zevalin® and Bexxar®. They are both radiolabeled monoclonal antibodies and both target CD20 receptors present on the surface of lymphocytes.

Zevalin® (ibritumomabtiuxetan, Spectrum Pharmaceuticals, Henderson, NV, USA), a yttrium-90 (^{90}Y) radiolabeled monoclonal murine antibody, was the first radioimmunotherapy approved by the United States Food and Drug Administration (FDA) for the treatment of cancer. CD20 antigen is expressed in most cases of NHL and on normal B lymphocytes but not on stem cells, plasma cells, or non-hematopoietic tissues.

In addition, the CD20 antigen does not shed from the cell surface to form free antigen that could compete the circulating antibody[33]. Because immature B lymphocytes do not have CD20 receptor, normal B lymphocytes will recover in about 9 months after treatment. After Zevalin enters the bloodstream, the monoclonal antibody ibritumomab recognizes and attaches to the CD20 antigen, allowing beta radiation emitted by the Yttrium-90 radionuclide to penetrate and damage B cells as well as neighboring cells. The Zevalin therapeutic regimen was approved by the FDA in 2002 to treat patients with relapsed or refractory, low-grade or follicular B-cell NHL. An added indication was approved by the FDA in 2009 for previously untreated follicular NHL in patients who

achieve a partial or complete response to first-line chemotherapy. The most common adverse reactions of Zevalin are cytopenias, fatigue, nasopharyngitis, nausea, abdominal pain, asthenia, cough, diarrhea, and pyrexia, while the most serious adverse reactions of Zevalin are prolonged and severe cytopenias (thrombocytopenia, anemia, lymphopenia, and neutropenia) and secondary malignancies.

A Phase III randomized controlled trial conducted in 143 patients on Zevalin therapeutic regimen with relapsed or refractory, low-grade or follicular NHL or transformed B-cell NHL revealed an overall response rate and CR rate of 80% and 30%. The rate was much higher than that in patients who received rituximab alone (56% and 16%)[34]. Another multi-center Phase III trial conducted in patients with follicular NHL reported that ^{90}Y-ibritumomab tiuxetan consolidation significantly prolonged median PFS (after a median observation time of 3.5 years) of 36.5 months, compared with no further therapy (13.3 months)[35]. Though some unacceptable hematologic toxicity has been reported, the promising efficacy of Zevalin® has been demonstrated in a recent randomized study which showed that standard-dose ibritumomabtiuxetan combined with BEAM high-dose chemotherapy is safe and possibly more effective than BEAM alone (2-year survival rate, 91% vs. 62%) as a conditioning regimen for autologous stem cell transplantation in patients with aggressive lymphoma[36].

Bexxar, also called as Bezzar (GlaxoSmithKline), a ^{131}I radiolabeled murine monoclonal antibody (I-131 Tositumomab), was approved by the FDA for the treatment of patients with CD20 positive, follicular, NHL, with and without transformation, whose disease is refractory to Rituximab and has relapsed following chemotherapy. Tositumomab is a murine IgG2a lambda monoclonal antibody directed against the CD20 antigen. Possible mechanisms of action of the Bexxar therapeutic regimen includes induction of apoptosis, complement-dependent cytotoxicity (CDC), and antibody-dependent cellular cytotoxicity (ADCC) mediated by the antibody. Additionally, cell death is associated with ionizing radiation from the radionuclide. Adverse events of Bexxar include infection, hematologic toxicity, allergic reaction, anaphylactoid reaction, gastrointestinal symptoms, fever, nausea, sweating, hypotension, and asthenia. Fisher et al.[37] summarized the results obtained in 250 patients in 5 clinical trials that included a subset of heavily pretreated patients. In this group of patients with a considerable disease burden, the median duration of response was 12.9 months with a range from 10.9 to 17.3 months; a complete remission (CR) was seen in 30% of the patients. In the CR group, the median duration of response was almost 5 years (58.4 months), with a minimum duration of 28.3 months. A recent phase III randomized intergroup trial compared the safety and efficacy of CHOP + Rituximab (CHOP-R) and CHOP + I-131 Tositumomab (CHOP-RIT) for 554 patients with previously untreated, advanced-stage follicular lymphomas. After a median follow-up period of 4.9 years, no evidence of significant improvement was found in 2-year PFS (80% vs. 76%) and 2-year overall survival (OS) (93% vs. 97%) comparing CHOP-RIT with CHOP-R[38].

A comparison between Bexxar® and Zevalin®, which was conducted in patients with low-grade refractory/relapsed NHL, showed no statistical significance in objective responses (70.9% vs. 77.8%), CR (35.5% vs. 41.7%), partial remission (PR) (22.6% vs. 25%) and grade 3/4 hematological toxicity (45.2% vs. 61.1%) between the two agents. Because of the relatively small size of the sample, convincing evidence from further large clinical trials is needed to be reported. So far, neither Bexxar®, nor Zevalin® is approved for clinical use in China.

Radiopharmaceuticals for bone metastases

Skeletal metastases occur in many patients with different malignant tumors, especially in the advanced stages of prostate, breast, and lung cancers. Pain secondary to bone metastasis is associated with general suffering, reduced QOL, reduced self-sufficiency, increased mortality, and increased health care cost. As one of the optional treatments for palliation of painful bone metastases, internal therapy by radiopharmaceuticals is generally applied in patients with multifocal bone lesions which cannot be treated by external beam radiation therapy (EBRT). Radiopharmaceuticals are radioactive agents, administered intravenously, that enable the radiation (typically beta/electron emission) to be emitted at the sites of bone metastases. An ideal radiopharmaceutical would be a radiolabeled compound that predominantly accumulated in bone lesions, with low toxicity to bone marrow and limited uptake by normal bone and other organs.

Strontium-89 (^{89}Sr) was the first radiopharmaceutical used in systemic radionuclide therapy for palliation of painful bone metastases. It was first reported by Pecher in 1942 for pain relief in osseous metastases[39] and was approved in the UK in 1989 and USA in 1993 as an unsealed radioisotope for internal radiation therapy. ^{89}Sr emits a pure β-particle with a maximum energy of 1.49 MeV and a physical half-life of 50.5 days. The maximum particle range in tissue is approximately 7 mm and an average soft-tissue range is 2.4 mm. ^{89}Sr is similar to calcium in chemical structure and is able to

be incorporated into the bone and reach the metastatic sites in proportion to the degree of osteoblastic activity. [89]Sr has a 10-fold proclivity for metastatic tumor compared to healthy bone[40]. In light of the relationship between the dose of ^{89}Sr and clinical responses in terms of bone pain palliation, studies suggested a threshold dose below 0.9 MBq/kg appeared ineffective and a response barely increased above 1.5 MBq/kg with more myelosuppressive effect. A recommended dose of 148 MBq (4.0 mCi) in USA, or alternatively dose of 1.5-2.2 MBq/kg may be used[41]. A randomized trial revealed less analgesic intake, pain relief, improved QOL and increased time to development of new bone metastases in patients receiving [89]Sr[42]. This therapy attains a symptomatic benefit in 55%-80% of patients with duration of responses ranging between 2 and 17 weeks[43]. Nevertheless, it did not prove to be effective in extending OS[44]. As ^{89}Sr is designed for malignant diseases involving osseous metastases, combination with chemotherapy is another consideration. [89]Sr is currently used on a worldwide scale and is clinically available in China.

Samarium-153 ([153]Sm) emits β-particle, with a physical half-life of 1.9 days. The β-particle has a maximum energy of 0.81 MeV, a mean energy of 0.23 MeV, and an average soft-tissue range of 0.6 mm. The β-ray is accompanied by a 103keV γ-ray, which allows simultaneous scintigraphic tracking with a gamma camera. [153]Sm has been chelated with bone-seeking polyphosphonates (EDTMP) and has the advantage of an optimum combination of high bone uptake, rapid blood clearance, and renal excretion when Sm is chelated with EDTMP. A dose of 1 mCi/kg for both clinical efficacy and safety was established from randomized trials for patients with painful bone metastases. There is no increase in pain relief but a greater degree of myelosuppression is present from higher administered activities. Pain relief was observed in 62%-72% of subjects with no effect on OS[45]; it usually begins in 1 to 4 weeks and has lasted about 11 months[46]. [153]Sm is also used countrywide in China.

Rhenium (Re)-1861, 1-hydroxyethylidenediphosphonate([186]Re-HEDP) is a bone seeking radiopharmaceutical which emits β-particle (1.07 MeV) with a maximum range of penetration of 5 mm, γ-photons (137 keV) suitable for imaging, and with a physical half-life of 89 hours. Response of pain relief can be observed in 65%-80% of patients undergoing radiotherapy with [186]Re-HEDP, with a mean duration of response of seven weeks[47], while there is no influence on OS. As an isotope of [186]Re, [188]Re-HEDP has also been used for bone pain palliation. It has the advantage of ready and on-demand availability of [188]Re from a generator and a kit is available for attaching it to HEDP. [188]Re-HEDP has a short physical half-life of 16.9 hrs and a higher energy of maximum beta-emission of 2.1 MeV. With similar biodistribution, dosimetry characteristics, toxicity, and benefits as [186]Re-HEDP in patients with osseous metastases, Chen et al. reported that [188]Re-HEDP significantly improved QOL in 81.5% subjects with administration of 1110 MBq (30 mCi), which enabled them to reduce their analgesic intake.

Radium-223 ([223]Ra) is a calcium-mimetic bone-seeking radiopharmaceutical, in the form of radium dichloride. In contrast to the above mentioned β-emitters which are generally limited by adverse effect on bone marrow, [223]Ra predominantly emits α particles, which is characterized by highly energetic radiation and short range (<0.1 mm). It is able to induce more lethal tumoricidal effect with less surrounding tissue exposure and less adverse effects such as hematologic toxicity and myelosuppression. So far, [223]Ra is the only bone-seeking drug demonstrated to extend OS in metastatic castration-resistant prostate cancer (CRPC) patients, thus confirming the key role of targeting bone metastases to improve patient prognosis. A phase III trial enrolled 922 symptomatic patients with only bone metastases due to CRPC, either failing (60%) or not eligible or refused (40%) a prior docetaxel-based chemotherapy (ALSYMPCA study), who received either 6 intravenous treatments of Ra-223 at 50 kBq/kg or placebo, with an interval of 4 weeks between each treatment. Compared with placebo, [223]Ra significantly improved OS in patients with CRPC with bone metastases (2-sided $P=0.00007$; HR: 0.658; 95% CI, 0.581-0.832; median OS 14.9 months vs. 11.3 months, respectively). Beneficial effect was also observed regarding time to first skeletal related events such as pathologic fractures and skeletal complications including nervous tissue compressions and hypercalcemia, as well as time to total serum bone-specific ALP or PSA progression. [223]Ra also improved QOL, especially in the pain, physical well-being, social/familial well-being, and emotional and functional well-being subscales, in terms of changes in the Functional Assessment Scale-Prostate subscale scores. The drug holds the promise of being evaluated as a viable monotherapy option in frontline or chemotherapy-progressed patients in the absence of visceral disease. [223]Ra was approved by the FDA in 2013 for the treatment of patients with metastatic CRPC with symptomatic bone metastases and unknown visceral metastatic disease. Its clinical use in China remains as "need-to-be-approved" by the Chinese Food and Drug Administration.

To summarize, advances in several areas of radionuclide internal radiation therapy have been reviewed in

this article, including benign and malignant thyroid disease, RIT for NHL, and radiopharmaceuticals for palliation of painful bone metastases. These molecular mediated internal radiation therapies are gaining increasing importance by providing palliative and curative treatments for an increasing number of diseases and becoming one of the important aspects of molecular nuclear medicine that should never be neglected to keep nuclear medicine as an integrity.

Acknowledgments

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