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Review

Clinical Perspectives of Theranostics

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Abstract: Theranostics covers combination of diagnostic and therapeutic techniques for various cancers throughout body using suitable drug combination. This review covers well-known treatment of thyroid cancer and pheochromocytoma with I-131 compounds and also new radiopharmaceuticals for prostatic cancer and pancreatic cancer. Of particular, new trends toward patient outcome has been focused. The theranostics will become an ever-increasing part of clinical nuclear medicine these days.

Keywords: PET, theranostics, radiopharmaceuticals

1. Introduction

Theranostics is a re-emerging new medical term of combination of diagnostic and therapeutic techniques mainly for oncology areas using suitable drug combination [1]. Theranostics has long been applied to treat thyroid cancer and neuroblastomas using suitable radiolabeled compounds, I-131 iodine and I-131-iodine-meta-iodobenzylguanidine (MIBG). More recently, theranostics has been refocused with advent of new therapeutic antibodies and small molecules which can be transformed into theranostic agents through radioconjugating with radioactive isotope materials [2]. A number of PET compounds labeled with Ga-68 or F-18 have been used for imaging, while beta- or alfa-emitting sister compounds are applied for therapy [3–5].

The theranostics play an important role for both detection of malignant lesions throughout the body using tumor affinity compounds, and also treating lesions with radiotherapy emitted from beta- or alfa-emission from the same targeted radiolabeled compounds. Table 1 summarizes various combination of diagnostic imaging and internal therapy with radiopharmaceuticals for the same target molecule. Thus, systematic imaging and radioisotope therapy is permitted with use of suitable radiolabeled compounds. There are a number of reports indicating not only the diagnostic values but also better prognostic values of oncology therapy as compared to the conventional systemic chemotherapy [6,7].

Table 1. Combination of diagnostic imaging and internal radiation therapy with radiopharmaceuticals for the same targe disease.

Target Disease	Diagnosis	Therapy
Thyroid cancer	I-131	I-131
Malignant pheochromocytoma, Neuroblastoma	I-123 MIBG I-131 MIBG	I-131 MIBG
Malignant lymphoma	In-111 Ibritumomab Tiuxetan	Y-90 Ibritumomab Tiuxetan
Neuroendocrine tumor	In-111 Pentetreotide Ga-68 DOTATE Ga-68 DOTATOC	Y-90 DOTATATE, Y-90 DOTATOC Lu-177 DOTATATE Lu-177 DOTATOC

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Bone metastasis of prostatic cancer	Tc-99m bone scan	Ra-223
Prostatic cancer	Ga-68 PSMA F-18 PSMA	Lu-177 PSMA Ac-225 PSMA

2. Prognostic Value of Theranostics for Thyroid Cancer

Radioiodine therapy with I-131 iodine is a well-established treatment modality for adjuvant postsurgical ablation of thyroid remnant tissue and therapy of nonresectable local recurrences, lymph node, and distant metastases [8].

Differentiated thyroid cancer has strong affinity to I-131 and thus, shows good response to iodine treatment. Dedifferentiated thyroid cancer lesions, on the other hand, tend to lose radioiodine affinity, but instead show an increased glucose metabolism [9]. Both histological and imaging studies provide evidence that increased glucose uptake correlates with a higher grade of malignancy and a worse prognosis [10–13]. Accordingly, FDG PET is considered a valuable tool for the detection of radioiodine-negative metastases in the follow-up of patients with DTC [14–17] (Figure 1 and Figure 2). In addition, FDG-PET holds a promise for valuable tool for predicting long prognosis of thyroid cancer.

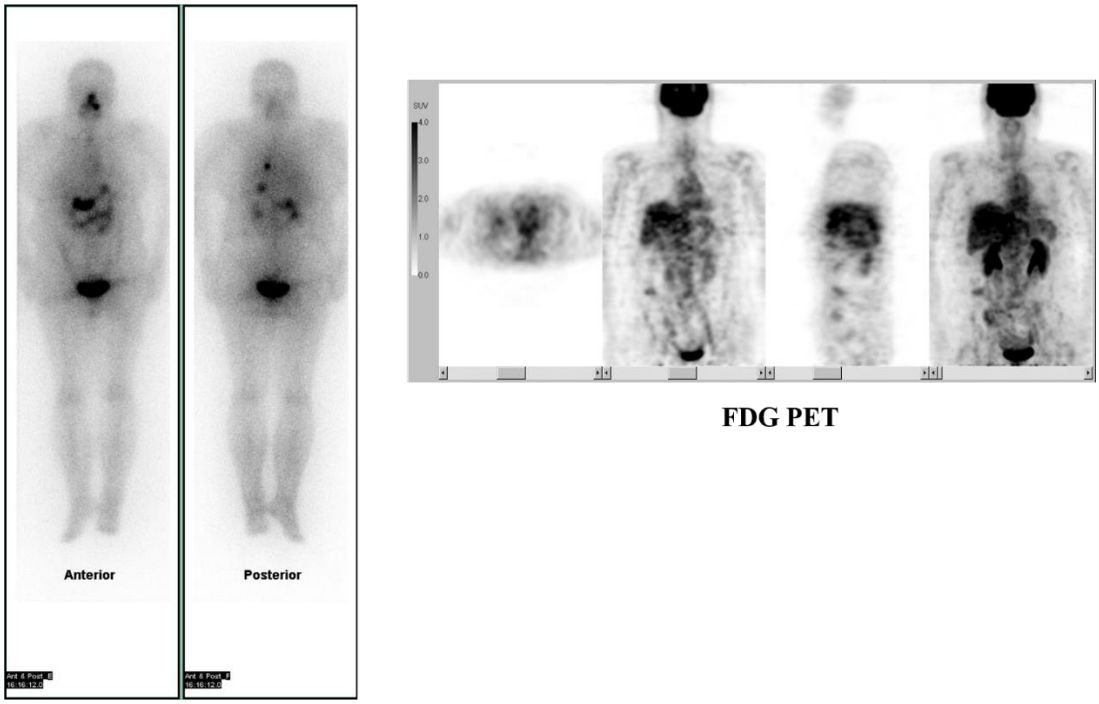

Figure 1. A case with thyroid cancer showing positive I-131 and negative FDG uptake in the lung.

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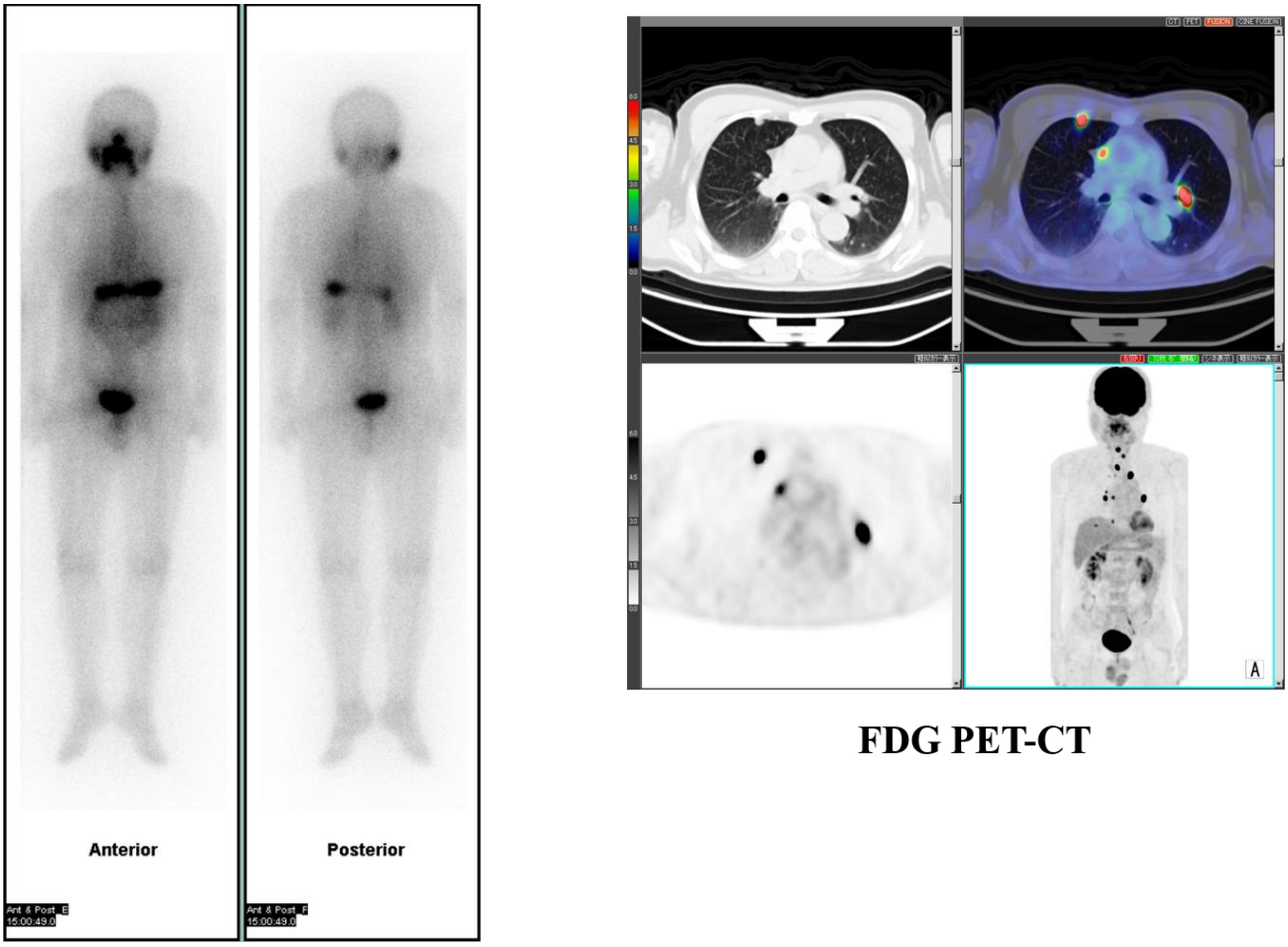

Figure 2. A case with thyroid cancer showing negative I-131 and positive FDG uptake in the lung.

We have analyzed the predictive value of FDG-PET in comparison with radioiodine uptake in 141 high-risk patients with differentiated thyroid cancer with radioiodine therapy after total thyroidectomy [18]. Our results indicate that FDG PET was more predictive for long-term survival, whereas radioiodine uptake was more important for short-term response. Therefore, FDG PET after at thyroid remnant ablation should hold a prognostic value for management of high-risk patients with differentiated thyroid cancer [18].

3. Prognostic Value of Theranostics for Neuroendocrine Tumor

Pheochromocytoma and paraganglioma (PPGL) may develop metastatic lesions. The mean expected survival time with pheochromocytoma is 20.7 years and with paraganglioma is 9.8 years [19,20]. After surgery, systemic chemotherapy is commonly performed for treating remaining and metastatic lesions, however, the survival benefits are not clear because of the lack of prospective comparative studies [21–23].

Iodine-131-meta-iodobenzylguanidine (I-131 MIBG) is a substrate of the norepinephrine transporter system and the structure is similar to norepinephrine [24]. Norepinephrine works as a neurotransmitter in the central and autonomic nervous systems. The concentrations of norepinephrine in the nervous systems are regulated by the norepinephrine transporter. I-131 MIBG also accumulates; however, unlike norepinephrine, I-131 MIBG has little or no affinity for adrenergic receptors [25]. I-131 MIBG radiotherapy has been used to treat neuroendocrine tumors (NETs), including metastatic PPGL, medullary thyroid carcinoma and carcinoid tumors that have the uptake-1 mechanism [24,26,27].

I-131 MIBG radiotherapy has shown some survival benefits in metastatic NETs. European Association of Nuclear Medicine (EANM) clinical guidelines for I-131 MIBG radiotherapy suggest a repeated treatment protocol, although none currently exists [28]. The

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existing single-high-dose I-131 MIBG radiotherapy (444 MBq/kg) has been shown to have some benefits for patients with metastatic NETs. However, this protocol increases adverse effects and it requires alternative therapeutic approaches.

A previous study reported that FDG PET SUVmax was reduced after I-131 MIBG radiotherapy in patients considered to have responded, suggesting the value of FDG PET imaging for treatment evaluation in patients with PPGL after I-131 MIBG radiotherapy [29] (Figure 3).

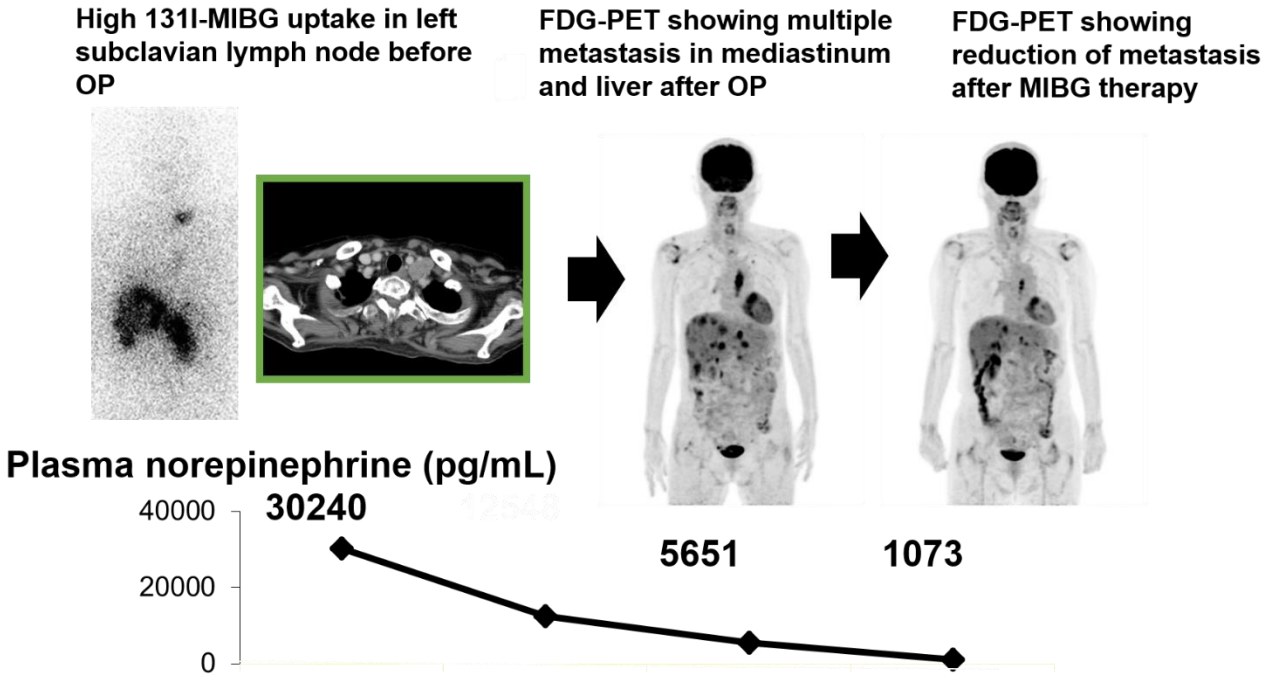

Figure 3. A case with pheochromocytoma.

Accordingly, we have evaluated the effects of repeated I-131 MIBG therapy on tumor size and tumor metabolic response in patients with metastatic NETs to find reduced tumor size and tumor metabolic activities according to lesion-based analysis in about one-third of patients and stabilized a majority with this therapy [30]. Thus, we concluded that this relatively short-term repeated I-131 MIBG treatment may have potential as one option in a therapeutic protocol for metastatic NETs [30].

Theranostics has recently been covered NETs with somatostatin receptor targeting small molecule tracers such as Ga-68 DOTATATE PET, In-111 Pentetreotide, and Peptide Receptor Radionuclide Therapy (PRRT) with Lu-177 DOTATATE therapy. The patients with positive uptake in Ga-68 DOTATATE PET or In-111 Pentetreotide are indication for Lu-177 DOTATATE treatment in European Medicines Agency (EMA) and Food and Drug Administration (FDA). Progression free survival (PFS) rate at 20 months was significantly increased from 11% of patients in the control group to 65% in the Lu-177 DOTA-TATE group ($p < 0.0001$) [31].

4. Prognostic Value of Theranostics for Bone Metastasis

Theranostic approaches for osseous metastasis have long been focused for alpha therapy using Ra-223 for various solid tumors, such as thyroid cancer and prostatic cancer. It is important that radionuclide therapy has not only a palliative effect but also a potential for prolong progression-free and overall survival [32–34]. This randomized control study nicely showed 6 month longer survival by Ra-223 therapy for bone metastasis from castrate-resistant prostatic cancer. Accordingly, Japanese government has approved insurance coverage for Ra-223 therapy for those with multiple bone metastasis from prostatic cancer [35].

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5. Future Perspectives of Theranostics

More recently, a number of new radio-labeled pharmaceutical compounds have been investigated for promoting theranosis. One of the most exciting new theranostics agents is prostate specific membrane antigen (PSMA) binding compound for prostatic cancer developed at Heidelberg University and many researches worldwide [36]. Prostatic cancer is the second most common cancer in men worldwide with an estimated about a million 1,276,000 new patients. About 30% of men experience biochemical recurrence, often progress to castration resistant prostate cancer (CRPC), and 359,000 deaths in 2018 [37,38].

The prognosis of the patients with CRPC has been better because of new drugs was developed in the last decade. Ga-68 or F-18 labelled PSMA has been used for whole body PET imaging to identify metastatic lesions. In addition, Lu-177 and Ac-225 labeled PSMA therapy is expected additional effect by unique mechanism using radiopharmaceutical. Lu-177 or Ac-225 PSMA therapies are main strategies on theranostics at present. PSMA PET detects recurrent and metastatic tumors more accurately than conventional imaging diagnostic tools such as computed tomography (CT), bone scintigraphy (BS), or F-18 Fluciclovine PET [39–41]. In the study of our group, the accuracy of Ga-68 PSMA PET was 99.8% which was significantly much higher than BS (84.3%) and BS + Single Photon Emission Computed Tomography (SPECT). Our group also reported that similar uptake is shown between pretherapeutic Ga-68 PSMA-PET and Lu-177 PSMA therapy, therefore, Ga-68 PSMA PET avid lesions are expected the effect of Lu-177 PSMA therapy (Figure oka1) [38]. Up to 4 cycles treatments with 6 weeks interval are standard course of Lu-177 PSMA therapy considering for kidney absorbed dose at a risk organ [42] (Figure 4).

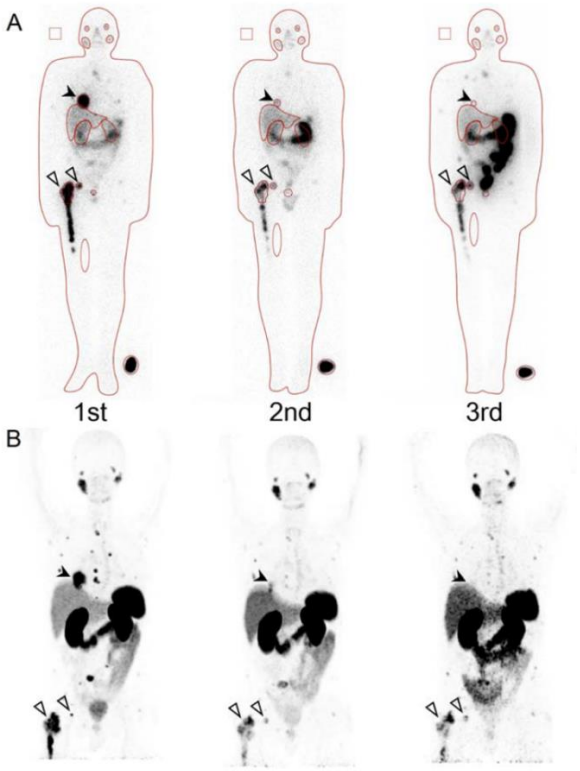

Figure 4. A patient with multiple metastases in lung (Black arrow) and bone (White arrows). A: posttherapeutic Lu-177 PSMA scintigraphy. B. Pretherapeutic Ga -68 PSMA PET (Okamoto et al. J Nucl Med 2017; 58: 445-450) [42].

Remarkable therapeutic effect of Lu-177 PSMA therapy for CRPC has been described in several reports [43–47]. PSA decline from baseline was seen in 68% of patients [40], greater than or equal to 50% seen in 44–64% of patients [39–43], At least 80% decline was seen in 44% of patients, and 16% achieved an at least 98% PSA decline (43). Regarding

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toxicity, no treatment-related deaths, and grade 2 or less xerostomia was reported in 8–66% of patients. Grade 1–2 nausea was seen in 6–48%, respectively. Grade 3–4 toxicity was primarily hematologic, including leukopenia (3–32%), thrombocytopenia (5–10%), and anemia (10%). Grade 1–2 renal injury occurred in 10% of patients [43,44]. Ac-225 PSMA therapy is expected excellent therapeutic effect even for PC which resistant to Lu-177 PSMA therapy [48]. PSA decline of more than 50% from baseline was observed in 21–63% of the patients [49–51]. This rate is similar as the biochemical response rates of Lu-177 PSMA therapy, however, note that many patients who underwent Ac-225 PSMA therapy were refractory to previous Lu-177 PSMA therapy.

Another exciting theranostic trial is for applying for cancer with poor prognosis. Most of theranostic radiopharmaceuticals have so far been applied for cancer with relatively good prognosis. On the other hand, pancreatic adenocarcinoma has an extremely poor prognosis. Five year survival rate of metastatic pancreatic adenocarcinoma is less than 5% [52]. At the time of diagnosis, most patients are ineligible for surgery due to metastatic spread pr local invasion. For metastatic disease cytotoxic chemotherapy is the only treatment choice in most occasion [52]. Neurotensin receptor 1 (is highly expressed in ductal pancreatic adenocarcinoma as well as hepatic metastasis but not in normal pancreatic tissue or chronic pancreatitis [53,54]. 3BP-227 is a DOTA-conjugated neurotensin receptor 1 antagonist [53] and Lu-177 labeled 3BP-227 significantly inhibited tumor growth [54]. The first clinical trial of Lu-177 labeled 3BP-227 indicated feasibility of treatment of ductal pancreatic adenocarcimona [55]. More clinical experiences are warrated to see whether this new agent may prolong survival of this disease.

6. Conclusion

This review has outlined old as well as recently developed nuclear theranostics which has been entered the clinic as well as evolving imaging and therapy. Of particular, new trends toward patient outcome has been focused. The theranostics will become an ever-increasing part of clinical nuclear medicine these days.

Funding:

Conflicts of Interest:

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