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Nuclear Theranostics in Taiwan

Ko-Han Lin[1] · Yi-Wei Chen[2] · Rheun-Chuan Lee[3] · Ling-Wei Wang[2] · Fong-In Chou[4] · Chi-Wei Chang[1] · Sang-Hue Yen[2] · Wen-Sheng Huang[1]

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Abstract
Boron neutron capture therapy and Y-90 radioembolization are emerging therapeutic methods for uncontrolled brain cancers and hepatic cancers, respectively. These advanced radiation therapies are heavily relied on theranostic nuclear medicine imaging before the therapy for the eligibility of patients and the prescribed-dose simulation, as well as the post-therapy scanning for assessing the treatment efficacy. In Taiwan, the Taipei Veterans General Hospital is the only institute performing the BNCT and also the leading institute performing Y-90 radioembolization. In this article, we present our single institute experiences and associated theranostic nuclear medicine approaches for these therapies.

Keywords BNCT · Radioembolization · FBPA-PET · Tc-MAA

Theranostic Approach Using ^{18}F-FBPA–PET in Boron Neutron Capture Therapy

The Boron Neutron Capture Therapy

Boron neutron capture therapy (BNCT) is a developing modern cancer-therapy technique. The theory of BNCT is different from the photon-beam or particle radiotherapy. The BNCT serves as a cellular-level radiation therapy which is based on the nuclear reaction of the 10B nucleus in tumor cells, followed by thermal neutron radiation to induce 10B nucleus fission reaction, which absorbs low-energy neutrons to produce two high-linear-energy transfer particles (^{4}He and ^{7}Li). These two particles have great biological effects on tumor cells, and the most advantage is that their cellular destruction of target lesions reaches only reach 4–9 μm, which confines just within a single tumor cell, causing little damage to the surrounding normal tissues [1, 2].

The key element of the success of BNCT lies in a high quality thermal neutron beam which could induce the reaction and a boron-containing carrier resulting in uptake selectively by the tumor cells while minimal uptake by normal tissues within the irradiated field. Therefore, the development of highly specific boron-containing compounds is crucial for BNCT [1, 2]. Theoretically, in order to obtain an ideal therapeutic effect, the concentrate ratio of Boron-10 between tumor cells and normal tissues should be over 2.5–3.0. Meanwhile, to illuminate the concentration of the boron-containing carrier with a non-invasive imaging method also becomes a critical issue to predict the efficacy of BNCT.

The Boron-Containing Compounds and Its Theranostic Derivative

At present, many boron-containing compounds are developing. However, most of them still remain in the laboratory synthesis or animal studies. Currently, two boron-containing compounds are used clinically, BSH (sodium borocaptate) and BPA (boronophenylalanine) [1, 2]. Both BSH and BPA are administrated through veins, aggregating in tumor cells via venous distribution.

✉ Sang-Hue Yen
sanghueyen@gmail.com

✉ Wen-Sheng Huang
wshuang2@vghtpe.gov.tw

[1] Department of Nuclear Medicine, Taipei Veterans General Hospital, No.201, Section 2, Shipai Rd., Beitou Dist., Taipei City, Taiwan, Republic of China

[2] Division of Radiotherapy, Department of Oncology, Taipei Veterans General Hospital, No.201, Section 2, Shipai Rd., Beitou Dist., Taipei City, Taiwan, Republic of China

[3] Department of Radiology, Taipei Veterans General Hospital, Taipei, Taiwan, Republic of China

[4] Nuclear Science and Technology Development Center, National Tsing-Hua University, Hsinchu, Taiwan, Republic of China

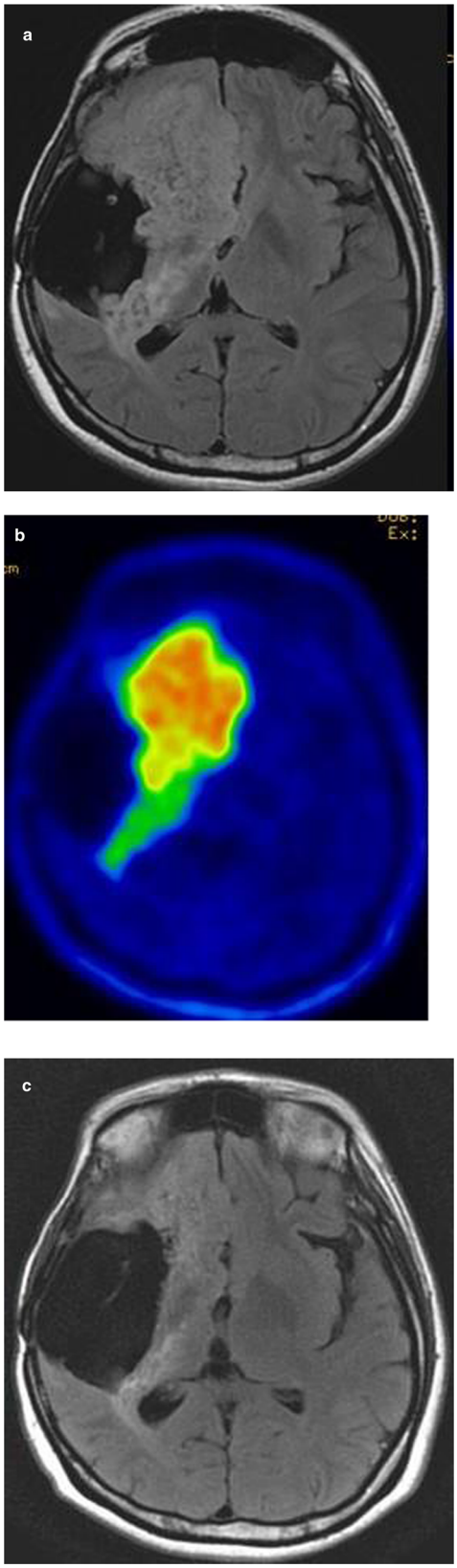


Fig. 1 This was a patient of recurrent and unresectable anaplastic astrocytoma (pre-BNCT MRI) (**a**). She was referred to receive compassionate BNCT therapy and the ^{18} FBPA–PET (**b**) revealed a high T/*N* = 4.7 of the tumor. The 6-month follow-up MRI confirmed tumor regression after BNCT (**c**)

Currently, most medical and research institutes use BPA as a boron-10 carrier. BPA is an analogue of the essential amino acid phenylalaine. Given that rapid growth of tumors requires large amount of protein synthesis, tumor cell surfaces often appear active L-type amino acid transporter 1 (LAT-1) to uptake a large number of phenylalaine [3]. Under this circumstance, tumor cells also uptake a great amount of BPA via LAT-1, leading to the accumulation of BPA in the tumor cells.

Meanwhile, the concentration of BPA in tumor cells and normal tissues could be monitored with ^{18}F- boronophenylalanine (^{18}FBPA), an ^{18}F-labeled radiopharmaceutical analogue of BPA which can be detected by PET imaging [4–7]. The ^{18}FBPA-BPA theranostic combination gives us a crucial picture to calculate the estimated tumor dose to assure safety and efficacy of BNCT. Based on the information by ^{18}FBPA-PET, physicians can draw up treatment plans and confirm the irradiation dose from boron neutron capture reaction.

Regarding the tumor and normal tissues dose calculation, nuclear medicine physicians will determine the uptake value from target tumors, normal tissues close to the tumor, and blood pool, respectively, according to the ^{18}FBPA-PET. Then, the absorption ratios between tumors and normal tissues (T/N ratio), tumors and the blood (T/B ratio) will be calculated.

Development and Clinical Experience of BNCT in Taiwan

In Taiwan, the only thermal neutron source for BNCT is from the Tsing-Hua Open-Pool Reactor (THOR), a 2 MW research reactor at National Tsing-Hua University. The THOR was constructed in 2004, and has been used for preliminary dosimetry studies and clinical treatments. With the assistance of Kyoto University, the Taiwanese BNCT project is undertaken by Taipei Veterans General Hospital and National Tsing-Hua University using THOR as the neutron source which is the first in Taiwan, the second in Asia, and the eighth worldwide for BNCT clinical trial, mainly focused on recurrent hear and neck cancers in the beginning in 2010. It extends to other malignancies such as malignant brain tumor owing to its potentially therapeutic efficacy.

A prospective phase I/II clinical trial of BNCT regarding recurrence head and neck tumor including 17 patients between 2010 and 2013 was conducted. The median tumor/normal tissue ratio was 3.4 for the first fraction and 2.5 for the second, whereas the median D80 for the first and second fraction was 19.8 and 14.6 Gy-Eq, respectively. After a median follow-up period of 19.7 months (range, 5.2–52 months), six patients exhibited a complete response and six had a partial response. Two-year survival was 47%. Two-year loco-regional control was 28% [8, 9].

Another BNCT project regarding 40 times of treatments was performed through compassionate therapy from 2017 to August 2018. Most patients are recurrent high-grade

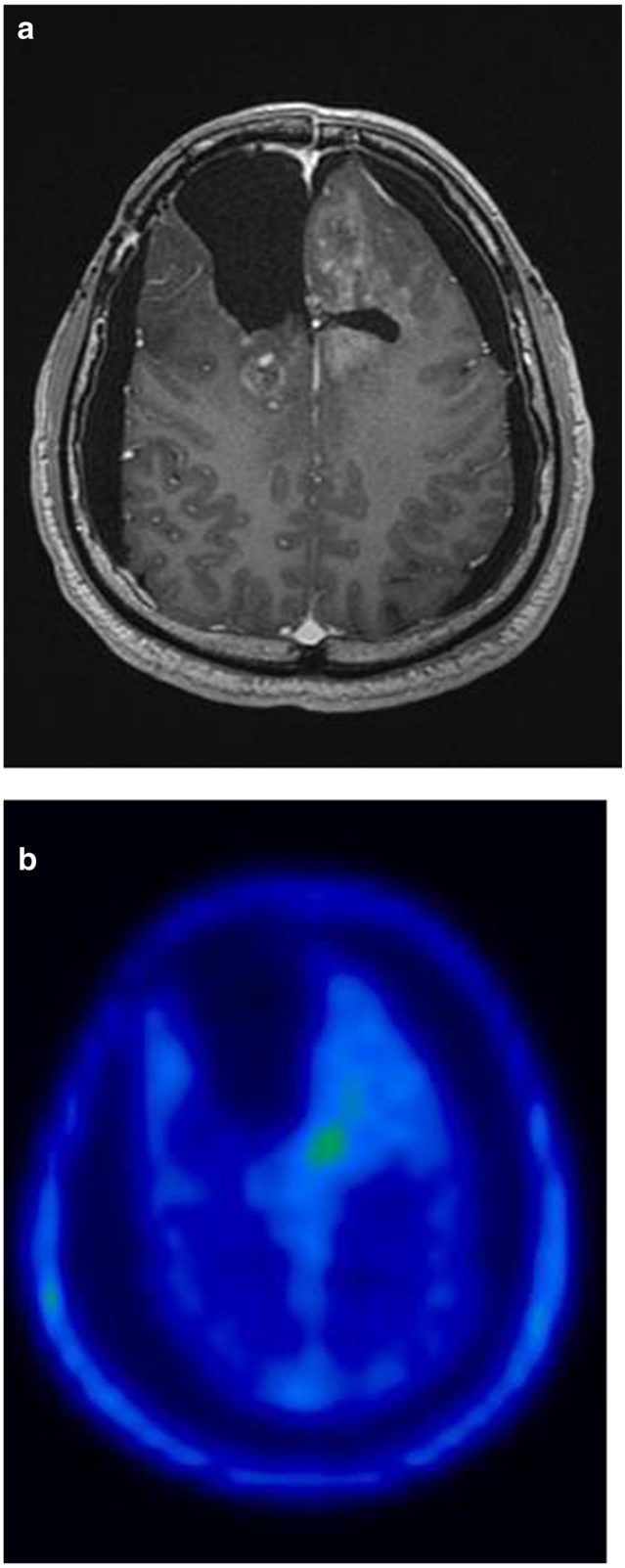


Fig. 2 A patient of recurrent anaplastic astrocytoma in the left frontal lobe (**a**) received ^{18} FBPA–PET for pre-treatment evaluation. However, the tumoral uptake of ^{18} FBPA is low (T/*N* = 1.9). The patient was not eligible for BNCT treatment (**b**)

astrocytoma of cerebrum (glioblastoma and anaplastic astrocytoma, 21 patients) and recurrent head and neck cancers (nasopharyngeal carcinoma and squamous cell carcinoma, 14 patients). Other patients include poor-differentiated thyroid carcinoma, parotid gland tumor, meningioma, and diffuse intrinsic pontine glioma (DIPG). Most of these malignant tumors appear highly specific to ^{18}FBPA uptake. Malignant brain tumor: $T/N = 3.01 \pm 0.93$ (median 2.80); (range 1.9–5.6). Head and neck tumor: $T/N = 3.31 \pm 1.58$ (median 2.84); range 1.35–6.8. The initial results are promising, as shown in the following figures (Fig. 1).

We also noticed that some high-grade or poorly differentiated malignancies did not uptake ^{18}FBPA as expected (Fig. 2). Thus, the "theranostics approach" with ^{18}FBPA-PET before BNCT is essential to guide the procedure to obviate unnecessary treatment for patients and to prevent side effects from the treatment.

Limitations of BNCT

One of the biggest challenges of BNCT is the source of thermal neutron. In most of countries, including Taiwan, thermal neutron used in BNCT is produced from a nuclear reactor, the so-called reactor-based BNCT (RB-BNCT). As a result, patients often receive this treatment in the institutes where the nuclear reactor is located, instead of the hospital. This hinders BNCT from becoming a standard treatment modality. At present, some institutes are building the accelerator to produce thermal neutron, permitting BNCT to be conducted in medical facilities, as we called accelerator-based BNCT (AB-BNCT), and this could render BNCT feasible to promote and to popularize [10].

The second problem is the development of Boron-containing compounds. Because the currently used compound, BPA/^{18}FBPA theranostic combination, is not well absorbed by some malignant tumors [11], therefore, it is mandatory to develop new boron-containing compounds in order to treat more types of malignant tumors.

Summary of ^{18}F-FBPA–PET in BNCT

BNCT is a cellular-level radiation therapy currently based on the high selectivity of BPA, the boron-carrier, into tumor cells. Thus, a "theranostic approach" using ^{18}FBPA to evaluate the eligibility of patients is essential before BNCT.

Theranostic Approach Using Tc-99 m Macroaggregated Albumin and Post Y-90 Imaging in Yttrium-90 Radioembolization

Y-90 radioembolization (Y-90 RE), also known as selective internal radiation therapy (SIRT) or trans-catheter arterial

radio-embolization (TARE), is an emerging method to treat locally advanced hepatocellular carcinoma (HCC), other primary liver malignancies, and liver-predominant metastatic diseases using radioactive Y-90 microspheres through intra-arterial infusion.

Y-90 microspheres are infused via hepatic artery and retains in the microvasculature that supplies the hepatic malignancies. The half-life of Y-90 is about 64 h. It degrades gradually and releases beta particles, which destroy the DNA strain of tumor cells. Through this process, Y-90 microspheres continue to deliver high radiation dose to the tumor for about 2 weeks.

All patients who are planned to receive Y-90 RE are required to undergo a comprehensive evaluation preliminarily 7–14 days in advance, including a series of biochemistry tests and image studies. Image studies include hepatic artery angiography to assess the vascular supply to the tumor cells, the collateral vascular distribution, computed tomography, and the nuclear medicine study of technetium-99 m-labeled macroaggregated albumin (Tc-MAA) simulation test, in order to set up the treatment plans.

Tc-99 M-MAA Simulation Test

Tc-MAA simulation test is the gold standard before Y-90 RE to evaluate the ratio of lung shunting and to simulate the distribution of microspheres in the liver [12, 13]. The process of this simulation test is to inject Tc-MAA via transarterial-catheter, as of the procedure for hepatic angiography. After Tc-MAA injection, patients then receive imaging of the lung and liver.

If there is too much pulmonary shunting, the radiation damage to lungs is expected to be raised, even causing intractable radiation pneumonitis in severe cases. Therefore, for patients with increased pulmonary shunting, dose for Y-90 RE should be reduced accordingly. These patients would even be excluded from the treatment.

Next step, tumor-to-normal tissue ratio (T/N ratio) in the liver would be calculated according to SPECT/CT. In general practice, for Y-90 RE, T/N ratio should be larger than three, which is to say, distribution dose in the liver tumor has to be at least triple of dose in normal liver tissue, so that the average radiation dose to the tumor could reach an ideal therapeutic dose 120 Gy, while dose in liver parenchyma can be controlled at a safe level of below 40 Gy. With this approach, we can prevent normal liver parenchyma from receiving over-dosed radiation which causes severe radiation-induced liver disease (RILD).

Limitation of Tc-99 M-MAA Imaging

Although Tc-MAA test is currently the optimal method to simulate the distribution of Y-90 microspheres, there are several circumstances causing inconsistency in distribution between Tc-MAA and Y-90 microspheres. First, the size of Tc-MAA particle is 10–90 μm, while the size of Y-90 microspheres is 40–60 μm. This difference in particle size results in inconsistency between the distributions of Tc-MAA and Y-90 microspheres. Second, the distributions of these two particles are not identical as the result of gravity and hemodynamic effects after intra-arterial infusion. Third, injections of Tc-MAA and Y-90 microspheres are separate procedures. Because of anatomical variations and technician dependence, injection sites in the vessels might be different in each operation, which cause distribution difference between these two particles in tumor and the liver.

Due to these limitations, the "estimated microsphere distribution" obtained by Tc-MAA image before Y-90 RE may not virtually represent the "actual microsphere distribution" in real Y-90 RE. Therefore, after Y-90 RE, patients are required to receive a validation scan in order to confirm that if the injected microspheres reach the planned targets. At present, there are two kinds of validation scan. One method is "Bremsstrahlung imaging," collected from SPECT/CT, and the other is "internal pair-production image," obtained with PET/CT or PET/MRI [14–16].

Post Y-90 RE Imaging and Its Challenges

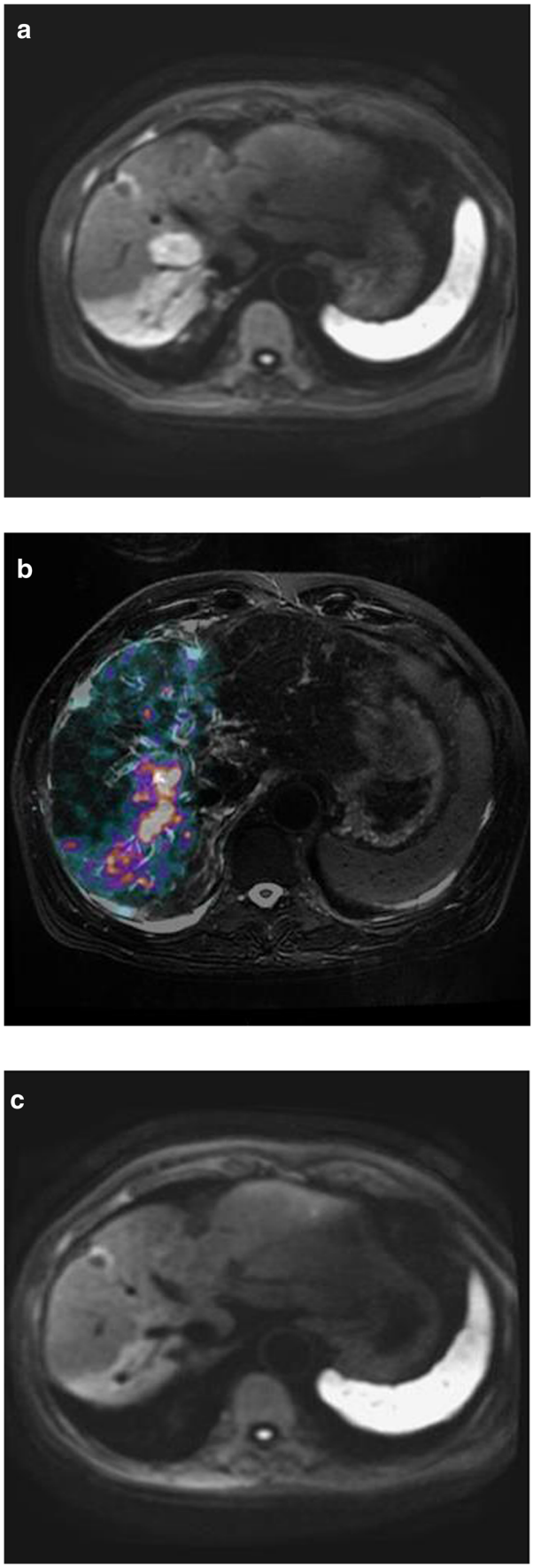
Because Y-90 is almost a pure beta-emitter, to detect its signal is always challenging. The low photon yield and continuous spectrum of the Bremsstrahlung imaging limit the quantitative accuracy of Y-90 Bremsstrahlung SPECT/CT [14, 15].

In addition to Bremsstrahlung imaging, another validation scan to confirm microspheres distribution is to collect internal pair-production (IPP) produced by Y-90 through PET. However, the signal of IPP is weak; it is very difficult to collect enough signals by general PET/CT. Currently, it is more recommended to use a time-of-flight (TOF) PET for the localization of Y-90 microspheres [16–19].

Clinical Experiences of Using Y-90 RE in Our Institute

Both kinds of Y-90 microspheres (resin, manufactured by Sirtex Medical and glass, manufactured by BTG) are available in Taiwan. In our institute, most patients received resin microspheres treatment because of early introduction since 2008. More than 400 times of treatment was performed for locally advanced primary hepatic malignancies (HCC and cholangiocarcinoma) and metastatic liver cancers. Majority of patients receiving Y-90 RE were HCCs. Among HCC patients, most of them were intermediate or advanced Barcelona clinic liver cancer (BCLC) stage because of the referral consensus [20, 21].

From 2008 to 2017, 200 consecutive patients of HCC were treated with Y-90 resin microspheres (BCLC stage A, B, C: 6, 92, 102, respectively). Factors affecting the overall survival from multivariate analysis were ECOG performance, presence



◀ **Fig. 3** A patient of HCC with right posterior portal vein branch thrombosis (as DWI-MRI revealed) (**a**) received Y-90 RE with 1.0 GBq resin microspheres injected into the right lobe of the liver. Post-treatment Y-90 IPP imaging acquired on a hybrid GE SIGNA PET/MR (**b**) showed well delivery and distribution of Y-90 microspheres in the tumor. Tumor regression was confirmed by 3-month follow-up DWI-MRI (**c**)

of ascites, low albumin level, tumor numbers > 7, and presence of extrahepatic disease at the time of Y-90 RE.

The median survival was 13.0 months (10.7–15.6). The 1-, 2-, and 3-year survival was 48.5%, 22%, and 12.5%, respectively. The result was very similar to the European evaluation [22]. The result for patients with BCLC stages B and C was also similar to the European study, which the median survival was 18.3 (13.6–23) months for stage B and 9.7 (7.4–12) months for stage C.

We also conducted sequential Y-90 RE and external beam radiation therapy (EBRT) for HCC patients with portal vein thrombosis which could not be treated with Y-90 RE, residual tumors after Y-90 RE, or extrahepatic metastases [23]. The results showed combined Y-90 RE and EBRT is feasible and safe.

Future Perspectives of Y-90 RE and Its Theranostic Use

Y-90 RE is a vascular-directed and local therapy for liver malignancies. Thus, for patients with extrahepatic disease or with tumors cannot be treated through this intraarterial method, to combine another effective treatment such as target therapy, immunotherapy, or external-beam radiation therapy is essential to achieve better prognosis of patients. More studies should be done to evaluate the timing, sequences, benefits, and possible side effects of the combination therapies.

Another current challenge is that there are no guidelines for Y-90 imaging about acquisition, reconstruction, and quantitative analysis, limiting the theranostic use of Y-90 itself. Developing and optimizing protocols for Y-90 imaging, therefore, is crucial for further theranostic use of Y-90. In addition, using a state-of-the-art PET/MRI might improve the imaging quality and provide more functional information (Fig. 3). It will be important that future studies address the advantages and limitations of PET/MRI imaging for Y-90.

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Author Contribution Ko-Han Lin, Yi-Wei Chen and Rheun-Chuan Lee contribute equally.

Compliance with Ethical Standards

Conflict of Interest Ko-Han Lin, Yi-Wei Chen, Rheun-Chuan Lee, Ling-Wei Wang, Fong-In Chou, Chi-Wei Chang, Sang-Hue Yen, and Wen-Sheng Huang declare no conflict of interest.

Ethical Approval This article does not contain any studies with human participants or animals performed by any of the authors.

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