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EDITORIAL

Present and future of target therapies and theranostics: refining traditions and exploring new frontiers—highlights from annals of Nuclear Medicine 2021

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Introduction

The first clinical application of nuclear medicine treatments can be dated back to 1936, when John H. Lawrence utilised an artificial radionuclide—phosphorus-32—to treat a case of leukaemia, although earlier reports on the therapeutic use of isotopes can be found in literature [1]. Ten years later, Samuel M. Seidlin, Leo D. Marinelli and Eleanor Oshry employed an "atomic cocktail" of iodine-131 to treat a thyroid cancer patient [1]. Later on, the use of iodine-131 was expanded to thyroid imaging and benign conditions [1], becoming the most widely referenced—and dated—example of theranostics. The basic principle of theranostics relies on the utilisation, for both diagnostic imaging and therapy, of the same radiolabelled agent with a specific metabolic pattern or molecular target. The in vivo visualisation of where the radionuclide will settle and act allows a proper selection of patients who would potentially benefit from treatment [2]. This approach offers the invaluable advantage of monitoring its effectiveness and the biological evolution of the disease over time, tailoring treatment to the individual clinical case. Moreover, the ever-expanding knowledge on cancer biology and the identification of new molecular targets increasingly grow the therapeutic applications available, thus making targeted radionuclide therapy the greatest opportunity and challenge in the field of nuclear medicine.

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The aim of the present editorial, within the initiative between the European Journal of Nuclear Medicine and Molecular Imaging (EANM) and the Annals of Nuclear Medicine (ANM) [3], is to provide a synopsis of the current main applications, innovations available and future perspectives in the therapeutic and theranostics field of nuclear medicine.

Overview

Overall, 144 papers were published in ANM between January and December 2021. Amongst these, we selected 19 original articles focused on radionuclide therapy. The main characteristics of the included studies are summarised in Table 1.

Thyroid cancer: iodine-131

Ledwon et al. [4] assessed the prognostic implications of thyroglobulin levels at 3 time points in 650 patients with differentiated thyroid cancer (DTC) treated with adjuvant radioiodine therapy (RAI) after the administration of recombinant human thyroid-stimulating hormone (rh-TSH). Thyroglobulin levels were assessed at the time of the first rh-TSH injection (day 1), after the second injection of rh-TSH (day 3) and after iodine-131 administration (day 6). Thyroglobulin levels assayed at day 1 and day 3 possessed independent prognostic value, whilst thyroglobulin assayed after iodine-131did not.

Ozdogan et al. [5] retrospectively analysed 115 patients with low-to-intermediate risk thyroid cancer treated with adjuvant RAI to investigate the effect of timing on the success rates of the ablation. They demonstrated a higher successful ablation ratio (> 80% of patients) when the adjuvant treatment was performed more than 3 months after surgery.

Table 1 Summary of the main characteristics of the included studies

Reference	Country	Disease	Patients, *n*	Aim	Radiopharmaceutical
Ledwon et al. [4]	Poland	DTC	650	Evaluating serial thyroglobulin measurements at the time of rhTSH-aided iodine-131 adjuvant treatment as prognostic marker	Iodine-131
Ozdogan et al. [5]	Turkey	DTC	503	Investigating the effect of RAI therapy timing on the success rates of the ablation	Iodine-131
Konishi et al. [6]	Japan	DTC	40	Investigating the relationship between quantitative parameters iodine uptake and disappearance of accumulation in the thyroid bed in adjuvant therapy using a 1.11-GBq or 3.70-GBq dose of iodine-131	Iodine-131
Albano et al. [7]	Italy	DTC	314	Investigating the potential role of Hashimoto thyroiditis in predicting 1-year and 5-year treatment response after RAI and prognosis	Iodine-131
Takata et al. [8]	Japan	DTC	88	Revealing the relationship between albumine-globuline ratio and OS in patients with thyroid cancer who received radioactive iodine therapy	Iodine-131
Uchiyama et al. [9]	Japan	DTC	280	Testing the prognostic performance of organ-based MTV in comparison to conventional MTV on [^{18}F]FDG PET in patients with DTC	Iodine-131
Lin et al. [10]	China	ATC	NA, in vitro study	Develop in a radioimmunoconjugate, the [^{131}I]Iodine-caerin 1.1 peptide, to treat human anaplastic thyroid cancer	[^{131}I]Iodine-caerin 1.1 peptide
Watabe et al. [11]	Japan	DTC	NA, animal model	Preclinical safety assessment of [^{211}At]NaAt to determine the FIH dose	[^{211}At]NaAt
Kobayashi et al. [12]	Japan	NET	6	Evaluating safety, pharmacokinetics, dosimetry and efficacy of PRRT in Japanese patients with NET	[^{177}Lu]Lu-DOTA-TATE
Parghane et al. [13]	India	PGL	9	Outcome of PRRT in patients with MIBG-negative, progressive paragangliomas	[^{177}Lu]Lu-DOTA-TATE
Sakashita et al. [14]	Japan	Neuroblastoma	NA, dosimetric study	Estimating [^{211}At]At-MABG absorbed doses by two conversion methods	[^{211}At]At-MABG
Chatachot et al. [15]	Thailand	mCRPC	8	Determining radiation dosimetry for [^{177}Lu]Lu-PSMA-617 therapy in patients with mCRPC	[^{177}Lu]Lu-PSMA-617
Tuncel et al. [16]	Turkey	mCRPC	65	Investigating predictive factors for tumour sink effect in patients with mCRPC	[68 Ga]Ga-PSMA-11 and [^{177}Lu]Lu-PSMA-617
Huang et al. [17]	Germany	mCRPC	46	Identify pre-therapeutic factors for the prediction of response in patients treated with [^{177}Lu]Lu-PSMA-617	[^{177}Lu]Lu-PSMA-617

Table 1 (continued)

Reference	Country	Disease	Patients, *n*	Aim	Radiopharmaceutical
Sen et al. [18]	India	mCRPC	38	Reporting the centre's experience with [^{225}Ac]Ac-PSMA	[^{225}Ac]Ac-PSMA
Santos et al. [19]	Brazil	Osteoarthritis	40	Assessing efficacy and safety of knee RS with [^{153}Sm]Sm-HyA compared to [^{90}Y]Y-HyA	[^{153}Sm]Sm-HyA and [^{90}Y]Y-HyA
Liepe and Baehr [20]	Germany	Osteoarthritis	125	Evaluating the efficacy of RS in thumb basal joint arthritis	[^{169}Er]Er-citrate
Gu et al. [21]	Japan	TNBC	NA, animal model	Exploring the potential of three-step pre-targeting radioimmunotherapy	[^{90}Y]Y-StAv
Lee et al. [22]	Korea	Lymphoma	NA, in vitro study	Evaluating the radiation dosimetry of [^{225}Ac]Ac-DOTA-rituximab using Monte Carlo simulation of [^{64}Cu]Cu-DOTA-rituximab	[^{225}Ac]Ac-DOTA-rituximab and [^{64}Cu]Cu-DOTA-rituximab

DTC, differentiated thyroid cancer; *RAI*, radioactive iodine; *MTV*, metabolic tumour volume; *ATC*, anaplastic thyroid cancer; *NA*, not applicable; *FIH*, first-in-human; *NET*, neuroendocrine tumour; *PRRT*, peptide receptor radionuclide therapy; *PGL*, paraganglioma; *mCRPC*, metastatic castration–resistant prostate cancer; *RS*, radiosynovectomy; *TNBC*, triple negative breast cancer

Konishi et al. [6] investigated the relationship between iodine-131 intake, [18F]FDG PET/CT quantitative parameters and therapeutical success in patients with DTC treated with RAI (1.11 or 3.7 GBq). The rate of disappearance of the uptake in the thyroid bed was higher in patients treated with 3.7 GBq than in those who received 1.11 GBq. Patients successfully treated showed higher values of absolute radioactivity concentration and SUVmax/mean, suggesting the usefulness of these indicators as predictive factors.

Albano et al. [7] investigated the role of Hashimoto thyroiditis in the efficacy of RAI in thyroid cancer. Coexistent Hashimoto thyroiditis was associated with higher cumulative iodine-131 administrated activities and a higher number of re-treatments. Moreover, the rate of indeterminate response/progressive disease was significantly higher in patients with Hashimoto thyroiditis both 1 year and 5 years after RAI, suggesting that it can reduce the success rate and the probability of an excellent response to this treatment.

Takata et al. [8] evaluated the clinical application of the albumin-globulin ratio (AGR)—a biomarker of cancer-related inflammation—as a new, independent prognostic factor in patients with thyroid cancer treated with radioiodine. The overall survival (OS) rate was significantly shorter in patients with low AGR (< 1.32), whilst there was no difference in terms of progression-free survival (PFS). Moreover, both OS and PFS rates were significantly shorter in under 65-year-old patients with low AGR, suggesting its usefulness especially in younger patients.

Uchiyama et al. [9] established a prediction model based on organ-based metabolic tumour volume (MTV) in DTC patients with [^{18}F]FDG-avid metastatic lesions treated with iodine-131. The prognostic stratification of the organ-based MTV, establishing the adjusted whole-body MTV calculated by giving a different weight according to the organ of spread, outperformed conventional MTV models.

Thyroid cancer: beyond iodine-131

Lin et al. [10] exploited the synergistic therapeutic effects of radiation and immunotherapy of a new developed peptide—[^{131}I]Iodine-caerin 1.1—in anaplastic thyroid cancer cell line CAL-62. The radioimmunoconjugate compound inhibited tumour growth and migration and arrested the S phase to induce apoptosis, exhibiting promising results in vitro.

Watabe et al. [11] preclinically evaluated the safety of a single-dose administration of [^{211}At]Sodium-Astatide (NaAt) in mice, to determine the activity to be administered in a first-in-human trial to treat differentiated thyroid cancer. The administration of high [^{211}At]NaAt activity (50 MBq/kg) caused weight loss, transient bone marrow suppression and pathological alterations in the testis. These results suggested an activity of 5 MBq/kg as reasonable safe reference to set for the first-in-human application.

Neuroendocrine tumours: radiolabelled somatostatin and guanethidine analogues

Kobayashi et al. [12] studied the tolerability, safety, pharmacokinetics, dosimetry and efficacy of peptide receptor radioligand therapy (PRRT) in six Japanese patients with unresectable well-differentiated neuroendocrine tumours (NET). The cumulative renal absorbed dose for 29.6 GBq of [^{177}Lu][Lu-DOTA^{0}, Tyr^{3}] Octreotate (DOTA-TATE) was 16.8 Gy, and the biological effective dose was 17.0 Gy.

[^{177}Lu]Lu-DOTA-TATE was eliminated from the blood in two phases according to non-compartment model analysis, with a cumulative urinary excretion of 60% within 6 h. Administration of [^{177}Lu]Lu-DOTA-TATE was well-tolerated, with no dose-limiting toxicities. The treatment was effective, achieving partial response in four patients, stable disease in one case and progressive disease in the remaining one.

Parghane et al. [13] assessed the long-term outcome of nine patients with [^{131}I]Metaiodobenzylguanidine (MIBG) negative paragangliomas (PGL) treated with [^{177}Lu]Lu-DOTA-TATE. All patients presented with progressive and symptomatic locally advanced or metastatic disease. The treatment was well-tolerated and showed a significant improvement in clinical symptoms in six patients resulting in a disease control rate of 67%. [^{177}Lu]Lu-DOTA-TATE resulted a promising therapeutic option in this subset of PGL, with an estimated PFS and OS rate of 63% and 65%, respectively, at 40 months. PFS was significantly associated with the site of PGL (non-head and neck PGL), the total cumulative dose of PRRT (> 22.2 GBq) and the number of PRRT cycles (≥ 4).

Sakashita et al. [14] developed the ratio of pharmacokinetics (RAP) as a novel simulation method to estimate the absorbed doses by using percent injected dose/g. They compared this new method with the basic one to assess in vivo [^{211}At]Metabenzylguanidine (MAGB) absorbed dose using [^{131}I]MIBG biodistribution data from a previously reported neuroblastoma xenograft model. The RAP dose conversion approach provided an excellent estimation of [^{211}At]MAGB absorbed doses and would be applicable to a large number of subjects for targeted radionuclide therapy.

Prostate cancer: PSMA-targeted radionuclide therapy

Chatachot et al. [15] performed a dosimetric study in eight metastatic castration-resistant prostate cancer (mCRPC) patients treated with 12 cycles of [^{177}Lu]Lu-PSMA-617. The lacrimal glands and kidneys received the highest absorbed doses; however, median absorbed doses were below recommended dose limits in all critical organs. PSMA-targeted therapy was safe and personalised treatments, increasing the number of cycles and activity, were feasible, without an excessive radiation exposure to healthy organs.

Tuncel et al. [16] investigated the relationship between tumour sink effect—a phenomenon consisting in the reduction of the uptake in healthy tissues in favour of an increased tumour retention of radiopharmaceuticals—and baseline clinical/imaging characteristics, identifying baseline PSA level, PSA velocity and total lesion PSMA index as feasible predictors in mCRPC patients treated with [177Lu]Lu-PSMA-617. A better understanding of this phenomenon would allow personalised administered activities to increase therapeutic efficacy whilst sparing healthy organs.

Huang et al. [17] developed a score to predict disease response in mCRPC patients treated with [177Lu]Lu-PSMA-617. The predictive score, which included PSA, alkaline phosphatase and SUVmax of the hottest lesion, was able to separate two groups of patients with different outcomes: the presence of ≤ two predictive factors led to disease progression in 19% of patients, whilst the presence of three predictive factors in 90%.

Sen et al. [18] reported their experience with [^{225}Ac]Ac-PSMA therapy in 38 mCRPC patients who previously failed therapy with taxanes. [225Ac]Ac-PSMA was a safe and well-tolerated treatment with a significant improvement in quality of life.

Osteoarthritis: radiosynovectomy

Santos et al. [19] prospectively assessed the efficacy and safety of knee radiosynovectomy with [^{153}Sm]Sm-Hydroxyapatite (HyA) in comparison to the more commonly used [^{90}Y]Y-HyA in haemophiliac patients to prevent secondary arthropathy. Knee radiosynovectomy with [^{153}Sm]Sm-HyA was safe and the reduction of hemarthrosis episodes after 12 months was higher compared to patients treated with [^{90}Y]HyA (87.5% vs 50%), especially in adults/adolescents.

Liepe and Baehr [20] studied the effectiveness of radiosynovectomy with [^{169}Er]Er-Citrate in thumb basal joint arthritis. Although treatment resulted effective with pain relief in 68% of the cases, almost 50% of patients experienced symptom relapse after 3 months, suggesting a follow-up of 3–4 months to accurately assess response to treatment.

Other therapies

Gu et al. [21] performed biodistribution and therapeutic studies in a xenograft model of triple negative breast cancer of a three-step pre-targeting radioimmunotherapy (PRIT), consisting in the sequential injection of biotinylated bevacizumab (Bt-BV), avidin and [^{90}Y]Y-Streptavidin (StAv). The 3-step PRIT strategy allowed a rapid blood clearance, tumour uptake at early time points and a decreased kidney uptake. In the therapeutic study, tumour growth was significantly suppressed with [^{90}Y]Y-StAv PRIT compared to the controls.

Lee et al. [22] evaluated the dosimetry of the alpha-emitter [^{225}Ac]Ac-DOTA-rituximab using Monte Carlo simulation of [^{64}Cu]Cu-DOTA-rituximab PET/CT images in CD20-positive lymphoma xenograft models. [64Cu]Cu-DOTA-rituximab specifically targeted CD20-positive lymphoma cells in both cell binding assay, biodistribution, autoradiography and tissue staining. Monte Carlo

simulation with [64Cu]Cu-DOTA-rituximab was successful in the dosimetry of [^{225}Ac]Ac-DOTA-rituximab. PET/CT imaging showed a higher radiopharmaceutical uptake in the tumour compared to healthy organs, consistent with CD20 expression.

Discussion

Insights on tumour microenvironment, tumour biology and physiopathology of co-morbidities are progressively increasing, shifting the focus from diseases to patients, according to one of the most acclaimed Hippocratic postulate. Moreover, radiopharmaceuticals available for therapy are constantly developing, reflecting the great worldwide excitement for the latest breakthroughs. Accordingly, research in the field of nuclear medicine is increasingly focusing on radionuclide therapy, the challenge and the promise of the next decades. Solid tumours represented the hottest therapeutic topic in 2021 ANM publications, especially thyroid cancer, prostate cancer and NETs.

Although RAI is the oldest established treatment in the field of nuclear medicine, related clinical research is still ongoing. Iodine-131 is the standard of care treatment not only in hyperthyroidism, but also in well-differentiated thyroid cancer, for thyroid remnant ablation, adjuvant purposes and persistent/recurrent disease treatment [23, 24]. Nonetheless, several aspects are still under investigation, as underlined by our review. A relevant issue is the lack in current guidelines of an exact timing for iodine-131 adjuvant treatment after total thyroidectomy [24, 25]. Indeed, although some studies have showed that timing may affect clinical outcome of RAI [26–30], there is no definite consensus on the optimal schedule. Ozdogan et al. [5] found that iodine-131 administration more than 3 months after surgery was more successful, shedding light on this still controversial topic. Reliable predictive prognostic factors represent another open issue in DTC. The current risk stratification strategy relies on clinical features (age and family history) and histopathological factors (tumour histotype and TNM) [24]. The identification of novel prognostic factors, including molecular and image-derived biomarkers, is ongoing with the goal of improving risk stratification and patients' management. In this regard, papers published by Ledwon et al. [4], Konishi et al. [6], Albano et al. [7], Takata et al. [8] and Uchiyama et al. [9] provided insightful promising results.

Recently, combination therapies employing more than one therapeutic approach have been explored in different clinical settings. This method aims to circumvent tumour resistance by simultaneously targeting compensatory signalling pathways or bypassing survival selection mutations acquired in response to monotherapy [31]. Immunotherapy, acting through different mechanisms, represents one of the cornerstones of combination treatments. Zevalin and Bexxar, introduced in the early 2000s as treatment options in lymphoma, represent successful examples of this concept. Since then, other radioconjugates have been developed and tested. Recently, Lin et al. [10] reported promising results of radioimmunotherapy in anaplastic thyroid cancer cell lines. A step forward has been represented by Gu et al. [21], who proposed radioimmunotherapy with a three-step pre-targeting approach, in a xenograft model of triple negative breast cancer.

Although theranostics is a highly modern concept, its roots lie very deep in the history of nuclear medicine. Saul Hertz is considered the pioneer of the field, establishing a historical landmark with the first clinical use of iodine-131 in patients with hyperthyroidism in the 1940s [1]. Since then, great strides have been made until today. After decades from the development of iodine-131, a breath of innovation came from the promising results of [^{177}Lu]Lu-DOTA-TATE and [^{177}Lu]Lu-PSMA-617, representing important milestones in the pipeline of theranostics [32] (Fig. 1). The randomised, controlled, phase III, NETTER-1 trial is one of the most influential studies of recent years. In the primary analyses, [177Lu]Lu-DOTA-TATE prolonged PFS and demonstrated a significantly higher response rate than standard of care alone (octreotide long-acting repeatable therapy) in patients with advanced progressive midgut NETs [33]. In 2017, these favourable results led to the authorisation for the treatment of metastatic, progressive, well-differentiated, somatostatin receptor-positive gastro-entero-pancreatic NETs from European Medicines Agency (EMA) and, in 2018, from Food and Drug Administration (FDA) [34, 35]. Recently, the final analyses of NETTER-1 were published, showing a slightly improved OS in the [^{177}Lu]Lu-DOTA-TATE group (+ 11.7 months), although it was not statistically significant. The safety of PRRT was confirmed, as only 3 out of 111 patients experienced treatment-related serious adverse events of grade 3 or higher (2 patients developed myelodysplastic syndrome and one patient died) [36]. Positive results of PRRT in terms of dosimetry, safety and efficacy of PRRT have been even recently confirmed in Japanese patients [12] and in [^{131}I]MIBG-negative PGL [13].

In addition to PRRT, the spotlight of theranostic is shining on PSMA-targeted therapy. Great expectations arose from the open-label, randomised, international, phase 3 VISION trial that evaluated the efficacy and safety of [^{177}Lu]Lu-PSMA-617 plus protocol-permitted standard of care compared to best standard of care alone in mCRPC patients. [^{177}Lu]Lu-PSMA-617 significantly impacted OS (15.3 vs 11.3 months) and PFS (8.7 vs 3.4 months). Despite the adjunction of [^{177}Lu]Lu-PSMA-617 was related to an increased incidence of adverse events, toxicity consisted of predominantly grade 3 or lower symptoms (fatigue, dry mouth and nausea were the most common), without

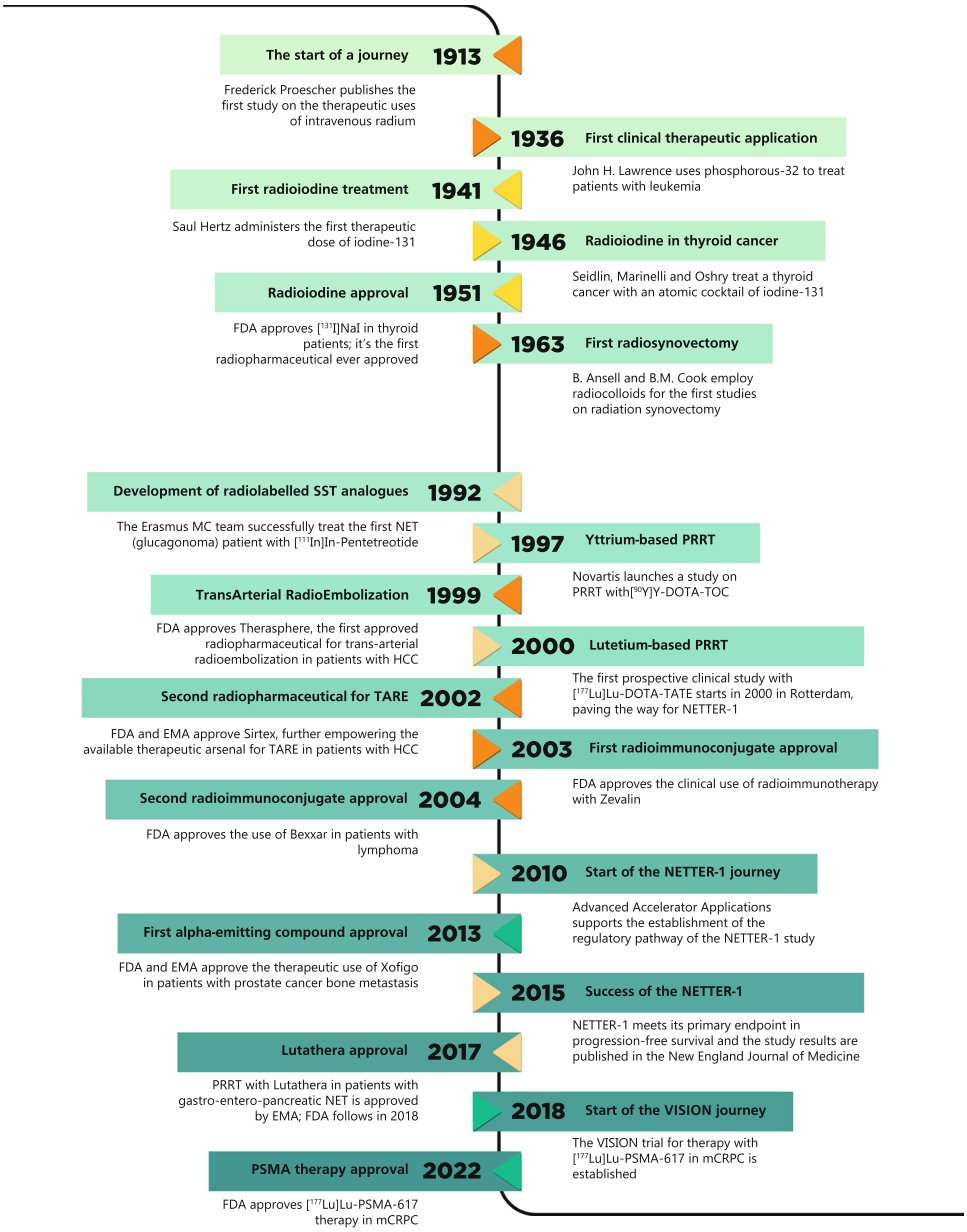

Fig. 1 Historical timeline of the main milestones in radionuclide therapies and theranostics

negatively impacting on quality of life [37]. On March 2022, following the announcement of the results of the VISION trial, the FDA approved the clinical use of [^{177}Lu]Lu-PSMA-617 for the therapy of patients with PSMA-positive mCRPC with progressive disease after treatment with androgen receptor inhibitors and taxane-based chemotherapy, authorising [^{68} Ga]Ga-PSMA-11 as the first PET/CT diagnostic radiopharmaceutical to select patients for radioligand therapy with [^{177}Lu]Lu-PSMA-617 [38].

Several clinical trials are ongoing to refine PSMA-targeted radioligand therapy with the beta-emitting [^{177}Lu]Lu-PSMA-617, to confirm its efficacy and explore its employment in different stages of prostate cancer or in combination strategies [15–17, 39]. Evidence derived from these studies may improve selection of patients eligible to this kind of treatments, providing insightful steps towards personalised therapy.

The introduction of alpha-emitting molecules contributes to the process for the development of personalised target therapies [40]. The greatest potential of alpha-emitters lies in their higher linear energy transfer and their lower range of action compared to beta-emitters. These properties provide increased cytotoxic activity on malignant cells, with a higher probability of double-strand DNA damage, whilst sparing surrounding healthy tissues, resulting in lower toxicity. Moreover, radiation protection concerns are minimised, and patient management simplified due to the lower radiation release to the outside environment [40–42].

The identification of specific molecular targets is essential to pursue these therapeutic goals. In 2013, [^{223}Ra]Radium-dichloride was the first alpha-emitter to receive FDA and EMA approval for the palliative treatment of bone metastasis in mCRPC patients [43, 44]. Several compounds labelled with alpha-emitting radioisotopes, such as bismuth-213, astatine-211 and actinium-225, were developed to treat other oncological and haematological malignancies [11, 18, 40, 45, 46]. However, issues in the production, supply and dosimetry of alpha-emitting radiopharmaceuticals are still limiting their widespread employment [40, 47]; innovative approaches are needed to overcome these hurdles [14, 22, 45].

Although not covered by selected articles published in 2021 ANM, research focus on intraarterial radioembolization, a well-established therapeutic option in patients with hepatocellular carcinoma [48], is still on-going to confirm the efficacy of the treatment—also in a low-disease burden setting—to tailor ad-personam activities to be administered, and to compare or combine it with other treatments.

Albeit nuclear medicine treatments have been mainly engaged in oncology, some benign conditions, including hyperthyroidism and osteoarthropathy, may benefit from radionuclide therapy [49, 50]. Santos et al. [19] reported less hemarthrosis episodes using [^{153}Sm]Sm-HyA compared to the more commonly employed [^{90}Y]Y-HyA, in haemophiliac patients. Liepe and Baehr [20] accounted the effectiveness of erbium-169-based—one of the most interesting beta-emitting isotopes [51]—radiosynovectomy in thumb basal joint arthritis.

The latest breakthroughs provided evidence that radionuclide therapy not only improves the quality of life but also achieves survival endpoints with an acceptable safety profile. Great enthusiasm has rekindled in the world medical community even outside nuclear medicine, increasingly ready and eager to include radionuclides in therapeutic flowcharts. The great expansion of this novel frontier certainly poses new, important challenges. Transposing a new therapeutic insight through the preclinical phase to the patient's bedside requires prolonged and scrupulous studies capable of meeting the rigorous requirements needed. Conducting prospective randomised controlled trials and head-to-head comparison with standard of care treatments is paramount to generate high-level evidence on the efficacy and safety of radioligand therapy on a large scale [52, 53].

From a logistical perspective, nuclear medicine departments will be dealing with an exponentially greater influx of patients, up to unprecedented numbers especially considering the prevalence of some of the conditions to be treated, such as prostatic cancer. A profound reorganisation should be addressed to adapt the existing healthcare infrastructure to the expected increased demand for radionuclide therapy [54]. A joint EANM, SNMMI and IAEA guide that undertakes these practical issues was recently published, emphasising the urgent need for high-quality theranostics centres in referral hospitals, where dedicated multidisciplinary boards and a highly specialised staff comprehensively manage patients undergoing radionuclide therapies [55].

Since the official recognition of the role and the establishment of a dedicated training of the nuclear physicians in 1971, the discipline has been constantly evolving [56]. Although there are differences worldwide in the structure of residency programmes in medical imaging area, currently, in most European countries, nuclear medicine represents a curriculum independent from radiology [57]. The European Union of Medical Specialists and the European Board of Nuclear Medicine drafted a list of fundamental competencies required for nuclear medicine residents to ensure high-quality standards of education and harmonisation across the European countries [58]. The hallmark and the strength of nuclear medicine have always been the translational interdisciplinary approach, combining knowledge of physics, chemistry, molecular biology, pathophysiology, clinics and imaging. The introduction of hybrid imaging modalities has required a realignment of the education to better interlace with the functional counterpart, the new morphologic image-reading expertise requirements [56]. Similarly, the next generation of nuclear medicine physicians will change their professional profile to deal with the ever-increasing expansion of radioligand therapies, focusing strongly on clinical competences and patient management, especially in the field of oncology. Residency schools will be expected to keep up the pace by providing adequate interdisciplinary training programmes to adequately update and train nuclear medicine physicians with a renewed focused on clinical skills [59, 60].

Conclusions

This editorial spotlighted the central role of radionuclide therapy in the field of nuclear medicine showing the booming preclinical and clinical research on targeted therapy and theranostics, from the well-established treatment with iodine-131, to theranostics of neuroendocrine tumours and metastatic castration–resistant prostate cancer, to the field of new drug development. These frontiers will certainly open exciting new opportunities. The professional figure of the nuclear physician will be able to become more prominent, forging increasingly close collaborative links with other specialties, to the extent of serving a central role as an expert not only in advanced diagnostic techniques but also in advanced therapeutic techniques, theranostics and personalised medicine. The new frontier is here. Are you ready?

Author contribution CP, FG and MS conceptualised the paper. CP, FG and MS performed data selection and drafted the paper. CP provided the figures and tables. All the authors approved the manuscript.

Declarations

Ethics approval Institutional Review Board approval was not required because the paper is an editorial.

Consent to participate Not applicable.

Conflict of interest The authors declare no competing interests.

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