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Rhenium-188 in the treatment of non-melanoma skin cancer

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Abstract

Non-melanoma skin cancer (NMSC) is one of the most frequently diagnosed malignancies worldwide, especially among fair-skinned individuals [4]. Basal cell carcinoma (BCC) is the predominant subtype, whereas squamous cell carcinoma (SCC) accounts for a smaller but increasing proportion of cases. The incidence of these tumors continues to rise due to aging populations, cumulative ultraviolet exposure and improved detection [4]. Lesions are commonly located on cosmetically sensitive regions such as the face, scalp and neck, where treatment may significantly affect both function and appearance. Conventional therapeutic approaches include surgery, radiotherapy, cryotherapy and topical agents; however, these treatments may be associated with recurrence, cosmetic impairment or prolonged treatment duration [1]. Rhenium-188 skin cancer therapy is a topical radionuclide-based treatment designed for superficial lesions. Owing to the limited tissue penetration of beta radiation, it can deliver high doses to the lesion while preserving surrounding healthy tissues [2, 3]. Published clinical evidence suggests high local control rates, good cosmetic outcomes and acceptable toxicity profiles [2, 3, 5]. Therefore, Rhenium-188 may represent a valuable alternative for carefully selected patients with superficial NMSC.

Keywords: Non-melanoma skin cancer; Basal cell carcinoma; Squamous cell carcinoma; Rhenium-188; Skin brachytherapy

Introduction

Non-melanoma skin cancers are the most frequently encountered skin malignancies and constitute an important public health issue worldwide. Their incidence is increasing steadily over time, especially in countries with aging populations and high sun exposure [4]. Although these tumors generally have low mortality, they may significantly affect patients' quality of life due to their location, recurrence and cosmetic consequences.

Most NMSCs develop in chronically sun-exposed areas, particularly in the head and neck region. Approximately 90% of lesions are located on the face, scalp, ears, lips or neck. These anatomical sites are of particular importance because treatment may affect both function and appearance.

Basal cell carcinoma is the most common NMSC subtype, accounting for approximately 80% of cases, while squamous cell carcinoma represents around 15% [4]. Although melanoma usually attracts greater attention because of its aggressive behavior, NMSCs are substantially more common.

Current therapeutic options and limitations

Current therapeutic options for NMSC include surgical excision, Mohs surgery, cryotherapy, external beam radiotherapy, topical agents and photodynamic therapy [1]. The choice of treatment depends on lesion size, depth, location, histology and patient-related factors.

Despite the availability of several treatment modalities, there are important limitations. Surgical treatment may lead to cosmetic deformity, loss of function and the need for reconstructive procedures, especially in facial lesions. Radiotherapy often requires multiple sessions over several weeks. Topical therapies may require prolonged application periods and may show variable efficacy. Furthermore, recurrence remains an important issue in selected patients.

For this reason, there is growing interest in minimally invasive therapeutic approaches that can provide effective tumor control while maintaining a favorable cosmetic result and low toxicity.

Rhenium-188 skin cancer therapy

Rhenium-188 is a beta-emitting radionuclide with physical properties that make it particularly suitable for the treatment of superficial skin lesions. Rhenium-188 SCT is based on the topical application of a paste containing the radionuclide directly onto the lesion.

The emitted beta radiation penetrates tissues up to approximately 3 mm in depth, allowing high radiation doses to be delivered to superficial lesions while minimizing exposure to deeper tissues [2, 3]. Approximately 92% of the radiation dose is absorbed within the first 3 mm. Typical prescribed doses are around 50Gy to the target area.

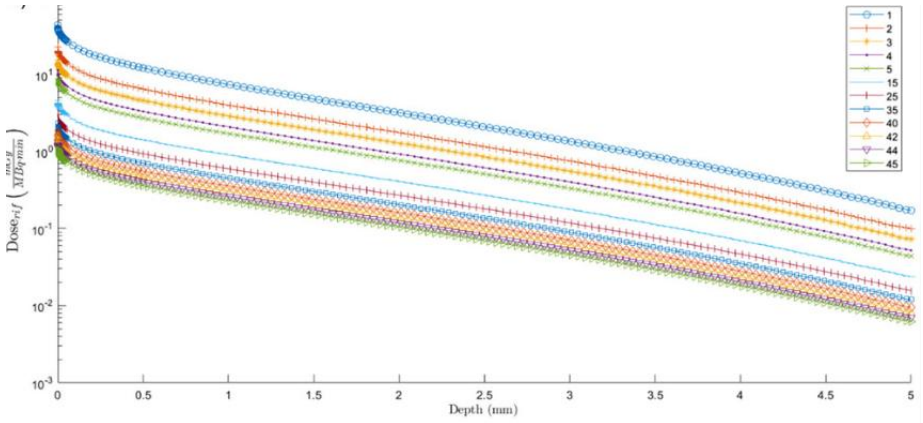
The treatment procedure includes lesion delineation, protection of surrounding healthy tissues, application of the radioactive paste and calculation of treatment time according to lesion depth and administered activity.

From a medical physics perspective, individualized dosimetry is essential for treatment planning. Lesion thickness, surface area and anatomical location must be accurately assessed in order to estimate the delivered dose and treatment duration. Dedicated calibration tables and software tools may be used to calculate the activity required to achieve the prescribed absorbed dose at the target depth. Because the beta particles emitted by Rhenium-188 have a short penetration range, dose fall-off is very steep beyond the first few millimeters of tissue. This dosimetric characteristic is particularly advantageous for superficial lesions, as it allows adequate

irradiation of the tumor while minimizing unnecessary dose to deeper healthy tissues and underlying critical structures [2, 3].

Treatment time calculation and decay correction

For treatment planning, the required exposure time can be calculated from calibration tables reporting absorbed dose rate values in mGy/(MBq·min) as a function of lesion depth and application surface area (1-45cm²).



Using the absorbed dose per unit activity and time at the prescribed target depth (Doseref) and the total applied activity (Aapplied), the uncorrected treatment time is given by:

$$t_0 = \frac{D_{min}}{A_{applied} \cdot D_{ref}}$$

where t_0 is the treatment time in minutes, Dmin is the prescribed target dose, Aapplied is the applied activity in MBq, and Doseref is the absorbed dose rate at the target depth in mGy/(MBq·min). To ensure unit consistency, Dmin should be expressed in mGy when Doseref is taken from tables in mGy/(MBq·min); for example, 50Gy corresponds to 50,000mGy.

However, the value of t_0 does not account for radioactive decay of Re-188 during the application. Therefore, the actual treatment time should be corrected by a decay correction factor (CF):

$$CF = \frac{\lambda \cdot t_0}{1 - e^{-\lambda \cdot t_0}}$$

where λ is the decay constant of Re-188 and t_0 is the uncorrected exposure time. The corrected treatment time is then calculated as:

$$t_{treat} = t_0 \cdot CF.$$

This correction is particularly important for accurate delivery of the minimum prescribed dose in Re-188 skin therapy, especially when longer application times are required.

Clinical Results

Several studies have demonstrated high complete response rates exceeding 90% in selected patients with superficial basal cell and squamous cell carcinomas [2, 3, 5]. Recent prospective and interim clinical data have also confirmed high patient satisfaction rates, good tolerability and favorable cosmetic outcomes [5, 6]. Local control rates are high, and cosmetic outcomes are generally excellent.

Treatment-related toxicity is usually mild and limited to local skin reactions such as erythema, crusting or temporary ulceration [2, 3, 5]. Healing is generally predictable and acceptable, especially compared with surgery in cosmetically sensitive areas.

The single-session nature of Rhenium-188 represents an additional advantage, particularly for elderly patients or patients with comorbidities who are not ideal candidates for surgery or prolonged radiotherapy [5, 6].

Discussion

Rhenium-188 SCT may represent an attractive treatment option for selected superficial NMSCs, especially lesions located in cosmetically sensitive areas. Compared with surgery, it may offer superior cosmetic results, lower treatment burden and avoid reconstructive procedures [6]. Compared with external beam radiotherapy, it is simpler, more convenient and usually completed in a single session [1, 2].

However, the method is not suitable for melanoma, deeply infiltrating lesions or tumors with extensive subcutaneous involvement. Appropriate patient selection remains essential.

Future studies with larger patient populations and longer follow-up are needed to further define the role of Rhenium-188 in routine clinical practice.

Conclusion

Rhenium-188 skin cancer therapy is a safe and effective treatment option for selected patients with superficial non-melanoma skin cancers. It combines high local control rates with favorable cosmetic outcomes and limited toxicity. Its role is particularly important in lesions of the face and other cosmetically sensitive areas, as well as in patients who are poor surgical candidates.

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The experience of Nuclear Medicine Department of G.N.A. Evangelismos on the therapy with ^{177}Lu-PSMA

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Abstract

The aim of the presented study was to evaluate the efficacy and safety of ^{177}Lu-PSMA radioligand therapy in patients with metastatic castration-resistant prostate cancer (mCRPC) in a hospital clinical setting.

Keywords: Prostate cancer -mCRPC -^{177}Lu-PSMA -PSMA PET/CT

Introduction

Prostate-specific membrane antigen (PSMA)-targeted radioligand therapy with 177Lutetium (^{177}Lu-PSMA) has emerged as an effective therapeutic option for patients with metastatic castration-resistant prostate cancer (mCRPC). Following the results of the VISION trial, ^{177}Lu-PSMA has been incorporated into treatment algorithms, demonstrating improved overall survival and biochemical response rates. However, clinical data remain essential to validate efficacy and safety outside clinical trial settings.

Materials and Methods

A total of 94 consecutive patients with advanced mCRPC were involved, all of whom had previously received standard therapies, including androgen deprivation therapy, novel hormonal agents (abiraterone or enzalutamide) and taxane-based chemotherapy. Patient selection was based on PSMA PET/CT imaging, while exclusion criteria included the presence of extensive PSMA-negative disease or mismatch findings between PSMA and FDG PET/CT. Treatment was administered in repeated cycles of ^{177}Lu-PSMA, with systematic hematological and biochemical monitoring after each cycle and imaging reassessment after three cycles. The primary endpoint was biochemical response, defined as a prostate-specific antigen (PSA) decline greater than 50% (PSA50), while secondary endpoints included overall response rate, treatment completion and safety profile.

Results

The mean age of the study population was 74.6 years (range: 47–86), with a mean Gleason score of 8, reflecting predominantly high-risk disease. A PSA decline greater than 50% was observed in 49.25% of patients, comparable to 46% reported in the VISION trial, while a PSA decline of less than 50% was observed in 10.76%. Stable disease was noted in 1.53%, where PSA progression occurred in 38.46%. Regarding treatment course, 33 patients (35.1%) completed therapy, 42 patients (44.7%) discontinued treatment, while 19 patients (20.2%) remain on treatment. Among patients who discontinued therapy, PSA increase was observed in most of the cases (31 patients), whereas 11 patients discontinued despite PSA decline, suggesting the contribution of non-biochemical factors to treatment interruption. Discontinuations were more frequently observed during early treatment cycles, suggesting disease aggressiveness or limited tolerance in a subset of patients.

Overall, treatment was well tolerated, with predominantly mild-to-moderate adverse events, including fatigue, xerostomia, and gastrointestinal symptoms, ^{177}Lu-PSMA radioligand therapy demonstrates clinical effectiveness comparable to the VISION trial, with similar biochemical response rates and an acceptable safety profile.

Discussion

The observed biochemical response rates and safety profile are consistent with previously reported data, supporting the effectiveness of this therapy in routine clinical practice. Treatment discontinuation was mainly associated with disease progression, although discontinuation despite

biochemical response suggests the influence of additional clinical factors. These factors may be investigated through the results of expanding therapy to a larger patient population, which would allow for more in depth analysis and a more comprehensive evaluation.

Conclusion

Lutetium-177 prostate-specific membrane antigen radioligand therapy is an effective and safe treatment option in patients with metastatic castration-resistant prostate cancer. It is well tolerated treatment which improves quality of life, delays disease progression and contributes to overall survival.

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OncoSil - A new radionuclide therapy for pancreatic cancer

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Gastrointestinal cancer, poses a significant global health challenge, encompassing a spectrum of malignancies affecting various parts of the digestive system and account for a substantial portion of cancer-related morbidity and mortality worldwide. Cancers of the digestive tract can develop anywhere between the stomach and the intestinal canal, from the esophagus down to the anus. Most cancers that start in the digestive tract, start in the gland cells lining the gastrointestinal tract - adenocarcinomas. Tumor types such as melanomas, neuroendocrine tumors, gastrointestinal stromal tumors and sarcomas can also occur.

Nuclear medicine therapies are focused on delivering targeted radiation to tumors using radiopharmaceuticals, such as:

Therapy	Indication	Agent	Radionuclide
PRRT (Peptide receptor radionuclide therapy)	NETs	DOTATATE DOTATOC	^{177}Lu, ^{90}Y
TARE (transarterial radioembolization)/SIRT (Selective internal radiation therapy)	Liver mets, HCC	Y90 microspheres	^{90}Y
RIT (Radioimmunotherapy)	CRC, others (trial)	Anti-CEA/MUC1 Ab	^{131}I, ^{90}Y, ^{225}Ac
FAPI (fibroblast activation protein inhibitor) Therapy	GI tumors (trial)	FAPI compound	^{177}Lu
TAT (Targeted alpha-particle therapy)	Advanced/metastatic disease (trial)	Various	^{225}Ac, ^{213}Bi

Nuclides used for radioisotope therapy, are: alpha-α, beta-β, and Auger particle emitters. Various biomaterials have been utilized as multifunctional nanocarriers, including targeting molecules, macromolecular monoclonal antibodies, peptides, inorganic nanomaterials, and

organic and polymeric nanomaterials. Therapeutic radioisotopes have been labeled onto these nanocarriers via different methods (chelating, chemical doping, encapsulating, displacement) to inhibit or kill cancer cells.

Pancreatic cancer is projected to become the second leading cause of cancer death before 2030; its aggressive nature and poor survival rate have resulted in a significant global burden of disease. Pancreatic ductal adenocarcinoma (PDAC) accounts for 80% of pancreatic cancer and is often diagnosed at a late stage due to early metastasis, lack of markers for early detection, and an absence of proven screening programs. More than one-half of patients, have metastatic pancreatic ductal adenocarcinoma (mPDAC) at presentation, which carries a dire 5-year survival rate of 3%.

A novel type of radiation therapy is brachytherapy, whereby radioisotopes are placed inside or near the tumor. In patients with unresectable pancreatic cancer, CT-guided percutaneous implantation of 125-Iodine seeds has been shown to be feasible and safe, and to achieve pain relief, although an effect on survival has not been shown.

In Calistri S, Ottaviano G, Ubaldini A. Radiopharmaceuticals for Pancreatic Cancer: A Review of Current Approaches and Future Directions. Pharmaceuticals. 2024; 17(10):1314, is stated that: "To date, the European Medicines Agency (EMA) has not approved any radio-drugs for treating pancreatic cancer…the fact that there are no approved options for pancreatic cancer highlights the struggles in finding good treatments for this disease."

Another radioisotope used for brachytherapy in PDAC is Phosphorus-32 (^{32}P) delivered as ^{32}P-microparticles (OncoSil™) comprising an alloy of silicon and phosphorus activated in a nuclear reactor and suspended in a diluent. The ^{32}P-microparticles are administered by injection through an EUS-guided needle. When combined with chemotherapy for nonmetastatic locally advanced PDAC, it has shown promising results, with 1 study reporting a 42% downstaging to surgical resection, whereas a 50-patient pilot study found a 90.5% local disease control rate (LDCR) at 16 weeks' postchemotherapy commencement.

- OncoSil™ is intended for intratumoural implantation into a pancreatic tumour via injection under endoscopic ultrasound guidance.
- It is indicated for the treatment of patients with locally advanced unresectable pancreatic cancer, in combination with gemcitabine-based chemotherapy.
- It is intended for single-patient, single-use and is generally an outpatient procedure.

Greece was the third European country that in December 2023, utilized this new therapy and General Anticancer Oncological Hospital of Athens "Agios Savvas", was the 1st Treatment Center in Greece.

Preparation: The implanted device is prepared by the treating facility's radiopharmacist or medical physist. 32P activity is calculated by using the patient's target tumor volume (max 110cc)

to deliver a 100Gy absorbed dose - calculated before the procedure to achieve an implanted volume/tumor volume ratio of 8%.

Procedure: The implanted volume is inserted into the center of the lesion, followed by a 1,5mL saline flush, then the needle sheath is pushed out into the gastric lumen and the needle retracted into the sheath, saline (3,5mL) is subsequently used to flush the sheath into the gastric lumen, the sheath, the scope and needle complex are then removed from the patient and further flushing is performed into a biohazard disposal container. After ^{32}P-microparticle implantation, bremsstrahlung Planar and/or SPECT/CT imaging is performed within 4 hours to confirm intratumoral distribution of the microparticles.

In conclusion, it was shown that gastrointestinal cancers, collectively represent a complex and diverse group of malignancies. Radioisotope therapies can be a valuable modality in the management of these neoplasms. Recent studies show promise in finding more targeted radioisotope therapies that can be used in clinical practice and brachytherapy has already affected the treatment plans of certain malignancies.

The difficulty in managing specifically the locally advanced pancreatic tumors, necessitated the development of novel therapeutic strategies as is this single-use brachytherapy device that can reduce the tumor size by destroying the cancerous tissue. In larger studies, it has shown promise in controlling tumor growth and managing patient's symptoms.

Our experience also showed that, after some practice, it's a fairly straightforward procedure that can be performed in any hospital where the Endoscopic Gastroenterology and the Nuclear Medicine Departments collaborate as an interventional Treatment Center.

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From uncertainty to clarity: The evolution of Nuclear Medicine towards precision theranostics and AI-driven digital twins

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Abstract

Nuclear medicine has progressed from an exploratory discipline, historically constrained by limited spatial resolution and qualitative interpretation, into a rigorously quantitative clinical specialty. This evolution represents a systematic conversion of uncertainty into actionable information. Uncertainty that was once implicit and observer-dependent is increasingly measured, modelled, and managed across the full imaging-therapy continuum.

Early tracer work established the foundational diagnostic logic of assessing function before structure. Subsequent instrumentation advances, culminating in the contemporary deployment of long axial field-of-view total-body positron emission tomography (PET) and digital cadmium-zinc-telluride detectors, have compressed spatial ambiguity and enabled true dynamic, multi-organ kinetic modelling. Hybrid imaging further reduced uncertainty by coupling functional signals to anatomical context, while artificial intelligence has emerged as a transformative force, enabling synthetic attenuation correction, automated total tumour volume segmentation, and the deployment of 3D vision-language foundation models for multimodal analysis. Parallel progress in radiochemistry and target biology has shifted tracer development toward highly specific receptor and antigen ligands. This momentum catalysed the theranostics revolution, where diagnostic imaging serves as an explicit, quantitative gatekeeper for radiopharmaceutical therapy. As the field transitions into the "Alpha-Era"—characterized by the clinical maturation of targeted alpha

therapies—dosimetry and radiobiology have become paramount. To harness this complexity, the discipline is adopting Theranostics Digital Twins, advanced computational frameworks that integrate physiologically-based radiopharmacokinetic models, radiobiological optimizers, and patient-specific multi-omics to predict dose-response and mitigate toxicity.

Though modern nuclear medicine has not eliminated biological uncertainty, it has formalized its quantification, establishing a highly personalized and augmented therapeutic paradigm capable of overriding sub-clonal tumour resistance and redefining systemic oncology.

Keywords: Quantitative imaging -Theranostics -Internal dosimetry -Artificial intelligence -Radiomics

Introduction

Nuclear medicine is undergoing a profound conceptual and technological shift, applicable to and increasingly benefitting broad patient populations. In its formative decades, the specialty's diagnostic utility was undeniable; interrogating perfusion, metabolism, and receptor expression across diverse physiological systems. However, interpretation was frequently qualitative and probabilistic. "Uncertainty" within the discipline was not merely statistical, resulting from Poisson counting noise, but also deeply contextual; prone to degrees of subjective interpretation. This lack of clarity was driven by limited spatial resolution, the overlapping of three-dimensional anatomy onto planar projections, variable acquisition practices, and highly observer-dependent image interpretation.

In the field of oncology, this implicit uncertainty has been steadily replaced with explicit measurement, culminating in the current era of precision theranostics. The arc of this transformation is demarcated by three interconnected technological transitions. First, the field moved from planar patterns to tomographic and total-body localization, enabling whole-body pharmacokinetic tracking. Second, qualitative visual "hot spots" were replaced by calibrated, harmonized, and AI-segmented biomarkers, facilitating the calculation of total tumour burden. Finally, nuclear medicine transitioned from isolated diagnostics to theranostics gating and personalized radiopharmaceutical therapy, underpinned by voxel-level dosimetry and predictive digital twins.

Crucially, every image and derived metric - standardized uptake value (SUV), lesion-to-background ratio, kinetic parameter, or absorbed dose - results from a composite modelling cascade that couples radiopharmacokinetics, acquisition physics, reconstruction algorithms, and analytical definitions. In the contemporary context, where molecular imaging informs treatment

selection and enables dynamic adaptation of targeted therapies at cellular and subcellular scales, such a structured and uncertainty-aware framework is indispensable.

For practicing nuclear medicine physicians, the current phase of the field's evolution is unusual in its scope: diagnostic imaging increasingly acts as a treatment gatekeeper; therapy increasingly demands post-therapy verification and standardized reporting; and health system stakeholders (tumour boards, regulators, payers, trial networks) increasingly treat nuclear medicine outputs as calibrated measurements rather or more than interpretive impressions.

This convergence has sharpened the clinical importance of three domains.

First, quantitative imaging has moved from "optional sophistication" to clinical infrastructure. The updated EANM FDG PET/CT procedure guideline [1] articulates a metrology-oriented view: PET is a quantitative technique that requires QC/QA, traceable calibration, and procedures that protect repeatability and reproducibility so that biomarkers are stable across time and sites. Second, theranostics have become mainstream: imaging does not merely stage disease but demonstrates in vivo target accessibility as a prerequisite for radiopharmaceutical therapy, as exemplified by PRRT and PSMA targeted radioligand therapy [2]. Third, dosimetry has changed status. It is increasingly treated as the methodological bridge between empiricism and personalization, under legal and professional expectations of individualized planning and verification and within an expanding guidance ecosystem that emphasizes not only absorbed dose estimation but uncertainty analysis and standardized reporting [3].

Following a concise historical overview of nuclear medicine, this article presents a synthesis structured around the three aforementioned, inextricably interlinked themes. The goal is not to summarize every technical development, but to describe how modern nuclear medicine converts uncertainty into enhanced clinical clarity - by governance of measurement, by explicit imaging gated therapy selection, and by uncertainty-aware verification and adaptation.

Discussion

1. Historical overview

The Tracer Principle: Function Before Structure

The foundational innovation of nuclear medicine is conceptual rather than technological: the tracer principle, introducing minute quantities of labeled substances to follow biological pathways without materially altering the system under study. Early tracer experiments demonstrated that radioisotopes could reveal dynamic metabolic processes in vivo, shifting medical inference from static anatomy toward measurable physiology. Two enduring implications followed. First, sensitivity eclipsed resolution: radionuclides enabled detection of molecular processes at concentrations unreachable by most modalities. Second, interpretation became inherently model-dependent, because what the camera records is biology filtered through pharmacokinetics and

imaging physics. The earliest era accepted this trade: low spatial precision in exchange for uniquely informative, dynamic biology. That trade would later be renegotiated by instrumentation, fusion imaging, and quantification [4].

Planar Scintigraphy: Seeing the Invisible

From the 1940s through the 1960s, nuclear medicine relied on planar imaging. Clinical value was tangible - thyroid uptake studies, renal function assessment, bone scans - but spatial ambiguity and organ overlap were fundamental limitations. The scintillation camera improved practicality and sensitivity, helping the specialty scale clinically. Nonetheless, dominant uncertainty sources persisted: superimposition of organs and lesions in projection images, limited correction for attenuation and scatter, and qualitative reporting strongly dependent on reader experience. Even so, planar imaging embedded a principle that remains central: tracer distribution constitutes a biological measurement, and biology can guide clinical decisions even when anatomical localization is imperfect [5].

Tomography: The First Major Compression of Ambiguity

Tomographic imaging represented the first transformative reduction of spatial uncertainty [6]. Clinical maturation of SPECT in the 1970s–1980s enabled true three-dimensional localization of gamma-emitting tracer uptake. SPECT's impact extended beyond image quality: it enabled lesion-based interpretation incorporating volume and location, meaningful separation of physiological from pathological uptake, and – critically - a viable path toward quantification once attenuation, scatter, and collimator-response modelling became routine.

PET's coincidence detection and more tractable attenuation correction made it inherently suited to quantification, especially as iterative reconstruction, normalization, and physical corrections matured. PET expanded from neuro-oncology and cardiology into broad oncological staging - accelerated by FDG adoption. Tomography's deeper contribution was epistemic: it converted nuclear medicine from pattern recognition under uncertainty into localizable biology amenable to cross-site standardization [7].

FDG: the Shift Beyond Metabolism

FDG-PET's broad oncological utility created a common clinical language for metabolic staging, response assessment, and prognostication, normalizing the expectation that nuclear medicine results directly alter management. Yet FDG also illuminated a limitation: glucose metabolism is sensitive but not always specific [8]. The subsequent era therefore emphasized biological specificity - somatostatin receptor (SSTR) imaging for neuroendocrine neoplasms [9], PSMA imaging for prostate cancer [10], and expanding tracer portfolios in neurology and cardiology. This meant not merely "more tracers" but a different epistemology: imaging as direct measurement of target expression, often coupled to therapeutic eligibility.

Hybrid Imaging: Anatomy Meets Function

PET/CT, SPECT/CT, and later PET/MR constituted a giant leap forward by rendering anatomical context intrinsic rather than inferential. This compressed two recurring uncertainty modes: localization ambiguity and specificity ambiguity. Combined PET/CT prototypes were clinically evaluated from the late 1990s, and commercial systems followed rapidly, driving routine functional-anatomical integration. CT-based attenuation correction became standard; SPECT/CT enabled patient-specific attenuation maps; registration errors shrank. Hybrid imaging moved nuclear medicine from "suggestive" toward "decisive" - particularly in oncology, where best management pivots on accurate staging [11] (Table 1).

***Table 1**. Selected Milestones and Their Impact on Uncertainty.*

Era	Milestone	Uncertainty Reduced
1930s	Tracer principle demonstrated *in vivo*	Conceptual: can physiology be measured without perturbation?
1950s	Scintillation camera	Operational: workflow, sensitivity, routine clinical imaging
1960s-80s	Emission tomography (SPECT)	Spatial ambiguity from planar overlap
1980s-2000s	Clinical PET expansion	Quantitative potential; improved physical corrections
Late 1990s-2000s	PET/CT, SPECT/CT	Anatomical localization and specificity
2010s	EARL harmonization programs	Inter-site variability in quantitative PET
2020s	Quantitative SPECT/CT formalization	Quantitative uncertainty in SPECT activity maps
2020s	Mainstream theranostics (PRRT, PSMA-RLT)	Treatment selection uncertainty
2020s	Uncertainty analysis guidance	Hidden uncertainty in the dosimetry chain
2020s-2026	Alpha-therapy dosimetry frameworks	Micro-scale uncertainty (RBE, daughters)
2020s-2026	AI-enabled dosimetry workflows	Operational bottlenecks (segmentation, kinetics, harmonization)

2. Quantitative Imaging

Why quantification is now a physician issue

Quantification is sometimes described as a physicist's concern: calibration, cross-checks, phantom work, reconstruction settings. In contemporary nuclear medicine, this framing is no longer clinically adequate. The reason is simple: the clinical decisions now attached to quantitative outputs - response categorization, treatment escalation or switching, trial enrolment,

therapy eligibility - are highly consequential decisions, often relying upon comparing measurements across time and across institutions and correlation with clinical history.

The EANM FDG PET/CT guideline makes this explicit by foregrounding repeatability and reproducibility as essential requirements for quantitative imaging biomarkers and by linking these directly to QC/QA and protocol standardization [1]. This is a conceptual shift in professional language: PET is framed as a measurement system rather than an imaging device. In day-to-day practice, the physician expression of that shift is the growing expectation that a reported SUV (or related metric) is not merely a local descriptor, but a value that can be trusted longitudinally and, increasingly, across sites.

This expectation matters because variability can be clinically indistinguishable from biology. A change in reconstruction settings between baseline and follow up, a drift in calibration, or a shift in uptake time can create apparent "response" or "progression" in borderline cases. When such changes alter management – such as continuing or stopping systemic therapy, adding local therapy, changing line of treatment - the technical variability becomes an unrecognized clinical confounder. The measurement-science approach treats this as a governance problem: if quantitative claims are to guide decisions, the conditions under which they are produced must be controlled and documented.

Harmonization: from "quantitative" to "comparable"

A central practical insight has matured across the field: two scanners can both be correctly calibrated and still produce systematically different quantitative results. Differences in detector technology, TOF and PSF implementations, filtering, and vendor specific defaults can alter recovery coefficients and noise behaviour, which in turn alter lesion metrics. From a physician's standpoint, the key issue is not the engineering detail but the clinical consequence: multicentre trials, inter-institutional follow up, and networked care requires that numbers be exchangeable - not merely internally consistent.

Harmonization has also become dynamic because technology has become dynamic. The emergence of digital detectors and long axial field of view (FOV) PET systems shift the achievable noise–resolution regime and expand feasible protocol classes, including whole-body dynamic imaging and low activity approaches. A recent review of LAFOV PET/CT summarizes advantages and challenges, including implications for static and dynamic protocols and broader tracer development [12]. For physicians, the practical point is that better sensitivity and resolution do not automatically imply better comparability. There is an ongoing tension between reconstructions optimized for detectability and reconstructions constrained for harmonized quantification; the correct choice depends on the clinical question, and the service must document which quantitative regime is being used.

Quantitative SPECT/CT: the therapy driven reason it matters

While PET established itself early as the "quantitative" modality, the rise of theranostics and radiopharmaceutical therapy has reshaped the role of SPECT. Post-therapy verification and absorbed dose estimation require activity concentration maps; semi-quantitative interpretation is often insufficient. The EANM quantitative SPECT/CT practice guideline responds to this service reality by providing a framework for departments to implement quantitative SPECT/CT, including protocol guidance and harmonization considerations [13].

The physician significance is that quantitative SPECT/CT makes "verification" clinically legible. It enables routine post-therapy imaging to move beyond confirmation of uptake toward structured estimation of time-integrated activity and absorbed dose - quantities that can support toxicity risk discussions, retreatment considerations, and, increasingly, adaptive therapy concepts.

In summary, the modern clinical role of quantitative imaging is not that it provides numbers; it is that it provides numbers that remain meaningful across time, across sites, and across clinical pathways that now include therapy. The clinician's interest lies in ensuring that quantitative metrics are governed as measurements, because the downstream decisions are governed as clinical actions.

3. Theranostics

The conceptual shift: from "lesion detection" to "therapy eligibility phenotype"

Theranostics is often described as the pairing of diagnostic and therapeutic radiopharmaceuticals directed at the same molecular target. Clinically, its deeper significance is more precise: it transforms target accessibility from a theoretical assumption into a measurable, patient-specific condition. By visualizing in vivo binding before treatment, it reduces a central uncertainty in systemic oncology - whether a drug will effectively reach and engage its intended target.

Once imaging functions as a therapeutic gatekeeper, the nuclear medicine report becomes a treatment-selection instrument. The scan defines a biological phenotype: total target-positive disease burden, spatial distribution, intra- and inter-lesional heterogeneity, and the presence of target-negative compartments that may predict resistance or require complementary strategies (Table 2).

***Table 2**. Comparative Profile of Key Theranostics Radionuclides.*

Isotope	Emission Type	Half-Life	Primary Application	Clinical Challenges / Limitations
Lutetium-177	Beta	6.65 days	Standard RPT (mCRPC, GEP-NETs)	Low LET; less effective for micro metastases or hypoxic cores.
Actinium-225	Alpha	9.92 days	Salvage therapy; highly radioresistant tumours	Complex decay chain; daughter isotope recoil causing off-target toxicity.
Lead-212	Alpha	10.6	Emerging TAT; SSTR and	Supply chain constraints; requires

		hours	PSMA targeting	rapid logistical radiopharmacy protocols.
Radium-223	Alpha	11.4 days	Bone-seeking monotherapy for mCRPC	Cannot be stably chelated to peptides; restricted to osseous metastases.

Peptide Receptor Radionuclide Therapy: the template that made imaging gated therapy routine

PRRT in neuroendocrine tumours is an early and influential example because it integrated patient selection, therapy delivery, and follow-up into a coherent workflow supported by professional guidance and randomized evidence. The NETTER 1 phase 3 trial demonstrated markedly longer progression-free survival and a higher response rate for 177Lu-DOTATATE compared with high dose octreotide in advanced midgut neuroendocrine tumours [14]. Beyond efficacy, its conceptual contribution lies in formalizing receptor positivity as a prerequisite for therapy: the treated population is defined by the imaging phenotype, and therapeutic benefit is inseparable from this selection framework.

Prostate-Specific Membrane Antigen radioligand therapy: scaling theranostics into major oncology pathways

PSMA targeted radioligand therapy extends this paradigm to a high-prevalence malignancy. The VISION phase 3 trial showed that adding 177Lu-PSMA 617 to standard care prolonged imaging-based progression free survival and overall survival in PSMA positive metastatic castration resistant prostate cancer [15]. As with PRRT, imaging defines the treatable phenotype; therapeutic value is conditional on documented target expression, now within increasingly complex treatment sequences.

Alpha-emitter therapy: increasing potency, increasing responsibility

The expansion of targeted alpha therapy represents the next conceptual step in theranostics. Alpha emitters deliver high linear energy transfer radiation over micrometric path lengths, producing dense ionization tracks and irreparable double-strand DNA breaks. Clinically, this offers the potential to overcome resistance mechanisms observed with beta emitters, particularly in micro metastatic or heterogeneous disease compartments.

However, the very properties that confer efficacy also narrow the therapeutic window. Short particle range, stochastic microdocumentary effects, and organ-specific retention amplify the consequences of imperfect targeting.

4. Dosimetry

Dosimetry: from "verification" to "adaptation"

Dosimetry translates administered activity into absorbed dose estimates for organs and lesions. In radiopharmaceutical therapy, absorbed dose is not directly observed; it is inferred from

quantitative imaging (or sampling), time-activity integration, and a dose calculation model. This makes dosimetry inherently uncertain, but also uniquely actionable: uncertainty can be quantified and propagated, and the result can support risk-based decisions rather than fixed empiricism.

Professional guidance provides an operational foundation for this inference chain. The joint EANM/MIRD guideline for quantitative 177Lu SPECT applied for dosimetry outlines acquisition and reconstruction approaches recommended for quantitative imaging suitable for dosimetry [16]. From a physician perspective, this matters because it anchors post therapy imaging within a standardized measurement framework: it is the methodological basis by which "delivery verification" becomes quantifiable rather than interpretive.

Legal and standardization drivers: planning and verification are explicit expectations

The European Basic Safety Standards (Council Directive 2013/59/Euratom) state that for radiotherapeutic purposes, exposures of target volumes should be individually planned and their delivery appropriately verified. The EANM position paper on Article 56 interprets this requirement for nuclear medicine therapy and emphasizes appropriate involvement of medical physics expertise [17].

For nuclear medicine physicians, the practical consequence is that dosimetry and verification increasingly function as part of clinical governance: they support defensible treatment planning and documentation, particularly as therapies become more potent, more widely deployed, and more scrutinized in multidisciplinary care.

Uncertainty becomes part of the result, not an afterthought

A key maturation is that absorbed dose is increasingly treated not as a single deterministic value but as an estimate with uncertainty. The EANM practical guidance on uncertainty analysis for molecular radiotherapy absorbed dose calculations proposes a framework to model and propagate uncertainties along the dosimetry chain [18]. This framing is physician relevant because it changes how dose information can be used clinically.

In risk-based practice, the relevant question is often not "what is the dose?" but "how confident are we that the dose is below a constraint or above a target?" Uncertainty-aware reporting enables probability based discussions (e.g., likelihood of exceeding an organ at risk threshold) that align more naturally with clinical decision making than binary threshold thinking. It also supports more transparent tumour board discussions in retreatment and escalation scenarios, where a single point estimate can be misleadingly precise.

Pragmatic personalization: recommendations designed for therapy providing centres

The principal barrier to full multi time point voxel dosimetry is often operational: scanner time, staffing, patient logistics, and analysis workload. The EANM dosimetry committee recommendations for 177Lu labelled somatostatin receptor and PSMA targeting ligands explicitly

aim to encourage patient specific dosimetry using methods judged to be within scope for centres offering these therapies [19]. This is clinically important because it legitimizes a tiered approach: personalization can be introduced without requiring every centre to adopt maximal workflows immediately. For physicians, such guidance supports realistic implementation paths while maintaining an expectation of measurement discipline and defensible reporting.

The alpha transition: why uncertainty governance becomes more central, not less

With the expansion of targeted alpha therapies, dosimetry and radiobiological modeling assume greater prominence. Accordingly, the EANM Dosimetry Committee recommendations for alpha-emitter therapies emphasize specific methodological challenges, rigorous reporting standards, and explicit consideration of uncertainty sources in treatment planning and analysis [20].

Clinical use of alpha emitters is established; ^{223}Ra dichloride provides a long standing example. The ALSYMPCA trial demonstrated improved overall survival with radium-223 in metastatic castration resistant prostate cancer with bone metastases [21]. However, as alpha emitters move from bone-seeking agents to vector-targeted therapies and broader indications, organ-level absorbed dose alone may insufficiently explain biological effects. Robust eligibility phenotyping - documenting sufficiently intense and spatially homogeneous target expression - thus becomes essential, both to optimize efficacy and to limit toxicity.

In this context, imaging-based selection, individualized dosimetry, and formal uncertainty analysis operate as a unified control framework. The higher radiobiological potency of alpha particles leaves little margin for hidden variability. Safe implementation and meaningful cross-trial comparability therefore depend on precise phenotype definition, quantitative verification, and structured uncertainty governance [22].

Artificial Intelligence as workflow compression under clinical governance

The practical bottlenecks in dosimetry - segmentation, registration, curve fitting, dose computation - are well known to nuclear medicine physicians because they affect throughput and timeliness. AI's immediate clinical relevance is therefore not philosophical but operational: it offers a way to standardize high variance steps and reduce analysis time, potentially enabling broader adoption of dosimetry supported decision making.

However, professional governance remains central. The EANM position paper on artificial intelligence in nuclear medicine emphasizes preconditions for implementation, including validation and post deployment monitoring, acknowledging that AI may introduce artifacts and errors that can propagate into clinical decisions [23]. For physicians, this implies that AI tools should be treated like any clinical technology: characterized, validated in the local context, monitored over time, and used with defined responsibility boundaries [24] (Table 3).

Table 3. AI Applications Across the Nuclear Medicine Workflow.

Workflow Step	AI Method	Uncertainty Addressed	Maturity
Organ/lesion segmentation	3D U-Net, nnU-Net	Inter-operator variability	Clinical validation
Time-activity curve fitting	Physics-informed neural networks	Sparse temporal sampling	Research/early clinical
Multi-centre harmonization	Federated learning	Scanner/protocol variability	Research
Attenuation/scatter correction	Deep-learning CT synthesis	CT mismatch artifacts	Clinical validation
Dose-response prediction	Gradient-boosted trees, GNNs	Outcome uncertainty	Research
Digital twin / adaptive RPT	Recurrent + Bayesian models	Cumulative treatment uncertainty	Concept/early research
Radiomic feature extraction	Standardized pipelines (IBSI)	Feature reproducibility	Maturing (IBSI v2)

Conclusions

For nuclear medicine physicians, the transition from implicit uncertainty to structured clinical clarity is defined by three converging developments [25].

First, quantitative imaging has become a metrological enterprise. PET and SPECT are increasingly managed as calibrated measurement systems in which repeatability, reproducibility, quality control, and cross-centre harmonization are prerequisites for generating exchangeable biomarkers. Such governance renders eligibility and response assessments scientifically defensible; without a stable quantitative framework, both therapy selection and longitudinal evaluation inherit unrecognized variability.

Second, theranostics have formalized imaging as a gatekeeper of treatments. By documenting in vivo target expression, molecular imaging delineates treatable phenotypes and constrains systemic therapeutic decisions, as exemplified by peptide receptor radionuclide therapy and PSMA-targeted radioligand therapy. Imaging thus defines not only disease extent, but therapeutic accessibility.

Third, radiopharmaceutical therapy is increasingly coupled to uncertainty-aware dosimetry and personalised medicine. Contemporary professional guidance and regulatory expectations support individualized dose verification, while artificial intelligence provides scalable tools for segmentation, kinetic modelling, and uncertainty propagation - acting as an accelerator and standardizer rather than a substitute for methodological rigor. This integration becomes

particularly critical as more potent agents, including alpha emitters, enter clinical practice and patient heterogeneity limits fixed-activity paradigms.

Nuclear medicine has not eliminated uncertainty; it has reframed it as an explicit clinical variable—quantified, communicated, and incorporated into decision-making. Clinical clarity, therefore, does not imply determinism, but the capacity to make high-stakes diagnostic and therapeutic decisions on the basis of measurements whose uncertainty is known, propagated, and governed. In this context, the role of the physician remains central: beyond quantitative metrics and algorithmic outputs, clinical expertise is essential to interpret results, recognize confounding factors, and integrate imaging data within the broader clinical picture, ensuring that increasingly automated processes remain clinically meaningful and patient-centered.

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The role of peptide receptor radionuclide therapy with Lu-177 Dotatate in metastatic gastroenteropancreatic neuroendocrine tumors

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Abstract

Peptide Receptor Radionuclide Therapy (PRRT) has emerged as an established treatment modality for patients with gastroenteropancreatic neuroendocrine tumors (GEP-NETs), particularly in the second-line setting following progression on somatostatin analogs. Evidence from trials such as NETTER-1 and NETTER-2 has demonstrated significant improvements in progression-free survival and objective response rates, with expanding indications into first-line treatment and higher-grade disease. Emerging data from comparative and combination studies highlight the potential role of PRRT alongside targeted therapies and chemotherapy, although uncertainties remain regarding optimal sequencing and overall survival benefit. Retreatment strategies, special population considerations, and novel approaches including alpha-emitting radionuclides and somatostatin receptor antagonists further broaden the therapeutic landscape. Ongoing prospective trials are expected to refine patient selection and define the future role of PRRT across different tumor grades and clinical scenarios.

Keywords: Neuroendocrine tumors -Peptide receptor radionuclide therapy -Lutetium 177-DOTATATE -Somatostatin receptors

Introduction

Peptide Receptor Radionuclide Therapy (PRRT) is now well established and widely accepted for the treatment of gastroenteropancreatic neuroendocrine tumors (GEP-NETs). Treatment with lutetium-177 (Lu-177) Dotatate was approved by the European Medicines Agency (EMA) in 2017 and by the U.S. Food and Drug Administration (FDA) in 2018 for the management of these tumors. The standard therapeutic regimen consists of four treatment cycles, each delivering a dose of 200mCi, administered at 8-week intervals [1].

There is now an approved indication, according to all major clinical guidelines, for patients with Grade 1 or Grade 2 GEP-NETs, positive somatostatin receptor positron emission tomography/ computed tomography (PET/CT) imaging, and metastatic unresectable disease, who have demonstrated progression after treatment with somatostatin analogs (SSA) [2].

Evidence from randomized trials

A major contribution to this indication has come from the final results of the NETTER-1 Study, which evaluated patients with Grade 1 and Grade 2 neuroendocrine tumors of the small intestine. In this study, patients were randomized into two groups: one group received SSA, while the other received Lu-177-Dotatate in combination with SSA. A significant improvement in progression-free survival (PFS) was observed in the Lu-177-Dotatate group compared to the control group (28.4 months vs 8.5 months). An advantage was also noted in overall survival (OS) (48 months vs 36.3 months for the control group), although this difference did not reach statistical significance, likely due to crossover during follow-up [3].

Thus, according to ESMO guidelines, PRRT is recommended as a second-line treatment for patients with metastatic Grade 1 and Grade 2 GEP-NETs after documented disease progression on SSA.

Following NETTER-1, the main questions were what the role of PRRT should be in the therapeutic algorithm for the remaining GEP-NETs, and what its role should be in Grade 3 neuroendocrine neoplasms (NENs).

Regarding the first question, at ENETS 2025, two important studies were presented. First, the COMPETE trial, which is the first phase III study comparing PRRT as monotherapy with targeted therapy in patients with Grade 1 and Grade 2 GEP-NETs, demonstrated a significantly improved median PFS in patients treated with PRRT compared to everolimus. Additionally, OS also favored the PRRT group, although this difference was not statistically significant, likely due to the need for longer follow-up [4]. A subanalysis presented at ENETS 2026 showed that both small intestine and pancreatic tumors exhibited improved PFS in the PRRT group compared to the control group treated with everolimus [5].

The second study was the OCLURANDOM trial, which included patients with metastatic pancreatic neuroendocrine tumors and compared PRRT with sunitinib. A significantly higher objective response rate (ORR) and improved PFS were observed in the PRRT group. In contrast,

OS favored the sunitinib group; however, this finding is largely attributed to a substantial crossover effect, as many patients switched between treatment arms during the study [6].

PRRT in high grade and first-line setting

Following NETTER-1, the NETTER-2 study evaluated a different patient population, including those with Grade 2 and Grade 3 GEP-NETs, with a Ki-67 index ranging from 10% to 55%. In this study, the first group received SSA, while the second group received a combination of Lu-177-Dotatate and SSA as first-line therapy. A clear superiority was observed in terms of PFS in the PRRT group, as well as an improved ORR compared to the control group. The NETTER-2 study is particularly important, as it was the first randomized trial to evaluate PRRT as a first-line treatment and the first to include patients with Grade 3 disease [7].

However, these findings raise important concerns. In Grade 3 NETs, treatment with SSA is not considered standard first-line therapy, which complicates interpretation of the comparator arm. There is also a lack of direct comparative data between PRRT and chemotherapy regimens such as CAPTEM or FOLFOX, and no definitive OS benefit has yet been established. The optimal timing of PRRT—whether as first-line or in later lines—remains unclear, particularly given the heterogeneity of tumors with Ki-67 up to 55%.

In a subanalysis of NETTER-2 presented at ESMO 2024, superiority of PRRT was confirmed in both Grade 2 and Grade 3 tumors, with a more pronounced benefit in Grade 2 disease. Small intestine tumors showed longer PFS, while pancreatic tumors exhibited higher ORR [8]. Table 1 compared median PFS in the four major studies.

Combination strategies

When comparing NETTER-1 and NETTER-2, a significantly higher ORR was observed in NETTER-2 (43% vs 18%). This is likely explained by increased radiosensitivity associated with higher Ki-67. Thus, higher ORR may be achieved, but potentially with shorter PFS due to tumor heterogeneity and resistant clones. In contrast, Grade 1 and Grade 2 tumors tend to demonstrate longer PFS, although they may remain morphologically stable for prolonged periods.

These observations suggest that, particularly in higher-grade tumors, combination strategies may be required. One of the most studied combinations is PRRT with chemotherapy using CAPTEM. Current evidence does not demonstrate clear superiority of the combination over PRRT alone. However, the CONTROL NET study demonstrated improved PFS for the combination compared to CAPTEM alone in pancreatic tumors, while no benefit was observed in small intestine tumors. Importantly, a significantly higher ORR (72.2% vs 33.3%) was observed in pancreatic tumors, suggesting a role in tumor downsizing [9]. Further evidence is expected from the PReCedeNT study [10].

Following NETTER-1 and NETTER-2, results are awaited from the ongoing NETTER-3 study, expected around 2028. This study includes low-grade (G1-G2) GEP-NETs with high tumor burden and evaluates PRRT as first-line therapy compared to high-dose SSA [11].

Retreatment with PRRT

Regarding retreatment, guidelines suggest PRRT can be repeated in patients with disease control for at least one year after initial therapy. No prospective studies are available. A meta-analysis showed a PFS of approximately 12.5 months with similar toxicity [12]. A large multicenter retrospective Australian study reported PFS of 17.4 months and OS of 40 months. Outcomes were better in lower grades, with no significant differences based on number of cycles or chemotherapy use [13].

Ongoing studies such as ReLUTH [14] and NET RETREAT [15] are expected to clarify the role of retreatment.

Special populations

PRRT can be safely administered in elderly patients (≥75 years) [16]. Amino acid co-infusion has a nephroprotective role, allowing safe use in chronic kidney disease. PRRT has also been administered in patients undergoing hemodialysis, requiring close coordination between nephrology and nuclear medicine. High peritoneal tumor burden may be managed with prophylactic corticosteroids. Special attention is required in carcinoid syndrome-related cardiac disease and hyperkalemia. Carcinoid crisis remains a challenging condition, where short-acting SSA and steroids are essential [17].

PRRT improves multiple aspects of health-related quality of life (HRQoL) [18], including:

- Global QoL
- Emotional and social functioning
- Symptom burden (fatigue, diarrhea, pain).

Emerging therapies

Alpha-emitting radionuclide therapy represents a promising future direction, with advantages such as high LET, short penetration range, high energy deposition, and independence from hypoxia. These properties result in strong targeted antitumor effects with limited damage to normal tissues. The main isotopes include actinium-225 and lead-212. Early studies show high disease control rates and ORR, although with notable toxicities including dysphagia [19].

PRRT with somatostatin receptor antagonists is also promising, demonstrating higher tumor uptake and improved tumor-to-background ratios. Phase II data show very high disease

control rates (94.7%), although with increased grade ≥3, primarily hematological toxicity (~42.5%) [20].

Conclusions

PRRT is an established second-line treatment for metastatic GEP-NETs, with expanding indications toward first-line therapy and higher-grade disease. Its role in tumors with high Ki-67 remains to be defined and will be clarified by ongoing studies. Combination strategies, alpha-emitters, and receptor antagonists represent important future directions, although careful evaluation of toxicity is required.

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Table I. *Key Clinical Evidence for PRRT.*

Trial	Median PFS (PRRT versus control group)
NETTER 1	28.4 vs 8.5 months

NETTER 2	22.8 vs 8.5 months
COMPETE	23.9 vs 14.1 months
OCLURANDOM	20.7 vs 11 months

Abbreviations: *PRRT - peptide receptor radionuclide therapy; PFS - progressive free survival*

What changes in the therapeutic management of papillary thyroid carcinoma. Emerging evidence

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Abstract

The low mortality of papillary thyroid carcinoma (PTC) has led to progressively less aggressive therapeutic approaches according to the latest 2025 guidelines. However, morbidity associated with persistent disease and cervical lymph node metastases remains a significant clinical challenge.

The presence of undetected “occult” metastases and the occurrence of nodal recurrences following apparently adequate treatment raise concerns regarding the effectiveness of current diagnostic and therapeutic strategies.

Improving preoperative diagnostic accuracy in assessing both the extent and aggressiveness of the disease could play a decisive role in selecting the most appropriate surgical approach and the need for adjuvant radioactive iodine (RAI) therapy.

Precise topographical localization of the tumor represents an additional risk factor that should be incorporated into therapeutic decision-making.

Keywords: Thyroid carcinoma -Lymphatic metastases -Radiomics -Upper pole papillary carcinoma

Introduction

The management of papillary thyroid carcinoma is primarily based on surgical intervention, complemented when indicated by radioactive iodine (I-131) therapy. Treatment strategies have evolved over the decades, guided by recommendations from international scientific societies [1].

A review of the literature, supported by clinical experience, indicates that metastatic disease occurs in approximately 20–50% of cases, even in small tumours without apparent aggressive features [2, 3, 4]. Micrometastases (<2mm) have been reported in up to 90% of cases in certain series [5,6]. These findings raise questions regarding the adequacy of current guideline recommendations concerning the extent of surgery and the use of RAI therapy.

Despite advances, the cornerstone of treatment for differentiated thyroid carcinoma remains thyroidectomy, with adjuvant RAI reserved for patients at increased risk of residual disease. Appropriate selection of the surgical procedure is critical to avoid reoperations, which carry increased risks due to postoperative fibrosis and adhesions.

Although international guidelines provide standardized recommendations and reassuring outcome statistics, there remains room for improvement in reducing recurrence rates [1, 6, 7].

In real-world clinical practice, patients are managed by heterogeneous teams of endocrinologists, radiologists, cytopathologists, and surgeons with varying levels of expertise and technical resources. This variability significantly impacts diagnostic accuracy and treatment outcomes.

Clinical scenarios range from well-documented cases with detailed imaging and cytology reports to delayed referrals with incomplete or inadequate diagnostic information.

Diagnostic Evaluation

Initial suspicion typically arises from the endocrinologist when a new thyroid nodule is detected or when an existing nodule demonstrates changes on ultrasound.

High-resolution ultrasound remains the cornerstone of thyroid imaging, providing critical information such as [1, 7, 9]:

- Nodule location
- Size
- Echogenicity
- Shape
- Margins/halo
- Vascularity
- Presence of calcifications
- Capsular contact or extrathyroidal extension
- Multifocality
- Associated thyroiditis (e.g., Hashimoto, De Quervain)
- Suspicious cervical lymph nodes

Predictors of occult metastases include:

- Tumor size (±10 mm threshold)
- Tumor location

- Chronic thyroiditis
- Extrathyroidal extension
- Multifocality
- Aggressive or mixed cytological subtype

Although these parameters are objective, they are not always appropriately weighted. A structured classification system, analogous to Bethesda score, could improve surgical decision-making [10].

Radiomics represents a promising advancement in imaging analysis, enabling extraction of quantitative features from medical images. It transforms imaging from a qualitative tool into a high-dimensional data source.

Using standardized imaging protocols (e.g., ACR TI-RADS), images undergo pre-processing (contrast enhancement, edge sharpening), followed by segmentation and feature extraction.

These features include:

- Semantic features: shape, location, vascularity
- Agnostic features: texture and heterogeneity metrics such as kurtosis, Haralick texture, Laws texture, and Minkowski functionals

Studies demonstrate that combined models significantly outperform traditional methods. Based on AUC (area under the curve) values:

1. Clin + ACR + Radiomics (AUC = 0.958) – highest performance
2. ACR + Radiomics (AUC = 0.943)
3. Clin + Radiomics (AUC = 0.895)
4. Radiomics alone (AUC = 0.890)
5. Clin + ACR (AUC = 0.784)

The integrated model shows excellent sensitivity (95.2%) and accuracy (91.8%), particularly for PTC (98.1%).

Limitations include heterogeneity in imaging protocols and lack of integration with laboratory and cytological data, suggesting further potential for improvement [11-15].

Cytological Assessment: Fine-needle aspiration (FNA) biopsy remains essential for cytological diagnosis, classified according to the Bethesda system.

Suspicious lymph nodes should also be evaluated with FNA, including thyroglobulin (Tg) measurement in needle washout [16, 17].

Surgical Management

Surgical strategy is tailored based on preoperative findings and may include:

- Lobectomy

- Total thyroidectomy
- Central compartment lymph node dissection (Level VI)
- Modified radical neck dissection (lateral compartments)
- Extended resections (e.g., recurrent laryngeal nerve, jugular vein, trachea) in advanced disease

Postoperative staging determines the indication for RAI therapy.

Lymphatic Spread and Surgical Strategy: The cervical lymphatic network is highly developed, complex, and exhibits considerable anatomical variability. The principal lymphatic drainage pathways are oriented along the course of the internal jugular vein, with bilateral convergence toward the thoracic ducts. In addition, transverse lymphatic interconnections have been described, predominantly communicating with the thoracic duct [18]. For descriptive and surgical purposes, the cervical region is conventionally subdivided into seven distinct anatomical levels. In the majority of individuals, lymphatic drainage from the thyroid gland—particularly from the mid-portion and the inferior pole of the lobe—is directed to the central compartment (level VI) and, in selected cases, most commonly on the right side, extends to the superior mediastinum (level VII).

The central compartment (Level VI) represents the primary drainage basin and a critical crossroads for metastatic spread. Patients without central compartment involvement (N0) are often considered disease-free and may not require RAI therapy [19]. When central compartment metastases are present (N1a), lateral compartment involvement occurs in approximately 15–18% of cases.

The dissemination of malignant cells from the primary tumour to the lateral cervical compartments typically occurs initially via level VI, unless lymphatic channels or nodal basins become saturated, thereby facilitating alternative lateral drainage pathways to the lateral compartment. Accurate assessment of lymph node status in both the central and lateral compartments is critical in guiding the surgical strategy, specifically in determining whether to proceed with total thyroidectomy combined with central compartment lymph node dissection (approximately two hours in duration with a one-day hospitalization) or to extend the procedure to include lateral neck dissection (typically lasting 4–5 hours and requiring approximately five days of hospitalization).

In tumours located in the mid or lower pole without evident nodal disease, prophylactic central neck dissection may reveal occult metastases in up to 53.4% of cases, supporting its therapeutic and staging value [19].

Prophylactic lateral neck dissection is not recommended due to increased morbidity and should only be performed when metastases are confirmed cytologically or biochemically (Tg) [1,20].

Upper Pole Tumours: Tumours of the upper pole exhibit a higher incidence of skip metastases (61–63%) compared to lower pole tumours (19–32%). In cases of tumours located in

the superior pole without clinically or ultrasonographically evident lymphadenopathy in the lateral compartment, the question arises as to the presence of occult metastases not detectable on ultrasound [22]. These metastases may bypass the central compartment, raising questions regarding optimal surgical strategy.

Evidence from the literature indicates that occult (skip) metastases to the lateral compartment are observed in approximately 11–20% of superior pole carcinomas. These metastases tend to manifest at a later stage and are more commonly identified in middle-aged patients, females, and in tumours measuring <10 mm [22]. Experimental studies utilizing carbon nanoparticle tracers have demonstrated the existence of a lymphatic pathway from the superior pole to level II, resulting in occult metastases in up to 70% of cases within the study cohorts [23,24].

In such cases, adjuvant RAI therapy should be strongly considered, even in the absence of clinically evident nodal disease.

Clinical Exceptions

Several atypical cases highlight the limitations of standardized approaches, including:

- Isolated lateral lymph node metastasis without identifiable primary tumour
- Late subcutaneous metastasis decades after initial treatment
- Incidental metastasis detected during surgery for unrelated malignancies
- False-positive PET findings

These cases emphasize the biological variability behaviour of PTC.

Conclusions

- Ultrasound and cytological findings are critical and should be interpreted by experienced specialists.
- Artificial intelligence and radiomics may significantly enhance diagnostic stratification and surgical planning.
- Accurate assessment of disease extent is essential for selecting the appropriate surgical approach.
- Prophylactic central neck dissection may provide both therapeutic benefit and accurate staging, identifying occult metastases in up to 50% of patients.
- In upper pole and/or multifocal tumours without evident lateral metastases, adjuvant radioactive iodine therapy should be considered.

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Cardiovascular risk assessment in oncologic patients. A narrative review

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Abstract

Systematic cardiovascular risk assessment and stratification across the entire cancer care continuum is essential among cancer patients, largely due to potential cardiotoxic effects of oncologic therapeutic regiments. Prior to initiation of cancer therapy, cardiotoxicity risk assessment should include comprehensive evaluation of baseline cardiovascular status and baseline measurement of cardiac biomarkers. Patient-related factors should be integrated with therapy-related risks associated with specific oncologic regiments and/or radiotherapy. During cancer treatment, continuous cardiovascular surveillance is necessary to detect early or subclinical myocardial dysfunction. Monitoring strategies involve periodic clinical evaluation, serial echocardiographic assessment and biomarker measurements. Surveillance protocols should be adapted according to the cardiotoxic potential of the administered regimen; as early detection of cardiotoxicity allows prompt cardioprotective interventions and adjustment of oncologic treatments. Cardiovascular assessment after cancer therapy is crucial due to potential delayed cardiotoxic effects. During the first year, post-treatment, structured follow-up is recommended to identify persistent or emerging cancer therapy-related cardiotoxicities. Long-term surveillance is also particularly important for cancer survivors exposed to cardiotoxic agents, given their increased risk of chronic cardiovascular complications. Digitalization improves cardio-oncology risk assessment through artificial intelligence, electronic health records, and remote monitoring enabling earlier detection and personalized cardiovascular surveillance. A multidisciplinary cardio-oncology approach and structured surveillance across the entire cancer care continuum is crucial to reduce cardiovascular morbidity and improve long-term outcomes.

Keywords: Cardio-oncoloy -Cardiotoxicity -Risk stratification -Surveillance -Cancer therapy

Introduction

Cancer and cardiovascular disease are the leading causes of morbidity and mortality worldwide. The evolution of anticancer therapies have significantly improved life expectancy in oncologic patients who subsequently face increased risk of potentially fatal acute, subacute and long-term cardiovascular events, due to anticancer interventions [1]. Additionally, cardiovascular disease and cancer share similar biologic pathways and risk factors, that should be taking into account when evaluating these group of patients [2]. Thus, risk stratification and cardiovascular optimization are essential to all oncologic patients. International societies have produced expert consensus documents and guidelines in cardio-oncology in order to standardize certain clinical pathways via multidisciplinary teams where the patient involvement and engagement is crucial during the entire process. The most current recommendations address limited evidence, based on consensus opinion or small studies, retrospective studies, or registries (Level of evidence C) [1, 2].

Risk stratification in cancer is challenging and dynamic and should performed before; during; and after cardiotoxic cancer therapies, using certain monitoring and surveillance protocols that closely related to certain therapeutic regimens. Furthermore, as oncologic drug development progresses rapidly and many modern therapies address lack or/and incomplete knowledge of cardiovascular safety profile, risk stratification are frequently modified and adapted to real world data and observational studies [1, 3].

Cardiotoxicity risk assessment before cancer treatment

Prospective validation is needed to support the use of the ESC guidelines of Heart Failure Association (HFA) and International Cardio-Oncology Society (IC-OS) baseline risk stratification score[1]. The HFA-ICOS score was developed, after a thorough analysis of the literature, for seven classes of potentially cardiotoxic cancer therapies (anthracycline chemotherapy, HER2 targeted therapies, vascular endothelial growth factor inhibitors, second and third generation BCR-ABL multi-targeted kinase inhibitors, proteasome inhibitors, RAF and MEK inhibitors, and androgen deprivation therapies for prostate cancer). The principle focusing the dynamic course of CTR-CVT development in patients with cancer is that the absolute risk depends on their baseline risk and changes with exposure to cardiotoxic therapies over time [1, 3].

Baseline risk is multifactorial and affected by patient demographics (age, sex), genetics, previous CVD, life style modificatable risk factors, previous oncologic history potentially

cardiotoxic agents, cancer type and prognosis, and current anticancer regimens' cardiotoxicity profile. Cardio-oncology referral is recommended when available; alternatively, patients should be referred to a specialized cardiologist with expertise in managing CVD in patients with cancer [1, 3]. A careful clinical history and physical examination is recommended as part of the baseline risk assessment including blood pressure, heart rate, height, weight, and body mass index. Complimentary tests, such as electrocardiogram; eGFR, HbA1c, transthoracic echocardiography (TTE), cardiac biomarkers (troponin and NT-proBNP, BNP) should be measured in patients at risk of CTRCD where available and results should be interpreted according to the patient clinical status, type of cancer treatment, and kidney function. Other CV tests in selected patients should be considered involving cardiac magnetic resonance (CMR), coronary computed tomography angiography (CTTA) and cardiopulmonary exercise testing (CPET) [1, 3, 4, 5].

All oncologic patients should be categorized as very high risk, high risk, moderate risk and low risk. Classifying patients is crucial as first, the recommended monitoring and surveillance protocols are based on their risk and secondly it allows proper and early implementation of personalized primary and secondary cancer therapy-related cardiovascular toxicity preventive strategies [1, 3]. Dose reduction remains the most reliable method to reduce cardiotoxicity risk and/or pegylated, liposomal forms of anticancer drugs if available, particularly in treatments with a clear dose response relationship, such as radiation therapy and anthracyclines. The role of cardioprotective medications to prevent cardiotoxicity is uncertain, while exercise has been proposed as a non pharmacologic intervention there is scant evidence of its cardioprotective effects during cancer therapy [1, 6].

Baseline cardiovascular risk assessment may provide an opportunity for healthcare professionals to promote preventive health actions and support healthy behavioral change. While this does not justify their inclusion in an assessment tool that aims to predict risk, including them in accompanying information and resources may be warranted, as it may support the provision of information, and facilitate appropriate referrals to risk reduction [7, 8]. It is critical to highlight that existing guidelines on baseline CVD risk assessment lack specific recommendations for incorporating sociodemographic factors, which play a significant role in health disparities [9].

Cardiotoxicity risk assessment during cancer treatment

A. Cardiovascular surveillance during cancer therapies

A careful clinical evaluation is recommended during cancer treatment to detect early signs and symptoms of Cancer Therapy-Related Cardiovascular Toxicity (CTR-CVT). Fortunately, there is general agreement concerning cancer therapy-related cardiovascular toxicity definitions. Oncologic patients may experience symptomatic Cancer Therapy-Related Cardiac Dysfunction (CTRCD), classified as very severe HF requiring inotropic support, mechanical circulatory support, or consideration of transplantation, severe HF requiring hospitalization,

moderate HF, need for outpatient intensification of HF therapy and mild HF, where no intensification of therapy required [1, 3, 4].

Additionally, asymptomatic CTRCD is classified as severe with a new LVEF reduction to <40%; moderate, with a new LVEF reduction by ≥10 percentage points to 40–49%, or a new LVEF reduction by <10 percentage points to 40–49% and either a new relative decline in GLS by >15% from baseline or a new rise in cardiac biomarkers; and mild, with LVEF ≥50% and a new relative decline in GLS by >15% from baseline and/or a new rise in cardiac biomarkers. Myocarditis as a life threatening effect of classic and/or targeted oncological therapies and immunotherapy is defined as either pathohistological diagnosis or clinical diagnosis, where CMR as diagnostic tool for acute myocarditis (modified Lake Louise criteria) is pivotal. Vascular toxicity, is classified as symptomatic involving arterial (ACS, CCS, PAD, stroke, transient ischemic attacks, Raynaud's phenomenon) and crucial venous (venous thrombosis and pulmonary embolism) adverse events and asymptomatic. Arterial hypertension and various life threatening cardiac arrhythmias may arise during treatment that may affect the anticancer therapeutic approach [1, 10, 11, 12].

Cardiac serum biomarkers are essential to identify CTRCD and monitor specific HF therapy taking into consideration age, sex, renal function, obesity, infections, and co morbidities such as AF and pulmonary embolism. Echocardiography and CMR facilitate early diagnosis and management of CTR-CVT. The cardiac imaging technique should be based on local expertise and availability, and the same imaging modality is recommended throughout the entire treatment. TTE, including 3D-LVEF and GLS assessment is the preferred technique to detect and confirm cardiac dysfunction (Class I). In patients with poor TTE image quality or when TTE is not diagnostic, CMR should be considered, including fast strain-encoded CMR when available (Class IIa), while MUGA should be a third-line modality (Class IIb) [1, 3, 13].

B. Monitoring and Surveillance protocols according specific cardiotoxic cancer regiments

Cardiovascular toxicity monitoring in high risk patients receiving anthracycline chemotherapy, echocardiography every two cycles and within 3 months and 12 months after completing treatment (Class Ib), cTn and NP monitoring before every cycle, 3 and 12 months after therapy completion are recommended (Class Ib). Monitoring patients receiving human epidermal growth factor receptor 2-targeted therapies involves TTE every 2–3 cycles, depending on absolute risk and local availability. Additionally, NP and cTn should be monitored every 2–3 cycles during therapy and at 3 and 12 months after the end of therapy in high- and very high-risk HER2+ EBC patients. (Class IIa) [1, 6].

In patients treated with VEGF inhibitors who are at moderate or high risk of QTc prolongation, an ECG is recommended monthly during the first three months and every three to six months thereafter (Class Ic). A TTE and NP should be considered at four weeks after starting treatment in very high-risk patients (Class IIa). Monitoring during second- and third-generation breakpoint cluster region-Abelson oncogene locus tyrosine kinase inhibitors CV, which are the

main therapies to chronic myeloid leukemia, includes risk assessment every 3 months during the first year and every 6–12 months thereafter (Class Ic); and QTc measurement at baseline, 2 and 4 weeks after starting nilotinib and 2 weeks after any dose increase (Class IIa). Echocardiography should be considered every 3 months during the first year in high- and very high-risk patients receiving dasatinib or ponatinib (Class IIa) [1,14,15].

Monitoring during Bruton tyrosine kinase inhibitor therapy (chronic lymphocytic leukemia, mantle cell lymphoma, Waldenström macroglobulinemia, and marginal zone lymphomas) involves transthoracic echocardiography in all patients who develop atrial fibrillation during therapy (Class Ic). Opportunistic screening for atrial fibrillation, by pulse-taking or electrocardiogram rhythm strip, is recommended at every clinical visit during BTK inhibitor therapy (Class Ic), as these conditions mainly affect high-risk elderly patients with comorbidities [1, 15, 16].

Risk assessment and monitoring during multiple myeloma therapies are essential. Blood pressure monitoring is recommended for patients treated with proteasome inhibitors at every clinical visit (Class Ic). Natriuretic peptide and cardiac troponin measurements are recommended at baseline and every 3–6 months in patients with AL amyloidosis (Class Ib). Echocardiography surveillance every three cycles should be considered in high- and very high-risk patients receiving carfilzomib (Class IIa) [1, 16].

The heart is considered a radiosensitive 'organ at risk' during radiotherapy (RT) and radiation exposure to the heart should be kept as low as reasonably achievable because there is no 'safe' dose. RT-induced CV toxicity risk categorization based on MHD. The incidence of cardiac events following RT may vary according to patient risk factors and synergistic effects of radiation with other potentially cardiotoxic agents (e.g cumulative dose of doxorubicin) [1,17].

Cardiotoxicity risk assessment after cancer treatment

A. Cardiovascular evaluation during the first year after cardiotoxic cancer therapies

High-risk patients can be identified at the end of their cardiotoxic cancer regimens according their clinical characteristics, history of CTR-CVT during treatment, elevated cardiac biomarkers and/or abnormal CV imaging at follow up. Especially, measurement of cTn after completion of anthracycline chemotherapy during the end-of treatment assessment should be considered because it may identify patients at risk of future cardiac dysfunction. Patients who should be evaluated in the first year after treatment include those stratified as high or very high risk based on the HFA-ICOS risk score at baseline, those who received cardiotoxic cancer therapy with a high risk of long-term cardiovascular complications, and those diagnosed with moderate or severe CTR-CVT during cancer treatment. This also applies to patients with echocardiography-detected abnormalities in cardiac function, newly elevated cardiac serum biomarkers, or new cardiovascular symptoms detected at the end of therapy [1, 18, 19].

B. Long-term follow-up and chronic cardiovascular complications in cancer survivors

As a 5-year survival rate of children and adolescents with cancer is above 80%, long term follow up is essential to identify CTR-CVT which is manifested as CTRCD, valvular heart disease (VHD) coronary artery disease (CAD), arrhythmias, autonomic dysfunction and pericardial disease. Risk stratification is crucial, taking into consideration the total cumulative dose of anthracyclines and/or chest-directed radiotherapy [20]. Thus, asymptomatic adults who are childhood and adolescent cancer survivors are classified as very high risk exposed of MHD >25Gy or total cumulative doxorubicin dose ≥400mg/m2 and a combination therapy MHD >15Gy and total cumulative doxorubicin dose (TCDD) ≥100mg/m2, high risk, those who exposed of MHD >15 to 25Gy, TCDD 250-399mg/m2 and a combination therapy of MHD 5-15Gy, and TCDD ≥100mg/m2; moderate risk, MHD 5-15Gy or TCDD 100-249mg/m2 and a combination therapy MHD <5Gy and TCDD ≥100mg/m2 and low risk; MHD <5 Gy or TCDD <100mg/m2. All cancer survivors should be assessed annually for CV risk (Class I) and re-stratified after 5 years ((Class I). Patient engagement and education is recommended, concerning CVRF optimization (class I). Particularly, very high-risk cancer survivors should be evaluated via TTE at years 1, 3, and 5 after cardiotoxic cancer therapy and every 5 years thereafter if they are adult cancer survivors (Class IIa), and every 2 years if they are childhood or adolescent cancer survivors (Class IIa) [1, 21].

Radiotherapy (RT) to the chest or infradiaphragmatic irradiation, if the apex of the heart is within the treatment volume, increases the risk of accelerated atherosclerosis, coronary artery disease (CAD), and RT-related vasculopathy. This risk is associated with the radiation dose, type of radiation source, larger exposed volume, younger age at treatment (under 25 years), time elapsed since treatment, and co-existing typical cardiovascular risk factors (CVRF). Thus non-invasive screening for CAD and carotid disease, 5 years after radiation and every 5-10 years thereafter should also be considered (class IIa) [1]. A multidisciplinary approach with cardiac surgeons, interventional cardiologists, and cardio-oncology specialists should review each case to guide appropriate treatment, due to specific characteristics of these long- term complications [22, 23]. Most of cancer survivors had experienced exposure of anthacyclines and chest RT which may affect the reproductive gears and pregnancy. High risk females CS should be thoroughly evaluated, including history, physical examination, ECG, NP, and TTE before considering pregnancy (Class Ic) or at 12 weeks and second TTE should be considered at 20 weeks (Class IIa). MDT management during pregnancy and around the delivery period is also recommended (Class Ic) [1].

Cancer survivors are at an increased risk of cardiovascular disease due to cardiotoxic therapies or concomitant cardiometabolic risk factors (insulin resistance, obesity, or tobacco exposure), advanced age, and decreased adherence to medications for non-cancer conditions following active cancer therapy [22, 23, 24]. Next generation risk markers, involving breast arterial calcification (BAC), coronary artery calcification (CAC), clonal hematopoiesis of indeterminate potential (CHIP) may provide efficient and synergistic analysis of CVD and cancer

disease and improved risk stratification [25]. Additionally, emerging risk factors, such as social determinants of health, environmental factors, and microbiome disturbances, play a critical role in the risk for both CVDs and cancer. Health insurance coverage is crucial in mitigating financial toxicity and ensuring access to necessary care [9, 26]. Figure 1 illustrates a proposed simplified diagram concerning the continuity of care in cancer patients receiving cardiotoxic cancer therapeutic regiments.

Novel methods of risk factor detection (wearable technologies, multi-omics) are essential to understand the complex interplay between various biological layers, identify key pathways, differentiate disease phenotypes, and guide appropriate personalized preventive and treatment strategies in cardio-oncology. As machine learning (ML) and large language models (LLMs) and AI reshape care, seamlessly integrating innovative approaches with established practices may unlock the secrets of complex and heterogeneous cardiovascular disease (CVD) in patients with cancer in the modern era of digitalized cardio-oncology [27, 28]. Figure 2 illustrates a proposed diagram concerning the continuity of care in cancer patients receiving cardiotoxic cancer therapeutic regiments in the modern era of digitalized cardio-oncology.

Conclusion

Cardiovascular risk assessment in oncologic patients is a dynamic process, where advanced diagnostic modalities enhances this vulnerable population's engagement, and active participation in screening and continuous chronic care programs, establishing the modern human-centered health system. A strong emphasis on interdisciplinary exchange, via the meaningful collaborations of professionals across cardiology, oncology, hematology and radiotherapy will foster driving innovation and progress in patient care.

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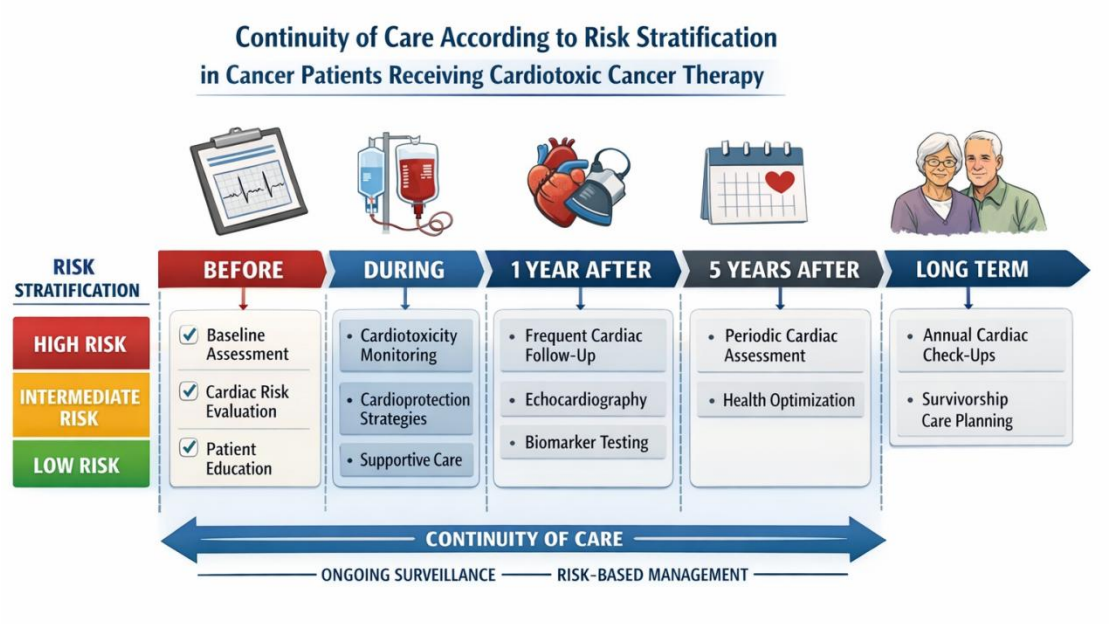

Figure 1. A proposed simplified diagram that illustrates the continuity of care in cancer patients receiving cardiotoxic cancer therapeutic regiments.

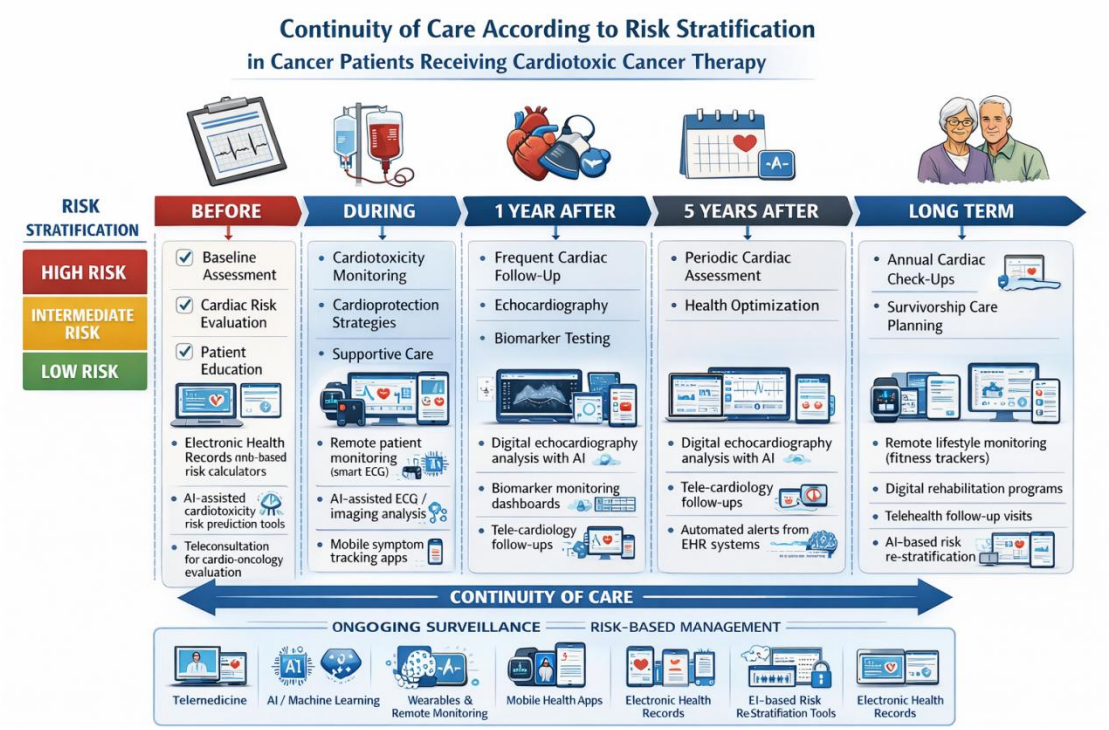

Figure 2. A proposed diagram that illustrates the continuity of care in cancer patients receiving cardiotoxic cancer therapeutic regiments in the modern era of digitalized cardio-oncology.

PSMA PET/CT in contemporary prostate cancer management: From initial staging to biochemical recurrence

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Abstract

Objective: Prostate-Specific Membrane Antigen (PSMA) PET/CT has rapidly become the preferred first-line imaging modality for primary staging of unfavourable intermediate-risk, high-risk, and very high-risk prostate cancer, and for restaging at biochemical recurrence. The objective of this review is to provide nuclear medicine physicians with a comprehensive and practical framework for PSMA PET/CT interpretation, structured reporting, and clinical decision integration, with emphasis on primary staging evidence, biochemical recurrence (BCR) detection rates, imaging pitfalls, and the PSMA-RADS reporting system. **Methods**: A narrative review of published evidence was performed, encompassing landmark randomised controlled trials and guideline documents from the EAU, EANM, and NCCN. Key trials reviewed included proPSMA, OSPREY, PRIMARY, CONDOR, and VISION. **Results**: PSMA PET/CT demonstrated diagnostic accuracy (AUC) of 0.92 versus 0.38 for conventional imaging in primary staging (proPSMA). Detection rates in BCR ranged from 38% at PSA <0.2ng/mL to 97% at PSA >2ng/mL. In a phase 3 RCT, ^{18}F-PSMA-1007 demonstrated superiority over ^{18}F-Choline (84% vs 69%, OR 2.53, p<0.001). **Conclusion**: PSMA PET/CT provides superior staging accuracy, enables detection of recurrence at low PSA levels, guides oligometastasis-directed therapy, and serves as the mandatory gatekeeper for ^{177}Lu-PSMA-617 theranostic eligibility. Structured reporting using PSMA-RADS and rigorous CT correlation – particularly to exclude unspecific bone uptakes

(UBUs) with ^{18}F-PSMA-1007 – are core professional competencies of the nuclear medicine physician.

Keywords (MeSH): Prostate-Specific Membrane Antigen -Positron Emission Tomography Computed Tomography -Prostatic Neoplasms -Biochemical Recurrence

Introduction

Prostate cancer is the most common solid organ malignancy in men, and accurate imaging at the time of primary staging and at disease recurrence is fundamental to treatment planning. Conventional imaging with CT and ^{99m}Tc bone scintigraphy has long underpinned staging decisions but suffers from limited sensitivity for small-volume nodal disease and for early BCR at low PSA levels. The advent of PSMA-targeted PET/CT has fundamentally altered this clinical landscape, emerging as the preferred first-line imaging modality for staging of unfavourable intermediate-risk, high-risk, and very high-risk prostate cancer, and for restaging at BCR.

PSMA is a type II transmembrane glycoprotein (folate hydrolase/GCPII) encoded by the FOLH1 gene on chromosome 11p11.2. It is overexpressed in more than 90% of prostate cancers at 100–1,000-fold higher levels than normal prostate tissue, and expression correlates with Gleason grade, T-stage, and castration resistance [8]. These molecular properties establish PSMA as an ideal target for both imaging and radionuclide therapy.

In this review we summarise the key clinical evidence in primary staging and BCR, describe imaging protocol and normal biodistribution, provide a structured approach to PSMA-RADS reporting, address common pitfalls with focus on UBUs with ^{18}F-PSMA-1007, and outline the role of PSMA PET/CT as the theranostic gateway. Where applicable, we reference our own Phase 3 RCT [6] and pitfall case series [7].

PSMA Biology and Approved Tracers

Molecular Biology

PSMA expression correlates positively with clinical aggressiveness, reaching its highest levels in mCRPC – making PSMA PET most sensitive precisely when treatment decisions are most consequential. Physiologic expression in the kidneys, salivary glands, small bowel, and liver defines the normal biodistribution pattern and the principal sources of interpretation pitfalls [8].

Approved PSMA Tracers

^{68}Ga-PSMA-11 (FDA 2020, EMA approved) is the most extensively validated tracer, underpinning proPSMA, OSPREY, and CONDOR. Its 68-minute half-life requires on-site generator supply and constrains the scanning window.

^{18}F-DCFPyL (Pylarify®, FDA 2021) allows centralised production and distribution. Higher urinary bladder activity requires careful pelvic interpretation.

^{18}F-PSMA-1007 (EMA approved) has the lowest urinary excretion, improving pelvic visualisation, but carries the highest UBU rate among all PSMA tracers – a pitfall first documented in our published series [7].

Our Phase 3 RCT [6] directly compared ^{18}F-PSMA-1007 with ^{18}F-Choline in BCR, demonstrating superior patient-level detection rates (84% vs 69%, OR 2.53, p<0.001), with citations in EAU and EANM guideline updates.

Imaging Protocol, Patient Preparation and Normal Biodistribution

Patient Preparation and Acquisition Protocol

Patients should fast 4–6 hours, be well hydrated (≥500mL water before injection), and void immediately before scanning. Injected activities follow EANM dosimetry guidance: 111–259MBq for ^{68}Ga-PSMA-11 and 296–370MBq for ^{18}F agents. Uptake phase: 50–70min (^{68}Ga) or 60–90min (^{18}F). Standard scan range: skull base to mid-thigh.

Critical caveat: ADT may modulate PSMA expression, with early upregulation and potential suppression in prolonged exposure and may lead to false-negative or altered tracer uptake patterns. Imaging should be performed before ADT initiation or after appropriate washout; ADT status must be documented in every report [9].

Normal Biodistribution and Physiologic Pitfall Sites

Intense physiologic uptake is expected in kidneys, salivary glands, liver, and small bowel. Key pitfall sites:

- **Ganglia (celiac, stellate):** Focal uptake mimicking nodes – CT reveals characteristic comma shape and para-spinal location.
- **Bowel loops:** Simulate pelvic nodes on MIP – CT fusion mandatory for all pelvic findings.
- ^{18}F-PSMA-1007 UBUs: Benign bone lesions (fractures, Paget, bone islands) – the most clinically significant pitfall, detailed in Section 5 [7].
- **Thyroid nodules:** Rare incidental uptake warrants endocrine workup.

Primary Staging of Prostate Cancer

Evidence Base: Pivotal Trials

proPSMA (Hofman et al., *Lancet* 2020) [1]: Phase 3 RCT, 302 men, high-risk PCa. AUC 0.92 vs 0.38; sensitivity 85% vs 38%; specificity 98% vs 91%. Clinically appropriate management change 28% vs 15% ($p<0.001$). Level 1b evidence.

OSPREY (Rowe et al., *J Urol* 2020) [2]: Phase 2/3. *18*F-DCFPyL. Specificity 95.8% for pelvic nodal staging; 84% patient-level detection rate in BCR.

PRIMARY and PRIMARY2: Detected malignant nodal disease in nodes ≤8 mm (below CT threshold) in 26–27% of cases, directly influencing surgical template planning.

Guideline Recommendations

Grade A (EAU), Category 1 (NCCN): PSMA PET/CT replaces CT and bone scintigraphy for primary staging of unfavourable intermediate-risk, high-risk, and very high-risk prostate cancer. EANM E-PSMA guidelines [9] provide the acquisition, reporting, and clinical integration framework.

Clinical Impact

Key consequences: (i) N0→N1 upstaging for sub-centimetre nodes enabling extended lymphadenectomy or adjuvant radiotherapy; (ii) detection of occult M1 disease; (iii) identification of oligometastatic disease (≤3–5 sites) qualifying for SBRT with deferral of systemic therapy [10].

Biochemical Recurrence: Detection Rates and Clinical Impact

Definition and Clinical Context

BCR: PSA ≥0.2 ng/mL (confirmed) after radical prostatectomy, or PSA rise ≥2ng/mL above nadir after radiotherapy (Phoenix criteria). Affects 20–40% of patients within 10 years of definitive therapy. PSADT <3 months indicates high-risk recurrence warranting early imaging regardless of absolute PSA.

Detection Rates by PSA Level

Pooled data from published series and CONDOR:

***Table 1**. Approximate PSMA PET/CT patient-level detection rates by PSA level in biochemical recurrence (pooled published data).*

PSA level (ng/mL)	PSMA PET Detection Rate (%)	Patient-level Localisation (%)
<0.2	~38	~30-38

PSA level (ng/mL)	PSMA PET Detection Rate (%)	Patient-level Localisation (%)
0.2-0.5	~57	~50
0.5-1.0	~72	~65
1.0-2.0	~86	~80
>2.0	~97	~90-95

Phase 3 RCT: ^{18}F-PSMA-1007 versus ^{18}F-Choline

Our Phase 3 multicentre RCT [6] enrolled 186 patients with BCR in a prospective, open-label, crossover design. Patient-level detection rates: 84% (95% CI 79.7-88.3%) for ^{18}F-PSMA-1007 vs 69% (95% CI 61.9-74.9%) for ^{18}F-Choline (OR 2.53; p<0.0001). Detection rate at PSA ≤0.3ng/mL: 51.6% for ^{18}F-PSMA-1007 vs equivalent rate for ^{18}F-Choline only at PSA ≤2.2ng/mL. This Level 1b evidence underpins current EAU and EANM guideline recommendations.

CONDOR Trial and Management Impact

CONDOR (Morris et al., *Clin Cancer Res* 2021) [4]: 84% correct localisation vs 19% with conventional imaging in BCR with negative/equivocal conventional imaging. Management change in 64% of patients.

Oligometastatic Disease

PSMA PET/CT serves as the principal stratification tool for oligometastatic disease (≤3-5 PSMA-avid lesions). STOMP and ORIOLE trials demonstrate that SBRT to PSMA-detected sites prolongs time to systemic therapy. Precise lesion count and location by the nuclear medicine physician directly determines therapeutic eligibility.

Pitfalls, Structured Reporting and the PSMA-RADS System

The PSMA-RADS Structured Reporting System

PSMA-RADS (E-PSMA v1.0, Rowe et al., *Eur Urol* 2018) [11] uses SUVmax/liver reference — not absolute SUV — to assign malignant probability:

Table 2. PSMA-RADS categories (E-PSMA v1.0). PCa: prostate cancer; RCC: renal cell carcinoma; MDT: multidisciplinary team.

Category	Label	Criteria	Action
PSMA-RADS 1	No uptake	No suspicious foci	PSA surveillance

Category	Label	Criteria	Action
PSMA-RADS 2	Likely benign	Non-specific uptake, benign context	Short-term follow-up
PSMA-RADS 3	*Equivocal*	*Atypical; cannot classify*	Biopsy or further imaging
PSMA-RADS 4	Likely malignant	Uptake > liver; consistent with PCa	Targeted biopsy / therapy
PSMA-RADS 5	Highly malignant	Intense uptake >> liver; PCa pattern	Treat as malignant
PSMA-RADS X	Variant uptake	Unusual; non-PCa (thyroid, RCC)	MDT discussion

PSMA-RADS 3 (equivocal) is a critical patient-protective category, preventing both over- and under-treatment. It should be assigned to any uptake that cannot be confidently classified, with an explicit biopsy or confirmatory imaging recommendation.

Minimum Report Elements

Every PSMA PET/CT report must include: (i) tracer, injected activity, uptake time; (ii) ADT status; (iii) scan extent; (iv) image quality assessment; (v) normal biodistribution; (vi) per lesion: site, CT size, SUVmax, SUVmax/liver ratio, PSMA-RADS category; (vii) overall PSMA-RADS impression; (viii) miTNM classification [8]; (ix) management recommendation.

Unspecific Bone Uptakes (UBUs) with ^{18}F-PSMA-1007

^{18}F-PSMA-1007 has the highest UBU rate among all PSMA tracers. UBUs occur at benign osseous sites — fractures, Paget disease, benign bone islands. In a multicenter series, UBUs were found in 51.4% of patients (ribs 57.5%, pelvis 24.8%), considered clinically relevant in 44.7% [Grünig et al., *Eur J Nucl Med Mol Imaging* 2021].

Our case series [7] (Panagiotidis et al., *Clin Nucl Med* 2019; EANM E-PSMA referenced) documented ^{18}F-PSMA-1007 uptake at healing rib fractures mimicking bone metastases in BCR. CT correlation revealed benign cortical irregularity, enabling PSMA-RADS 3 classification and sparing the patient unnecessary biopsy and systemic therapy.

The BUMP score (Bauckneht et al., *J Nucl Med* 2024) [12] is a validated composite tool incorporating ADT status, SUVmax, and HUmean on CT, achieving AUC 0.87 (internal) and 0.92 (external validation). A free web calculator is available at bump-score.com. Scores <10% indicate likely benign UBU; scores >70% warrant metastatic treatment.

Practical rules for ^{18}F-PSMA-1007 bone pitfall avoidance:

- CT fusion mandatory for all bone lesions – MIP review alone is insufficient.
- Cortical irregularity, callus, or sclerosis → PSMA-RADS 3; correlate with trauma history.
- Equivocal skeletal finding as sole basis for treatment decision → confirm with ^{68}Ga-PSMA-11.
- BUMP score provides a validated quantitative framework; reference it in the report.

Other Common Pitfalls

(i) **Ganglia** (celiac, stellate): focal uptake, comma shape on CT; (ii) **Bowel loops**: simulate pelvic nodes on MIP, mandatory CT fusion; (iii) **Meningiomas**: intense PSMA uptake → PSMA-RADS X; (iv) **Clear-cell renal cell carcinoma**: neovascular PSMA expression → PSMA-RADS X.

Theranostics and Future Directions

PSMA PET/CT as the Gateway to ^{177}Lu-PSMA-617 Therapy

VISION trial (Sartor et al., *N Engl J Med* 2021) [5]: ^{177}Lu-PSMA-617 (Pluvicto®, FDA March 2022) vs best supportive care in mCRPC after ≥1 ARPI + docetaxel. rPFS 8.7 vs 3.4 months (HR 0.40; p<0.001); OS 15.3 vs 11.3 months (HR 0.62; p<0.001).

The nuclear medicine physician is the mandatory gatekeeper: eligibility requires PSMA-avid disease (SUVmax > liver) in ALL lesions visible on conventional imaging. Comprehensive lesion-by-lesion PSMA-RADS reporting is a direct determinant of therapeutic access.

Emerging Tracers and Hardware

^{18}F-rhPSMA-7.3 (Posluma®, FDA 2023): minimal urinary excretion. ^{64}Cu-PSMA-617 ($T^{1/2}$ 12.7 h): dosimetric pairing pre-^{177}Lu. Alpha-emitters *225*Ac-PSMA and *161*Tb-PSMA in Phase 1-2 trials. PSMAfore (earlier ^{177}Lu lines): rPFS HR 0.41; p<0.001. Long axial FOV and total-body PET/CT systems offer a 8–40× sensitivity gain, enabling full-body imaging in 30 seconds, is expected to lower detectable PSA thresholds.

Artificial Intelligence and Quantitative PET

Automated TV segmentation improves inter-centre reproducibility. Deep learning-based PSMA-RADS classification reduces inter-reader variability. Delta-PSMA PET after ^{177}Lu cycles and SUVmean-based dosimetric prediction from diagnostic scans are areas of active clinical translation.

Conclusion

PSMA PET/CT has become the preferred first-line imaging modality for primary staging of unfavourable intermediate-risk, high-risk, and very high-risk prostate cancer, and for restaging at biochemical recurrence, supported by Grade A EAU and Category 1 NCCN recommendations grounded in Level 1b evidence. Detection rates of 38% at PSA <0.2ng/mL in BCR, and superiority of ^{18}F-PSMA-1007 over ^{18}F-Choline demonstrated in our Phase 3 RCT [6], underline its clinical value across all PSA strata. Structured PSMA-RADS reporting, meticulous CT correlation to exclude pitfalls – foremost UBUs with ^{18}F-PSMA-1007 as documented in our series [7] – and mandatory documentation of ADT status are core professional obligations. As central selection tool for ^{177}Lu-PSMA-617 eligibility and as the molecular map guiding all modalities of prostate cancer treatment, PSMA PET/CT positions the nuclear medicine physician at the centre of the multidisciplinary team.

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PET/CT in Lymphomas: Current clinical applications and future directions

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Abstract

FDG PET/CT imaging has transformed the way lymphoma patients are managed, playing a pivotal role in diagnosis, staging, prognostication, and treatment response evaluation. PET/CT guided treatment is a reality in HL, having spared patients from unnecessary toxicities while maximizing responses. Advancements in imaging technology and methodologies, along with the development of artificial intelligence, are expected to revolutionize the evaluation of complex imaging data, enhancing the diagnostic and predictive power of PET in lymphoma.

Introduction

One of the first applications of positron emission tomography (PET), back in 1990, was lymphoma, as most lymphoma types demonstrate high uptake of 18F-fluorodeoxyglucose (FDG). In fact, FDG avidity is high in Hodgkin lymphoma and in aggressive non-Hodgkin lymphomas (NHL), mainly in diffuse large-B-cell lymphoma (DLBCL), grade III follicular lymphoma (FL), Burkitt lymphoma, certain mantle cell lymphoma (MCL), peripheral T-cell lymphoma, and anaplastic large cell lymphoma, reflecting their high glucose metabolism. Indolent NHL subtypes demonstrate low to moderate FDG uptake, include grade I and II FL, marginal zone lymphoma (MZL), chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), lymphoplasmacytic lymphoma, certain MCL, and mycosis fungoides. In non-FDG avid lymphomas, none of the other tracers being investigated have found their way to routine clinical diagnostics.

FDG PET/CT was introduced in guidelines for the first time in 2007, in the revised response criteria for malignant lymphoma by the International Working Group [1]. In the published report by members of the International Harmonization Project (IHP), PET/CT was deemed

essential at the end of treatment (EoT) response assessment in HL and in DLBCL, eliminating the term complete remission unconfirmed (CRu) of the previous criteria using the CT alone to describe a residual mass after treatment that was most likely fibrous tissue [1]. In 2014, the Lugano classification recommended FDG PET/CT as a standard approach in the staging and EoT response assessment of FDG-avid lymphomas [2]. At that time, interim PET/CT (i-PET/CT) began to be widely investigated for personalized treatment in clinical trials and most of these practices have since been implemented in clinical practice in HL.

Management of lymphoma has seen great advances in recent years, with a shift in focus to immunotherapy and CAR-T-cell therapy. Several FDG PET/CT-based response criteria have emerged to address the response patterns in these novel therapies. In the contemporary era of artificial intelligence (AI) and radiomics, new PET/CT metrics are expected to add value to known prognostic parameters.

This article will summarize the current clinical applications of FDG PET/CT in lymphomas and a brief report of advancements in AI, radiomics and novel targets for PET imaging beyond FDG, particularly in the development of immune PET.

FDG PET/CT

Initial evaluation, staging and prognostication

In the diagnostic workup of lymphomas, FDG PET/CT can help identify the optimal biopsy site and indicate the most active area, particularly in patients with suspected high-grade transformation [3]. According to the Lugano classification, FDG PET/CT is recommended for routine staging of FDG-avid lymphomas as the gold standard, as it detects more nodal and extranodal lesions compared to CT [2, 4, 5]. Low-FDG avid lymphomas should be staged with a CT scan complemented by other conventional methods. FDG PET/CT scan characterize BM involvement with high certainty in HL and in most cases of DLBCL. Focal or multi-focal BM uptake is indicative of BM involvement, while diffusely increased BM uptake is considered due to reactive myeloid hyperplasia in HL and in most cases of DLBCL. Thus, BM biopsy has become unnecessary when performing a staging PET/CT in a patient with HL and is only needed for DLBCL if the PET is negative and identifying a discordant histology is important for patient management [2, 6]. In all other lymphoma types, a negative FDG PET/CT cannot rule out BM involvement and BM biopsy is recommended along with immunohistochemistry and flow cytometry.

Staging of FDG-avid lymphomas with FDG PET/CT provides also prognostic information and a baseline against which response or disease progression can be compared. Staging in lymphomas is based on the anatomic Ann Arbor four-stage system, which was proposed more that 50 years ago. A modification of the Ann Arbor descriptive terminology was made at the 11th

International Conference on Malignant Lymphoma in Lugano, in 2011 [2]. The presence of a bulky tumor has been recognized as a significant prognostic factor in lymphoma and the Lugano classification recommended recording the largest tumor size measured by CT instead of using the term bulky disease. The proposed size thresholds for bulky disease are: 10cm for HL, 6 cm for FL and 10 cm for DLBCL in the rituximab era. Not only the presence of a bulky tumor but also a high overall tumor burden has been suggested as an unfavorable prognostic parameter across all lymphoma subtypes. FDG PET/CT has enabled the estimation of overall tumor burden using total metabolic tumor volume (TMTV) or total lesion glycolysis (TLG), which is calculated as MTV × SUVmean. Recently, the Positron Emission Tomography Reanalysis consortium, which included a large number of patients with newly diagnosed DLBCL from five international trials, proposed a new prognostic index, called the International Metabolic Prognostic Index to include TMTV, age, and stage, and this index outperformed the International Prognostic Index alone [7]. The maximum tumor dissemination (Dmax) has been proposed as a simplified indirect feature of tumor burden and dissemination.

Response Assessment and PET/CT guided practices

In 2009, the Deauville criteria were defined for simple and reproducible interpretation of i-PET in HL and DLBCL using a 5-pointDeauville score (DS) [8]. The DS is a simple tool based on visual interpretation of ^{18}F-FDG uptake, with reference to the mediastinal blood pool and the liver. The DS is defined as follows: (1) no uptake above background; (2) uptake ≤ mediastinum; (3) uptake > mediastinum but ≤ liver; (4) uptake moderately > liver; (5) uptake markedly higher than liver and/or new lesions; X) new areas of uptake unlikely to be related to lymphoma. The terms “moderately” in score4 and “markedly” in score 5 suggest that uptake is > SUVmax in a large region of normal liver and 2× to 3× > SUVmax in the liver, respectively. Of note, uptake higher than liver in areas with high physiological uptake (e.g, Waldeyer’s ring, gastro-intestinal tract, esophago-gastric junction), may not always preclude the assessment of a CMR. DS of 1-3 represents CMR while a DS of 4-5 is considered partial response, stable disease, or progressive disease if there is a decrease, no change, or increase, or new lesions compared to the baseline scan, respectively. In 2014, the Lugano classification extended the use of the DS from interim to EOT PET [5].

EoT scanning is typically performed within 12 weeks after completion of treatment. As a general rule, the negative predictive value (NPV) of EOT-PET is higher than the positive predictive value (PPV). This is due to false positive PET/CT findings at the site of the residual mass because of post-therapy inflammatory changes, bone remodeling or even infectious or inflammatory processes, such as sarcoidosis or other granulomatous diseases [5]. It follows that, if further treatment is considered based on metabolically active residual disease on EOT PET, either biopsy or follow-up scan is advised due to the relatively lower PPV, particularly in aggressive NHL [9].

The prognostic value of iPET/CT, which is performed after treatment initiation but prior to its completion, typically after two cycles of cytotoxic chemotherapies, varies by lymphoma subtype. The theory behind iPET/CT is that it represents a biomarker for chemo sensitivity and early treatment response [10]. Failure to achieve complete metabolic response (CMR) on iPET/CT has been associated with inferior progression free survival (PFS) and event free survival (EFS), and in some cases, worse overall survival (OS). Beyond prognostication, iPET/CT has the potential to help guide response-adapted therapy in patients with lymphoma through the differentiation of poor responders who may benefit from treatment escalation from responders who may have excellent outcomes with de-escalated treatments. This approach has the potential to individualize the treatment paradigm, limiting patients' exposure to ineffective treatments and unnecessary toxicities with the goal of improving the likelihood and duration of remission.

Evidence supporting the prognostic value of iPET/CT is more robust for classical Hodgkin lymphoma (cHL), as several studies have shown that iPET/CT is an independent prognostic factor predictive of patient outcomes in both early and advanced HL, achieving a high NPV of 80-90% and a lower PPV, nevertheless outperforms the International Prognostic Index in patient's prognosis identification [11-14]. Major PET-response adapted clinical trials evaluating the role of PET after 2 or 3 cycles of ABVD in de-escalation of treatment, particularly in omission radiotherapy, in patients with early-stage HL are the RAPID, H10 and HD16 [15, 16, 17].Despite differences in trials' design, they all conclude that radiotherapy cannot be omitted from the standard first-line therapy (ABVD) for patients with negative iPET, even if they do not have clinical risk factors [15, 16, 17]. However, the 5-year OS was not significantly different between the two treatment groups, which infers that omission of radiotherapy can be an option in these patients taking into account the benefits from avoiding the side effects of RT and the fact that in HL there is a very effective second line therapy. Recently, a multicenter open-label randomized phase III trial involving patients with early-stage unfavorable HL reported that radiotherapy can be omitted without compromising efficacy in patients who achieve a complete metabolic response by iPET after receiving a two-cycle regimen of eBEACOPP plus two cycles of ABVD (2 + 2 regimen) [18].A prospective randomized controlled trial, known as RATHL, investigated the use of iPET after two cycles of ABVD to guide treatment for patients with advanced HL [19]. The long-term results of the RATHL trial recently reported that patients with a negative iPET can be de-escalated to AVD without inferior outcomes[20]. All the studies evaluating the role of iPET in patients with early-stage HL suggest that those with a positive iPET are at high risk for relapse and should be considered for intensified treatment options, such as eBEACOPP combined with IFRT or INRT [17, 20]. *Based on the above major trials, response-adapted treatment approaches guided by iPET/CT are a widely used standard of care for first-line therapy in HL.*

Although the benefit of response-adapted treatment approaches guided by iPET/CT has been well assessed in HL, it has not been clearly demonstrated in NHL. The predictive value of iPET/CT in DLBCL treated with RCHOP is compromised by false positive results, and many

studies have shown higher discriminative power and predictive value of the quantitative assessment of the change in standardized uptake value maximum (ΔSUVmax) rather than the DS [21]. PETAL trial, using the ΔSUVmax criteria, showed that early PET positivity identifies higher-risk patients, but PET-adapted intensification after 2 cycles did not improve survival outcomes [22]. Therefore, PET-guided escalation is not standard of care in unselected frontline DLBCL/aggressive B-cell lymphoma.A recent phase III randomized study succeeded to show that interim PET/CT after two cycles of RCHOP can guide treatment de-escalation (to total 4RCHOP for PET negative: DS1-3) in low-risk DLBCL, without compromising efficacy [23]. Extended follow-up will be essential to validate the efficacy of PET-guided therapy in low-risk DLBCL patients.

In a similar pattern, in FL, PET is prognostic, but PET-guided treatment adaptation has not yet demonstrated a validated role in clinical practice.

Currently, the most widely used treatment response assessment system for chemo therapeuticor chemo immunotherapeutic (primarily incorporating rituximab) regimens in FDG-avid lymphomas is the Lugano classification, which relies chiefly on the DS. Recently, antibody-drug conjugates such as brentuximab vedotin (BV) and immune checkpoint inhibitors (ICIs) such as nivolumab and pembrolizumab, which were originally approved for relapsed or refractory HL, have been incorporated into first-line therapy for advanced HL [24, 25]. To address the challenges in response patterns arising from the increasing use of immune checkpoint inhibitors and immune modulators, the lymphoma response to immunomodulatory therapy criteria (LYRIC) proposed in 2016 as a provisional modification of the Lugano criteria adapted for immune-based therapy [26]. In addition to the Lugano criteria, LYRIC introduces a new response category called indeterminate response (IR), to account for the pseudo progression pattern and therapy can be continued for up to 12 weeks before a definitive confirmation with FDG PET/CT or biopsy, is made [27].In an effort to harmonize lymphoma response criteria in clinical trials, the latest response evaluation criteria in lymphoma (RECIL) classification was introduced in 2017,based on the Lugano classification, attempting to simplify its use and to adapt to the RECIST evaluation for solid tumors [28]. Anatomically, lesions measurement was modified to include only unidimensional measurement of the long diameter of three selected target lesions. In addition, RECIL proposed measuring and comparing the difference in tumor burden. As a result, complete response (CR) has replaced CMR and would require at least a 30% reduction in tumor burden in addition to a DS range of 1-3 [28]. In a parallel fashion, a higher DS of 4-5 would indicate a PR, achieving a reduction in tumor burden of at least 30%. A new category labeled as a minor response has been proposed in cases of at least 10% tumor burden reduction, not exceeding the 30% threshold [28]. A stable disease pattern can be observed if the range of change in the tumor burden lies between -10% and +20%. Otherwise, disease progression implies a value of more than a 20% increase in tumor burden, with or without the appearance of a new lesion [28]. It is noteworthy that both the PD and minor response categories do not require correlation with 5PS

[28]. Additionally, disease relapse is considered when a newly appearing lesion exceeds 1.9 cm in the long axis [28]. The prognostic value of Lugano 2014 versus RECIL 2017 criteria has been assessed only in a few clinical trials.

PET tracers in Lymphoma beyond FDG

FDG PET/CT remains the gold standard of imaging in HL and aggressive NHL. Although a number of other tracers, such as FAPI, ^{18}F-FLT, ^{18}F-Fludarabine, ^{11}C-MET, ^{68}Ga-Pentixafor etc, have been investigated as potential options in non-FDG avid lymphomas, none proved its utility in clinical practice.

Another area for future development of PET imaging in lymphoma is related to the increasing clinical use of immune-modulating treatments, including and CART-cells therapy. Immuno PET combines the high sensitivity, resolution, and quantitative ability of PET imaging to the specific binding of monoclonal antibodies, making it a promising modality in developing and optimizing immunotherapies and radio-immunotherapies, allowing for real-time tracking of molecular targets (CD20, CD30, CD19, PD-L1 etc) and CD19-directed CAR-T-cells. Very limited literature data are currently available on the use of Immuno PET in patients with lymphoma mainly because of the need of specific facilities, unfavorable dosimetry, and unclear correlation of immuno-tracer biodistribution with patients' clinical and tumors' molecular characteristics. Further research, along with the development of total-body PET/CT systems, is expected to explore the clinical utility of immune PET in lymphoma [29].

New PET Metrics

The future of PET imaging in lymphoma is promising, driven by technological advancements and the development of new radiotracers. AI-based analysis of lymphoma FDG-PET/CT such as TMTV, are emerging as powerful biomarkers, which are expected to enable precise prognostication and treatment response prediction. The combination of radiomic features with molecular markers and circulating tumor DNA are expected to be included in clinical trial designs to enable the development of baseline and dynamic risk scores that could further advance the field to facilitate testing of novel treatments and personalized therapy in aggressive lymphomas.

Conclusions

FDG PET/CT imaging has transformed the way lymphoma patients are managed, playing a pivotal role in diagnosis, staging, prognostication, and treatment response evaluation. PET/CT guided treatment is a reality in HL, having spared patients from unnecessary toxicities while offering the most beneficial therapeutic outcomes. Future PET/CT in lymphoma is moving toward AI-driven metrics with scope to improve staging and therapy response prediction.

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Choline positron emission tomography/computed tomography imaging in parathyroid neoplasms

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Introduction

Parathyroid glands are the smallest organs in our body, that regulate calcium metabolism, by producing parathyroid hormone (PTH). They are four, at least, as they might be either supernumerary or ectopic, especially in patients with chronic renal failure. Hyperparathyroidism (HPT) is a common endocrine disease, characterized by hormone imbalance, which leads to increased secretion of PTH. Primary hyperparathyroidism (PHPT) is caused by hyperfunctioning parathyroid glands, mainly by a solitary parathyroid adenoma and less frequently by parathyroid hyperplasia or double parathyroid adenomas. The alteration in calcium homeostasis, that stimulates the excessive production of PTH is called secondary HPT. Diagnosis of HPT may be clinical or incidental on biochemical screening. Surgical removal of hyperfunctioning parathyroid gland is the only curative treatment available at the moment. Minimally invasive parathyroidectomy (MIP) seems to be the surgical procedure of choice, as it demonstrates multiple advantages, such as reduced duration of surgery shorter hospitalization, with better cosmetic outcome and fewer patient complications. Preoperative imaging is therefore essential for those patients who are going to be treated surgically [1].

Although conventional imaging modalities are effective in most cases, they yield negative or discordant results in approximately 10-15% of cases. Neck ultrasonography (US) and parathyroid scintigraphy (PS) are established, first line, imaging methods. Four-dimensional computed tomography (4D-CT) is also an emerging, second line, modality. Positron emission tomography/computed tomography (PET/CT), with certain radiotracers, including ^{11}C-methionine

and radiolabeled choline (^{11}C-choline or ^{18}F-choline), is a promising advanced, second line imaging technique, in the diagnostic evaluation of HPT.

The parathyroid gland consists of two major types of cells: chief and oxyphilic cells. The cation ^{99m}Tc-MIBI used in PS enters both types of parathyroid cells and accumulates in the mitochondria. The choline uptake mechanism, however, seems to have an advantage over ^{99m}Tc-MIBI. Choline also enters both parathyroid cells, through a membrane transporter and accumulates in the mitochondria of both oxyphilic and chief cells. In chief cells, choline is also phosphorylated by the choline-kinase enzyme and is then converted to phosphatidylcholine (lecithin), a necessary component of the cell membrane. This double mechanism of uptake gives choline a great advantage. In cases of HPT, there is increased intracellular transport of choline and up-regulation of choline-kinase enzyme [2].

According to the European Association of Nuclear Medicine (EANM) guidelines, parathyroid imaging methods are used for the detection and localization of hyperfunctioning parathyroid gland(s) in patients with PHPT who are candidates for surgery. In patients with secondary HPT, imaging is used presurgically to identify ectopic and supernumerary glands. The parathyroid gland with the lowest tracer uptake, should also be identified in order to be preserved or partially autografted. In patients with renal HPT, imaging techniques are suggested in case of revision surgery, while they are also useful in patients with hereditary endocrine diseases (MEN-1, MEN-2, MEN-4). However, the sensitivity of all imaging techniques is lower for hyperplastic glands than for sporadic adenomas [3].

Hindi et al. suggest the appropriate preoperative imaging algorithm in patients with PHPT, using as first line imaging techniques the ^{99m}Tc-sestamibi / ^{123}I subtraction scan and neck ultrasound. In case of first-line negative, discordant or inconclusive results, ^{18}F-fluorocholine (or ^{11}C-choline) PET/CT, or 4D-CT, is proposed as second line imaging modalities [4]. Ferrari S et al. retrospectively analyzed 138 patients with histologically confirmed PHPT. The patients underwent US and PS with Single Photon Emission Computed Tomography (SPECT) or SPECT/CT, followed by ^{18}F-choline-PET in cases of discordant results. Sensitivity rates for US, SPECT, SPECT/CT, and choline-PET were 47 %, 49 %, 71.7 %, and 97 %, respectively. Factors predictive of negative or equivocal SPECT outcome include lower PTH levels, serum levels and ionized calcium, a small or cystic adenoma, multiglandular disease and/or concomitant structural thyroid disease, adenomas with a low number of oxyphilic cells, and high expression of P-glycoprotein. US on the other hand is highly operator dependent, difficult to differentiate parathyroid adenomas from reactive cervical lymph nodes, as well as to detect ectopic parathyroid glands located in the upper mediastinum. The same study points out that urolithiasis, osteoporosis, and calcium values as measurement of activity and duration of disease showed no significant association with the detection rate [5].

The acquisition imaging protocol for ^{18}F-Choline PET/CT requires fasting for 4h followed by the intravenous injection of 1.5-3.2MBq/kg of ^{18}F-Choline. The proposed imaging time includes

an early scan at 10 minutes post injection, followed by additional imaging at 60 minutes post injection. The field of view should range from the nose to the chest, extending down to the base of the heart. However, the optimal imaging time for ^{18}F-choline PET/CT is still under discussion, although most parathyroid lesions are better defined at 60 minutes than at 10 minutes post injection. Another proposed protocol suggests a single-time-point imaging acquisition between 30 and 60 minutes post injection [3].

The APACH1 study, published in 2017, evaluated the sensitivity of ^{18}F-Choline PET/CT for parathyroid adenoma detection prior to surgery in patients with PHPT and negative or inconclusive cervical ultrasound and ^{99m}Tc-sestamibi SPECT/CT. ^{18}F-Choline PET/CT guided surgery in 22 (88%) patients, allowing for 17 minimally invasive parathyroidectomies, 1 bilateral cervical exploration for multifocality and 4 other surgical procedures. Furthermore, bilateral cervical exploration could be avoided in the majority (75%) of patients. The study concluded that second line ^{18}F-Choline PET/CT has high sensitivity and positive predictive value, suggesting that upfront use may improve patient care [6].

The APACH2 study, published in 2026, compared upfront ^{18}F-Choline PET/CT versus MIBI SPECT/CT. The primary endpoint was the proportion of patients in whom first-line imaging resulted in successful MIP and cure. The study concluded that first-line 18F-Choline PET/CT allows more patients to undergo successful outpatient MIP at minimal additional cost, raising the question of whether MIBI SPECT/CT could be replaced [7].

Other PET radiotracers used for parathyroid imaging include ^{11}C-Choline and ^{11}C-Methionine. ^{11}C-Choline has the same mechanism of uptake and similar diagnostic performance as ^{18}F-Choline. The physical characteristics of 11C, namely its short physical half-life, give the advantage of shorter acquisition time (max 30 minutes) and lower radiation burden, although a disadvantage is the requirement for an on-site cyclotron. Furthermore, the high average positron energy of ^{11}C results in increased image noise and poor spatial resolution of ^{11}C-Choline PET images compared to ^{18}F-Choline images. ^{11}C-Methionine is characterized by high uptake in hyperfunctioning parathyroid tissue, as it is involved in the process of PTH synthesis. It's uptake most probably depends on the expression and activity of amino acid transporters such as the L-type amino acid transporter 1, and secondarily on its incorporation into the protein prepro-PTH [8]. In a recent prospective study, the diagnostic effectiveness of ^{11}C-Methionine PET/CT, ^{11}C-Choline PET/CT and 4D-CT were compared head-to-head in patients with PHPT after failure of first-line imaging. The results showed that the sensitivity of ^{11}C-Methionine PET/CT was reported between 60 and 86%, of ^{18}F/^{11}C-Choline PET/CT between 87 and 96% and that of 4D-CT between 80 and 90%. Choline PET/CT was superior to Methionine PET/CT and 4D-CT in localizing parathyroid adenomas, allowing correct localization in 85% of cases. More studies are needed to directly compare these three techniques directly, and it still remains unclear which of these imaging techniques is most effective after negative first-line imaging [9].

Parathyroid carcinoma (PCa) is an exceedingly rare endocrine malignancy, accounting for less than 1% of all PHPT cases and representing globally less than 0.005% of all cancers. The two most important biochemical manifestations are pronounced hypercalcemia and markedly elevated PTH levels. The differential diagnosis between PCa and benign conditions based on imaging techniques can be challenging. US with advanced Doppler flow imaging allows detailed anatomical assessment and evaluation of vascular patterns of the primary tumor. ^{99m}Tc-MIBI scintigraphy might demonstrate prolonged tracer retention in PCa. Imaging with ^{18}F-Choline PET/CT or PET/MRI, has shown superior performance for detecting both primary tumors and metastatic disease (most commonly in the bones, lungs, and liver) due to their higher spatial resolution and molecular sensitivity. ^{18}F-fluorodeoxyglucose (FDG) PET/CT may have a complementary role in more aggressive cases that exhibit higher metabolism. ^{18}F-fibroblast activation protein inhibitor (FAPI) and ^{68}Ga-Gatrivehexin have shown potential in cases where initial imaging is inconclusive [10, 11].

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Theranostics of prostate cancer: PSMA and new targets

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Introduction

The aim of this presentation is to transfer the experience of the Institute of Nuclear Medicine at University College London Hospital with prostate cancer theranostics as a leading clinical and academic centre in the UK as well as to open a discussion on the current state and potential future developments in this field.

Prostate cancer has become the most common cancer in the UK in 2026 [1]. Prostate cancer is a relatively homogeneous cancer with more than 90% of the cases being of the acinar adenocarcinoma type or having an acinar adenocarcinoma component [2].

The current nuclear medicine theranostics paradigm is molecular target-centred consisting of a pair of radioligands which share the same carrier binding to the target with high affinity. The diagnostic tracer carries an isotope appropriate for imaging while the therapeutic radiopharmaceutical carries a different isotope to the same target which can deliver a lethal dose of radiation to the area of disease [3].

The most common theranostic target in prostate cancer is PSMA. Particularly at the early era of prostate cancer theranostics, there was a question whether different imaging or therapy tracers produced by different companies or academic radiopharmacies would have equivalent performance. The radiopharmaceutical uptake to the prostate cancer cells is mainly driven by the high over expression of the target [4] while the different radiotracers share the same binding motif. Therefore, the tracers are considered equivalent by convention and comparative studies have been published. Less comparative data is available on the intracellular radiation retention or on differences in toxicity profiles, although empirically no particular concerns have been raised.

The first clinical trial on ^{177}Lu-PSMA therapy was TheraP, a phase 2 trial comparing safety profile of ^{177}Lu-PSMA versus second line chemotherapy in mCRPC patients who had progressed after ARPI and 1st line taxane chemotherapy. This was a successful trial which showed a more tolerable toxicity profile of ^{177}Lu-PSMA in comparison to taxane chemotherapy. The trial also provided evidence of higher PSA50 response in the ^{177}Lu-PSMA arm. Of note, patient eligibility included a combination of PSMA and FDG PET imaging [5].

Soon after TheraP, a large phase 3 clinical trial called Vision compared the efficacy of ^{177}Lu-PSMA treatment Vs standard of care in mCRPC patients relapsed after ARPI and 1 or 2 lines of taxane chemotherapy. The results showed improved PFS OS and quality of life in the ^{177}Lu-PSMA arm. The trial also established the known toxicity profile of ^{177}Lu-PSMA including nausea and vomiting, xerostomia, fatigue, bone marrow suppression and nephrotoxicity most commonly [6].

At the Institute of Nuclear Medicine, the first patient treated with ^{177}Lu-PSMA was a Vision trial patient just 4 years after the first diagnostic PSMA PET scan at the department in 2015. The patient received 4 cycles of ^{177}Lu-PSMA and despite a good PSA response of 75%, he withdrew due to Grade 3 fatigue. The patient's survival was 6 months from the time the treatment started.

The success of the Vision trial led to a fast FDA approval just 9 months after the trial results' publication [7]. Marketing authorisation in the UK followed soon in August 2022 which was the first in Europe [8].

An early access scheme was soon established to provide earlier availability of this promising therapy to UK patients who had an unmet clinical need. Another aim was to collect real-world data to support a NICE approval application which would allow reimbursement of ^{177}Lu-PSMA by the National Health System. Eventually, the NICE approval was not granted due to reservations on cost-effectiveness [9].

The Institute of Nuclear Medicine used the opportunity of the early access scheme to establish the ^{177}Lu-PSMA service, streamline the patient pathway and optimise the therapeutic protocols.

Theranostics is a multidisciplinary effort.

A typical case of a patient who may be eligible for this therapy is discussed in two different but closely connected multidisciplinary meetings: a pelvic cancer meeting which confirms the appropriateness of the therapy for the patient's disease setting and a molecular radiotherapy multidisciplinary meeting led by INM which scrutinises the patient's baseline PSMA PET, other imaging, baseline laboratory tests and performance status to assert the patient eligibility.

Following this, the multidisciplinary team organises the therapy administration, monitoring between cycles and follow up after the end of treatment under the oversight of a molecular radiotherapy coordinator. This is a newly created role covered by an experienced and appropriately trained advanced radiographer to ensure smooth communication among the teams involved (Oncologists, nuclear medicine physicians, nurses, physicists and radiographers) (Figure 1).

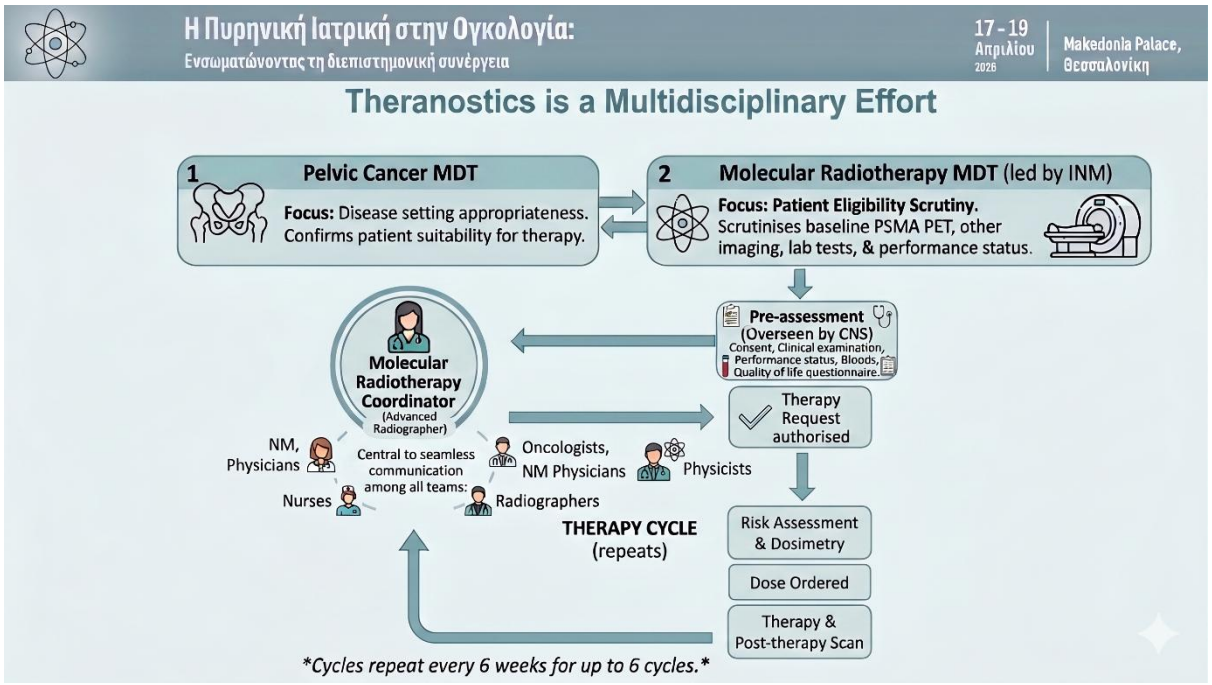

Figure 1. Flowchart of multidisciplinary synergy for the timely and safe administration of radioligand therapy at the Institute of Nuclear Medicine, UCLH.

The patient eligibility process follows the existing approvals and established guidelines (10). The patients treated so far at UCLH are «Vision-type» patients. However, a recent FDA and MHRA approval based on the PSMAfore trial allows a new indication of taxane-naive mCRPC patients after ARPI failure [11]. No such patient has been treated yet in our department.
No absolute contraindications exist [10].

The baseline PSMA PET assessment includes confirmation of high uptake at the sites of disease and no large lesions with low-grade PSMA uptake. The presence of liver metastases is a relative «red flag». The scan is also checked for suspicious cord compression findings particularly in symptomatic patients who may need to be further monitored with MRI or complete a stabilising course of radiotherapy before starting the ^{177}Lu-PSMA treatment. A synchronous FDG PET is not routinely offered unless justified by specific clinical inquiry.

Before treatment, a recent blood test (full blood count, renal, liver profile etc) is reviewed. Prophylactic antiemetics are given to the patient 30 minutes before the ^{177}Lu-PSMA infusion. The patients are routinely hydrated orally pre-treatment, but IV hydration may occasionally be applicable in patients with high risk for renal failure from the nephrotoxic effects of the treatment, e.g. patients with solitary kidney.

The therapy room is presented at Figure 2.

Figure 2. Outpatient radioligand therapy room at the Institute of Nuclear Medicine, UCLH.

A gravity method assisted by pump is used for the administration. The infused volume is typically 150ml over 12 minutes. Advantages of the method are:

- reduced dose to the staff handling the radiopharmaceutical
- low residuals
- reduced risk of contamination
- reduced risk of extravasation.

After the ^{177}Lu-PSMA administration, IV and oral hydration continue. The patient is monitored for immediate adverse affects. There is no routine dosimetry, but a whole-body planar scan is acquired approximately 2 hours after the administration in every cycle. The patient is provided with antiemetics and artificial saliva for home use as needed. The patient is discharged on average 2-3 hours after the administration based on a personalised risk assessment of his circumstances and measurements of dose rate at 1 meter.

Patient follow-up and side effects management adheres to the guidelines. In case of severe adverse effects, dose reduction, next cycle delay or discontinuation of treatment may be

decided. Particularly, in moderate to severe cases of xerostomia referral to oral medicine for specialised management is an option [12].

Assessment of response to treatment is a combination of clinical, biochemical and imaging findings. The degree of symptoms improvement and PSA drop are taken into account along with the post-treatment response PSMA PET, which is usually done at least 6-8 weeks after the last cycle.

UCLH is a recruiting centre for a multitude of phase 3 ^{177}Lu-PSMA trials such as PSMAfore (NCT04689828), PSMAddition (NCT04720157) and STAMPEDE2 (NCT06320067).

Our department has recently gained experience in alpha-emitting PSMA therapies by recruiting patients in the Pantha (NCT06217822) and Pelgi (NCT06052306) trials. Act-Resolute and AcTFirst (NCT06855277) are other trials being set up at the moment. The ^{225}Ac-PSMA tracers used in these trials are generally considered as «2nd generation» PSMA radioligands as despite sharing the same binding motif to the target, they are designed for higher serum albumin binding, which has been theorised to increase the affinity to the target and the retention of radiation within the cancer cell thus increasing their radiobiological effect.

The era of prostate cancer theranostics has just begun. The future of PSMA based theranostics may include investigations across the following themes:

- Cost effectiveness
- New indications incuding combination therapies
- Elucidation of radiobiological effects, radioresistance, and toxicity mechanisms, which could be translated to patient selection and personalised management
- Dosimetry and adaptive fractionation
- «New generation» tracers
- New radioisotopes e.g. ^{161}Tb

Future molecular targets for prostate cancer theranostics beyond PSMA may include hk2, STEAP1, DLL3, B7H3, CD46, nectin-4 etc. Some of these targets (e.g. hk2) could be used in a similar way with PSMA theranostics, using a pair of imaging/ therapy radiopharmaceuticals. Others are investigated for targeted therapies not involving radiation, such as T-cell engagers and ADCs. However, imaging radiotracers may be needed for the development of these treatments leading to an expanded theranostics paradigm.

Whichever radiopharmaceuticals prostate cancer theranostics will involve in the future, it is unlikely that there will be another one like ^{177}Lu-PSMA, particularly in terms of such speedy development and clinical adoption.

This is already evident in the development of ^{225}Ac-PSMA tracers which follow a much slower course due to strong phase 1/2 evidence base before proceeding to phase 3 trials, which may allow its clinical implementation.

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Genetic predisposition in gynecologic cancers: From knowledge to clinical management

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Abstract

Genetic predisposition contributes significantly to the development of specific gynecologic cancers, particularly ovarian and endometrial malignancies. Germline pathogenic variants in BRCA1 and BRCA2 genes account for a considerable proportion of hereditary ovarian cancer cases, while mismatch repair gene alterations underlie Lynch syndrome, strongly associated with endometrial cancer. Current international guidelines recommend universal genetic testing for all patients with ovarian cancer and systematic screening for mismatch repair deficiency in endometrial tumors. These molecular alterations directly impact therapeutic decisions, including the use of poly(ADP-ribose) polymerase inhibitors and immune checkpoint inhibitors, while enabling preventive strategies through cascade testing in relatives. The integration of genetic data with nuclear medicine imaging enhances disease characterization and treatment monitoring. Multidisciplinary collaboration is essential for the effective implementation of precision medicine in gynecologic oncology.

Keywords: gynecologic cancer, BRCA1/2, germline mutations, molecular profiling, genetic counseling, nuclear medicine

Introduction

Gynecologic cancers include malignancies of the ovary, endometrium, cervix, vulva and vagina, representing a heterogeneous group of diseases with diverse etiological mechanisms. While most cases are sporadic, approximately 5–10% are associated with hereditary cancer syndromes [1].

Hereditary breast and ovarian cancer syndrome and Lynch syndrome represent the most clinically relevant genetic conditions in this group. Advances in molecular genetics have significantly improved the understanding of tumor biology and have introduced new opportunities for personalized medicine. Identification of germline variants not only affects therapeutic decisions but also enables risk assessment and prevention strategies for family members.

In parallel, developments in nuclear medicine imaging contribute to improved disease evaluation and therapeutic monitoring, supporting a multidisciplinary approach in oncology.

Materials and Methods

A narrative review of the literature was conducted focusing on genetic predisposition in gynecologic cancers and its clinical implications. Relevant publications were identified through PubMed and international guideline repositories, including the National Comprehensive Cancer Network (NCCN) and the European Society for Medical Oncology (ESMO).

Priority was given to recent clinical guidelines and high-impact studies (2023–2025), as well as foundational research describing key genetic syndromes. The analysis focused on clinically actionable genetic alterations and their integration into diagnostic and therapeutic pathways.

Results

Genetic predisposition is most prominent in ovarian and endometrial cancers. Approximately 20–25% of ovarian cancers are associated with germline mutations, mainly in BRCA1 and BRCA2 genes [2]. Based on current guidelines, genetic testing is recommended for all patients diagnosed with ovarian cancer regardless of age or family history [1, 2].

Endometrial cancer is associated with Lynch syndrome in approximately 3–5% of cases, caused by pathogenic variants in mismatch repair genes such as MLH1, MSH2, MSH6 and PMS2 [3]. Universal screening for mismatch repair deficiency in endometrial tumors is recommended [3, 4].

These genetic findings have direct therapeutic implications. BRCA-associated tumors are sensitive to poly(ADP-ribose) polymerase inhibitors, while mismatch repair-deficient tumors demonstrate responsiveness to immune checkpoint inhibitors [5]. Furthermore, identification of hereditary cancer syndromes enables cascade testing and implementation of preventive strategies in at-risk relatives.

Discussion

The role of genetic testing in gynecologic oncology has evolved from a selective approach to a standard component of clinical management. Current guidelines emphasize universal or broad testing strategies, reflecting the increasing importance of molecular profiling in treatment planning.

From a nuclear medicine perspective, tumor biology influenced by genetic alterations may affect imaging characteristics and response evaluation. Molecular imaging modalities, including positron emission tomography, provide valuable insights into tumor metabolism and therapeutic response, particularly in the era of targeted therapies.

The integration of genetic and imaging data represents a key element of precision medicine. Effective implementation requires close collaboration between oncologists, geneticists, radiologists and nuclear medicine specialists.

Conclusion

Genetic predisposition plays a critical role in selected gynecologic cancers, with significant implications for diagnosis, treatment and prevention. The implementation of international guidelines for genetic testing and counseling improves patient outcomes and supports personalized care. Integration with nuclear medicine imaging enhances clinical decision-making and underscores the importance of multidisciplinary collaboration.

The author declares that they have no conflicts of interest.

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The role of ^{18}F-FDG PET/CT in the imaging of patients with breast cancer

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Introduction

Diagnosis of the Primary Tumor

In initial diagnosis, ^{18}F-FDG PET/CT has questionable clinical value and, for this reason, is not used in routine practice to evaluate potential primary breast tumors. It has low sensitivity but high positive predictive value (PPV) (PPV 81%–100%). So, if increased uptake is found on ^{18}F-FDG PET/CT in a breast lesion as an incidental finding, there is a high probability that it is due to malignancy.

The sensitivity of ^{18}F-FDG PET/CT depends on tumor size, histological type (invasive ductal carcinoma has a higher SUVmax than lobular carcinoma, and hormone receptor expression.

Prognosis

High ^{18}F-FDG uptake, meaning a high SUVmax, is significantly associated with a poor prognosis ($p=0.001$). That means that when the primary breast tumor takes up ^{18}F-FDG intensely, patient survival is worse, with a higher likelihood of metastases to lymph nodes and organs.

For example, triple-negative breast cancer, an aggressive form of malignancy, has significantly higher ^{18}F-FDG uptake compared to other subtypes.

Initial Staging

The TNM staging system is used. For the T stage, which depends on the exact size, mammography and ultrasound are clearly superior methods to PET/CT. Axillary lymph node involvement (N stage) is the most important prognostic factor, but in the early stages, ^{18}F-FDG PET/CT cannot replace sentinel lymph node mapping because it is inferior in detecting micrometastases in small infiltrated lymph nodes.

Conversely, ^{18}F-FDG PET/CT has a role in the staging of patients with locally advanced breast cancer, where it allows for the evaluation of all lymph node chains (axillary, supraclavicular, internal mammary) and is a more sensitive test than CT.

Furthermore, in locally advanced breast cancer, ^{18}F-FDG PET/CT plays a significant role in detecting distant metastases, a factor crucial for making the correct treatment decision. In these cases, ^{18}F-FDG PET/CT detects metastases in 11.5%–37% of patients, which were not visible on conventional imaging, with a high sensitivity of 95% and specificity of 98%. The most common site of distant metastases is the bones, where ^{18}F-FDG PET/CT outperforms bone scintigraphy in detecting lytic and intramedullary metastases.

Overall, performing ^{18}F-FDG PET/CT leads to a change in clinical stage in 40%–52% of cases and modifies the treatment decision in a significant proportion of cases, ranging from 14% to 35% in the studies conducted.

Assessment of Treatment Response

Anatomical imaging methods do not allow for differentiation between residual cancerous tissue and scar tissue, which often forms post-treatment (following surgery and radiation therapy). ^{18}F-FDG PET/CT visualizes metabolism and is not affected by post-treatment changes.

At the end of neoadjuvant chemotherapy ^{18}F-FDG PET/CT can be useful to perform a whole-body examination, to exclude metabolically active regional lymph nodes or distant metastases before breast surgery.

In patients receiving neoadjuvant chemotherapy, it is very important to differentiate between responders and non-responders at an early stage, which is crucial for determining the optimal timing of surgery. This is crucial for avoiding unnecessary treatment toxicity; furthermore, if the treatment is ineffective, a therapeutic agent can be switched to a more effective one.

^{18}F-FDG PET/CT appears to be able to predict treatment response after just one cycle of chemotherapy and allows for the early identification of patients who do not respond to or are resistant to chemotherapy.

Detection of Recurrence

Detection of local recurrence and metastatic disease influences treatment, but conventional imaging has limitations in distinguishing between scar tissue/fibrosis and recurrence.

However, since ^{18}F-FDG PET is based on functional criteria, its accuracy is significantly higher than that of conventional imaging techniques in the diagnosis of distant metastases.

Several studies have demonstrated that when there are equivocal results or findings suspicious for recurrence on conventional imaging (CT, MRI, ultrasound, bone scan, and mammography) or when tumour markers (cancer antigen 15.3, CA15.3, or carcinoembryonic antigen, CEA) increase during follow-up, the inclusion of ^{18}F-FDG PET/CT in the diagnostic algorithm of breast cancer relapse, changes clinical management in 40–50% of patients.

Conclusions

^{18}F-FDG PET/CT in the imaging of patients with breast cancer:

- Not indicated for the diagnosis of primary tumors, although it provides prognostic information.
- Detection of metastases in mediastinal, axillary, and internal mammary lymph nodes, but cannot replace sentinel lymph node biopsy.
- Detection of distant metastases: greater accuracy in osteolytic metastases compared to bone scintigraphy.
- Recommended when advanced-stage disease is suspected and conventional imaging is inconclusive.
- High sensitivity and specificity in detecting regional recurrence and is recommended in asymptomatic patients with elevated tumor markers.
- A promising role in predicting response to neoadjuvant chemotherapy.

Radioembolization (Selective Internal Radiation Therapy-SIRT). Changes in clinical practice, points of our experience

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Abstract

Radioembolization (SIRT) was initially introduced in the early 21st century as a whole-liver, primarily palliative treatment, for hepatocellular carcinoma (HCC) and liver metastatic colorectal cancer (mCRC). Over time, its application expanded to include other primary and secondary liver tumors. Clinical experience and emerging studies have demonstrated a clear relationship between higher tumor-absorbed radiation doses and improved tumor response. Such dose escalation can be achieved through advanced, more precise, and synchronous dosimetric approaches (personalized dosimetry), or in selected cases, through targeted treatments such as segmentectomy or lobectomy. These strategies have been associated with improved survival outcomes and, in certain cases, have enabled a shift toward curative treatment intent.

Introduction

Radioembolization in its current form was established at the beginning of the 21th century [1]. Since then there is an increasing number of centers performing SIRT worldwide, including in Europe [2]. At the University Hospital of Patras, we started SIRT in February 2017. At that time, we were the third medical center in Greece to begin using SIRT. Discussing SIRT at that time proved challenging, as it was not yet incorporated into most clinical guidelines nor endorsed by official medical associations. Both SARAH [3] and SIRveNIB [4] RCT trials, showed that SIRT was comparable to, but not superior to, sorafenib for survival in HCC, with fewer side effects. Notably, SIRT in these studies was used mainly in more advanced HCC (BCLC stages B-C). A 2020 sub-analysis of 120 patients from the SARAH trial showed that higher scheduled tumor doses were linked to improved survival [5]. In metastatic colorectal cancer (mCRC), a pooled analysis of three randomized controlled trials (RCTs) comparing first-line chemotherapy alone versus chemotherapy combined with SIRT demonstrated no overall survival benefit with the addition of SIRT, while being associated with increased toxicity [6]. While a subgroup analysis suggested improved survival with SIRT in patients with right-sided colon cancer, this effect was not validated

in a subsequent RCT evaluating SIRT in combination with second-line chemotherapy [7]. In this study (EPOCH), SIRT was associated with improved progression-free survival (PFS) and hepatic PFS, but not overall survival, and was accompanied by a higher incidence of adverse events.

With the growing use of SIRT, it has become evident that higher tumor doses may lead to improved tumor responses and prolonged survival, particularly in patients with HCC [8]. Higher tumor doses can be achieved by replacing traditional dosimetric algorithms with newer personalized approaches, such as multi-compartment or voxel-based dosimetry, or by performing more targeted liver segment treatments, such as segmentectomy or lobectomy. The use of personalized dosimetry has been shown to correlate with improved survival for both Glass and Resin microspheres in HCC [9–11] and mCRC [12]. For local SIRT treatments, one, two, three, or even more liver segments can be selectively targeted with curative intent, a strategy associated with improved survival [11]. A key prerequisite for this approach is the presence of an adequate healthy liver remnant beyond the treated segments. In such cases, the tumor dose can be substantially increased, as there is no need to limit exposure of normal liver within the perfused area. Additionally, delivering higher doses to the surrounding liver parenchyma may help eradicate undetectable satellite tumor foci, that later could give birth to tumor recurrences. Our interim results, from such a focused and intensified approach, at the AMARA (As Much as Reasonably Achievable) trial (ClinicalTrials.gov: NCT06257030) are highly encouraging. Among 55 patients with large primary and secondary liver tumors (mean diameter 8.1±2.53cm, range 5-14cm), complete response (CR) was achieved in 74.5% of cases, and overall response (OR) in 92%. A mean tumor-absorbed dose of 239Gy predicted CR with a sensitivity of 80.5% and specificity of 85.7%.

In the USA, the first FDA premarket approval (PMA) for resin microspheres (SIR-Spheres) was granted in 2002 for metastatic colorectal cancer (mCRC), while a Humanitarian Device Exemption (HDE) was issued for glass microspheres in hepatocellular carcinoma (HCC). At that time, SIRT treatments were predominantly performed as whole-liver therapies [1]. Gradually, SIRT became available worldwide, including in Europe, with EMA CE-mark approvals in 2002 and 2006. In the UK, NICE approved SIRT for metastatic colorectal cancer in 2020, for HCC in 2021, and for neuroendocrine tumor (NET) liver metastases in 2024; however, these approvals were mainly attributed to palliative use rather than curative intent. Over time, SIRT has been increasingly recognized as a valid treatment for liver malignancies, both for multifocal and solitary lesions. In 2022, the American College of Radiology [13] classified SIRT as “usually appropriate” for solitary HCC lesions of 3–5cm, multifocal bilobar HCC, HCC with vascular invasion, and multifocal neuroendocrine tumor (NET) liver metastases. It was considered “probably appropriate” for solitary HCC <3cm, solitary or multifocal mCRC liver metastases, and intrahepatic cholangiocarcinoma <3cm. In 2021, following the Legacy study [14], glass microspheres received FDA PMA approval for the treatment of solitary HCC up to 8 cm. Similarly, based on interim results from the DOORway study, resin microspheres (SIR-Spheres) obtained

FDA PMA approval for solitary HCC in 2025. It is important to note that in both studies, nearly 90% of patients had tumors smaller than 5cm. Over the past years, SIRT has been increasingly integrated into international guidelines. NCCN includes it alongside other intra-arterial therapies for HCC, iCCA, mCRC, and NET liver metastases, including segmental applications. Both AASLD (2023) [15] and EASL (2025) [16] recognize SIRT as a local ablative option and as therapy for more advanced liver disease.

The adoption of SIRT as both an ablative and palliative therapy has led to its increasing use worldwide. This trend is reflected at our center, where the number of treatments has grown steadily over the years. As of April 2026, we have performed 165 SIRT procedures: 28 two years ago, 36 last year, and 18 so far this year. In Greece, the number of medical centers offering SIRT has also expanded, from three centers in 2017 to nine active centers in 2026 (six in Athens, two in Thessaloniki, and one in Patras), with at least three additional Peripheral University Hospitals planning to initiate SIRT programs.

Economic analyses of the global radioembolization market indicate a rising trend in SIRT utilization, with the number of treatments projected to nearly double between 2025 and 2030. Market size is expected to increase from approximately $1.2 billion to around $2 billion by 2030. Among intra-arterial therapies, radioembolization appears to be the most frequently employed modality today.

The oncologic patient with liver cancer, whether primary or metastatic, can be likened to a marathon runner, navigating a long sequence of therapies in the effort to prolong life. Unfortunately, for most patients, the end of this journey does not result in complete cure, and a minority achieve total disease control. Throughout this process, all treatment modalities—including SIRT—aim to extend survival while minimizing discomfort and adverse effects. SIRT, in particular, meets these objectives and, in selected cases, provides critical interventions that can meaningfully alter disease prognosis.

Based on our experience, several aspects of SIRT are underrepresented in the literature. SIRT can be safely combined with other treatments without significantly interrupting ongoing therapeutic schedules. It is generally well tolerated, with few adverse effects, and can be applied even in patients of advanced age or with significant comorbidities, including heart failure, respiratory insufficiency, COPD, thrombocytopenia, renal failure requiring dialysis, esophageal varices, or cirrhosis at Child-Pugh B—and occasionally C—stages. Our experience demonstrates that SIRT can be safely and effectively applied in a such patients. Among 165 treatments, 23 were performed in patients over 80 years of age, 9 in patients over 85, and 5 in patients over 90. SIRT can also be administered repeatedly; in our series, 18 patients received two treatments, and 2 patients received three. Consistent with our previous results, SIRT is effective in large and very large tumors. Notably, it also shows remarkable efficacy in patients with intrahepatic cholangiocarcinoma. In our series of 10 patients included in the AMARA study, 83% were alive at 18 months. Achieving optimal outcomes with SIRT requires careful case evaluation and

meticulous treatment planning. With growing experience, the method can be successfully applied in scenarios previously considered unfeasible. In our practice, we have treated HCC and CCC patients with parasitic tumor perfusion via the cystic artery, phrenic artery, or internal mammary artery, as well as performed selective, focused treatments in patients with high lung shunt fractions, including one case with L-S of 44%.

In conclusion, SIRT is an emerging and increasingly accepted treatment for liver malignancies. It is generally well tolerated and can be employed both as a palliative therapy and, more recently, as a focal ablative technique with curative intent.

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Quantitative imaging in Nuclear Medicine

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Abstract

Quantitative imaging in nuclear medicine has evolved from simple photon counting to the estimation of absolute physical quantities such as activity concentration. This transition enhances diagnostic accuracy and supports personalized treatment planning. The present work reviews the principles of quantitative imaging in SPECT and PET, highlighting major degrading factors and correction techniques. Emphasis is placed on clinical applications including dosimetry, theranostics, and functional organ assessment, as well as on dynamic imaging approaches. Finally, current developments and future perspectives toward standardized and automated quantification are discussed.

Keywords: Nuclear Medicine -SPECT/CT -PET -SUV -Dosimetry

Introduction

Nuclear medicine imaging provides functional information through the detection of emitted photons. Traditionally, imaging was based on relative count distributions; however, recent advances have enabled absolute quantification of radiotracer uptake [1]. This evolution allows improved reproducibility, objective assessment of disease, and optimization of patient-specific therapeutic strategies [2]. Quantitative imaging is inherently complex, as it depends on multiple physical, biological, and technical factors. The integration of hybrid imaging systems such as SPECT/CT and PET/CT, combined with advanced reconstruction algorithms and correction techniques, has significantly improved the accuracy and clinical applicability of quantitative measurements.

Quantification Principles

Quantitative imaging involves the conversion of detected photon counts into physical quantities such as activity concentration (e.g., kBq/ml). This requires appropriate system calibration and correction techniques to compensate for physical and technical limitations.

Quantification in SPECT

Quantification in SPECT is affected by several degrading factors, including photon attenuation, scatter, collimator-detector response, and limited spatial resolution [3]. To improve accuracy, a Computer Tomography, CT is used in collaboration with SPECT; the SPECT/CT hybrid system. Modern systems utilize the following advanced methods: a) Iterative reconstruction algorithms, b) Attenuation correction, c) Scatter correction and d) Resolution correction. These corrections significantly enhance the reliability of quantitative measurements [4].

Quantification in PET

PET imaging enables quantification that is more direct, commonly expressed using the Standardized Uptake Value (SUV), which normalizes tracer uptake relative to injected activity and patient characteristics [5]. PET systems provide higher sensitivity and improved quantification accuracy compared to conventional SPECT.

Dynamic Imaging

Dynamic studies involve multiple sequential acquisitions, allowing the generation of time-activity curves (TACs) and parametric images. These methods provide additional information on tracer kinetics and physiological processes [6].

Clinical Applications

Quantitative imaging has become increasingly important in routine clinical practice, particularly in the context of personalized medicine. A major application is internal dosimetry and theranostics, where accurate quantification of radiotracer distribution is essential for treatment planning and response assessment. In radionuclide therapies using isotopes such as Lu-177 (DOTATATE and PSMA), patient-specific dosimetry enables optimization of administered activity and reduction of toxicity [7]. The implementation of dosimetry workflows requires calibrated imaging systems and dedicated software, as demonstrated by the introduction of SPECT/CT-based dosimetry protocols in clinical centers. In bone imaging, quantitative SPECT allows the use of SUV-like metrics, improving the evaluation of metastatic disease and therapy response. Similarly, in organ function studies, quantification supports more accurate estimation of physiological parameters such as glomerular filtration rate (GFR) and thyroid uptake.

Quantitative imaging also contributes to cardiac applications, particularly in myocardial perfusion imaging, where absolute flow estimation enhances diagnostic accuracy compared to relative perfusion assessment. Another important application is pre-therapeutic planning, such as the use of Tc-99m MAA imaging prior to Y-90 radioembolization, where quantitative analysis helps predict microsphere distribution and optimize treatment strategy. Furthermore, dynamic imaging studies provide additional insight into tracer kinetics. Through repeated acquisitions,

time-activity curves (TACs) can be generated, enabling the extraction of parametric images and kinetic modeling of physiological processes [6]. These approaches extend the role of nuclear medicine from static imaging to functional and quantitative assessment of biological systems.

Future Implementations

Future developments in quantitative nuclear medicine are expected to further enhance accuracy, standardization, and clinical impact. A key direction is the integration of artificial intelligence (AI) and automated workflows for image reconstruction, segmentation, and quantification. AI-based tools can reduce operator dependency and improve reproducibility, especially in complex dosimetry calculations. The concept of personalized radionuclide therapy is also expected to expand, with quantitative imaging playing a central role in tailoring treatment to individual patient characteristics. This requires robust dosimetric models and standardized imaging protocols.

Standardization and accreditation initiatives, such as the EARL program, are critical for ensuring consistency of quantitative measurements across institutions [8]. These efforts facilitate multicenter studies and the clinical adoption of quantitative biomarkers. Advances in reconstruction algorithms and physics-based corrections are continuously improving image quality and quantitative accuracy, particularly in SPECT imaging, where challenges such as attenuation, scatter, and resolution loss remain significant [3]. Additionally, the development of new radiopharmaceuticals and hybrid imaging systems is expected to expand the range of quantitative applications. The evolving role of combined PET/SPECT technologies may further enhance diagnostic capabilities and therapeutic planning. Finally, the increasing availability of dynamic imaging protocols and kinetic modeling techniques is expected to play a decisive role in the future, enabling a more comprehensive understanding of disease processes and treatment response.

Conclusion

Quantitative imaging in nuclear medicine has transformed image interpretation into a measurable and reproducible process with significant clinical impact. The implementation of accurate calibration, correction techniques, and standardized protocols is essential for reliable quantification.

Advances in hybrid imaging, dynamic studies, and dosimetry support the transition toward personalized radionuclide therapy, where treatment decisions are increasingly based on patient-specific data.

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Personalized dosimetry in molecular radiotherapy: Current advances and clinical challenges

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Abstract

Personalized dosimetry is increasingly recognized as a key component of molecular radiotherapy. The aim of this study is to present recent advances in individualized dosimetry and to discuss current challenges in its clinical implementation. Quantitative imaging techniques, such as SPECT/CT, enable absorbed dose calculations [1, 2], while voxel-based dosimetry offers improved precision in dose distribution, spatial resolution, and biological relevance compared to conventional organ-based methods [3]. Clinical evidence supports the role of individualized dosimetry in improving therapeutic outcomes and reducing toxicity [4-6]. However, routine clinical adoption remains limited due to workflow complexity, increased workload, and lack of standardization [7, 8]. Emerging artificial intelligence (AI) applications provide promising solutions for automation and optimization [9-11]. Personalized dosimetry is expected to improve therapeutic efficacy while minimizing toxicity, supporting its integration into routine clinical practice.

Keywords: Personalized dosimetry -Nuclear medicine -SPECT/CT -Voxel-based dosimetry -Artificial intelligence

Introduction

Molecular radiotherapy has traditionally relied on fixed administered activities, assuming similar dose distribution among patients. However, this assumption is increasingly recognized as inadequate, as inter-patient variability leads to significant differences in absorbed dose and clinical outcomes. The concept that the same administered activity does not result in the same absorbed dose has driven the transition toward individualized dosimetry. Personalized dosimetry aims to optimize treatment by calculating the absorbed dose for each patient, thereby maximizing tumor control probability (TCP) and minimizing normal tissue complication probability (NTCP)

[12,13]. This paradigm shift is supported by established internal dosimetry frameworks, such as the MIRD schema [14], and by advances in quantitative imaging [2].

Current Applications, Challenges and Future Work

Patient-specific dosimetry is primarily based on quantitative imaging using SPECT/CT systems. The methodology includes the conversion of detected counts into activity concentration (Bq/ml), followed by corrections for attenuation, scatter, and partial volume effects, as well as system calibration [1, 2]. Organ-based dosimetry assumes homogeneous dose distribution using standardized S-values [15, 14], whereas voxel-based dosimetry provides three-dimensional dose mapping and improved biological prediction [3]. Multiple imaging time points are often required to accurately model radiopharmaceutical kinetics, increasing complexity and workload [8]. Voxel-based dosimetry has demonstrated improved accuracy in dose distribution assessment compared to organ-based methods, particularly in heterogeneous tissues [3]. Quantitative SPECT/CT imaging enables reliable estimation of absorbed dose at the individual patient level [1, 2]. Clinical studies in PRRT and PSMA-targeted therapies have shown improved correlation between absorbed dose and treatment outcomes [4-6]. However, multi-time-point imaging protocols increase workload and resource demands. Although personalized dosimetry improves treatment individualization and outcome prediction [12, 13], several barriers limit its widespread implementation. These include lack of standardization, increased workload, and high costs [7, 8]. Artificial intelligence offers potential solutions, including automated segmentation, accelerated Monte Carlo simulations, and dose prediction models [9-11]. These developments may facilitate routine clinical adoption by improving efficiency while maintaining accuracy.

Conclusion

Personalized dosimetry represents a paradigm shift toward dose-based therapy in molecular radiotherapy, improving both efficacy and safety [12, 13]. AI-driven technologies are expected to enhance feasibility and support broader clinical implementation.

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Comparative review of contemporary guidelines for differentiated thyroid cancer management

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Abstract

Clinical practice guidelines are indispensable tools for evidence-based decision-making, yet they are not inherently free of subjectivity and cannot replace clinical expertise or critical judgment. This is particularly relevant in differentiated thyroid cancer, where disease heterogeneity, overdiagnosis of low-risk tumors, and variability among available recommendations often complicate management, especially in relation to postoperative radioiodine administration.

This review critically appraises contemporary guideline documents relevant to differentiated thyroid cancer, with emphasis on their evidence base, practical applicability, and implications for nuclear medicine practice. Major European recommendations from ESMO, ETA, and SNMMI/EANM were compared with the 2025 American Thyroid Association guidelines, focusing on risk stratification, radioiodine use, molecular testing, surveillance, and multidisciplinary implementation. Real-world applicability was also considered in light of published comparative analyses.

Across the reviewed documents, a clear trend toward individualized, risk-adapted management was observed. Routine radioiodine ablation is increasingly discouraged in low-risk disease, while selective use is recommended in intermediate-risk patients and retained in high-risk settings. Dynamic reassessment, structured follow-up with ultrasound and thyroglobulin monitoring, and incorporation of molecular markers are now integral components of modern

management frameworks. However, differences in terminology, structure, and implementation persist between European and American guidance.

Overall, contemporary guidelines support a precision medicine approach to differentiated thyroid cancer while underscoring the need for contextual interpretation and critical appraisal. European recommendations offer a practical framework for everyday clinical use, whereas ATA 2025 contributes methodological refinement through dynamic reassessment. The findings highlight the importance of combining evidence-based recommendations with physician judgment to optimize individualized patient care.

Keywords: Differentiated thyroid cancer Radioiodine therapy -Risk stratification -ESMO -ETA -ATA guidelines -Nuclear Medicine

Introduction

Clinical practice guidelines constitute highly valuable tools that support clinicians in delivering evidence-based recommendations for decision-making across the spectrum of diagnosis, management, and treatment of patients. Authoritative guidelines should be clear, specific, and rigorously evidence-based. They should undergo regular updates, follow a structured format, be readily applicable in clinical practice, and maintain independence from external influences. Under no circumstances can guidelines substitute for clinical expertise and the physician's critical judgment. Moreover, it must be acknowledged that a uniform, "one-size-fits-all" approach is not feasible in medical practice. Not every clinical scenario can be fully encompassed within rigidly defined categories, nor does every therapeutic intervention invariably lead to the anticipated outcome [1]. For these reasons, the systematic study, critical appraisal, and contextual interpretation of guidelines are essential. Such an approach ensures their appropriate integration into individualized patient care.

Building upon these considerations, it is reasonable to question the extent to which clinical practice guidelines consistently meet these standards—particularly with regard to their evidence-based foundation. An influential editorial published in 2011 underscored a key concern: recommendations labeled as "evidence-based" are not necessarily devoid of bias. The formulation of guideline statements may be shaped by the authors' interpretation of the available data, introducing a degree of subjectivity that can influence both the strength and direction of recommendations [2]. In this context, there is a recognized tendency for evidence to be selectively interpreted in a manner that aligns with pre-existing assumptions, rather than being appraised with complete neutrality.

However, objectivity is not the only aspect that warrants scrutiny when considering clinical practice guidelines. Equally important is their applicability in routine clinical practice. In the

setting of thyroid cancer, the implementation of guidelines often proves particularly challenging—especially with regard to decision-making for the administration of iodine-131. This difficulty arises, on the one hand, from the inherent heterogeneity of the disease, and, on the other, from the multiplicity of available guidelines, which in several instances exhibit discrepancies or even conflicting recommendations. Collectively, these factors contribute to a shift in clinical practice—from a strictly evidence-driven scientific process toward a more individualized, and at times almost "artistic," approach to patient management [3].

A closer examination of the factors that render the implementation of clinical practice guidelines challenging is warranted. Thyroid cancer represents the most common endocrine malignancy, accounting for approximately 3% of all newly diagnosed cancers annually, and has exhibited the most pronounced increase in incidence worldwide over recent decades. It generally carries an excellent prognosis, although outcomes vary substantially according to tumor biology, extent of disease, and response to therapy [4]. Concurrently, there has been a notable rise in the detection of small, early-stage tumors compared with more advanced forms of disease—a trend largely attributed to the phenomenon of overdiagnosis. As a result, low- and intermediate-risk patients now constitute the majority of cases encountered in clinical practice. Within this heterogeneous population, diverse therapeutic strategies have been applied [5]. Over the last decade, management strategies have evolved considerably, driven by the need to balance excellent disease control against the risks of overtreatment. This shift has been especially relevant in the context of postoperative radioiodine administration, surveillance intensity, and the incorporation of molecular diagnostics.

Radioactive iodine therapy in differentiated thyroid cancer represents one of the earliest forms of targeted molecular therapy in oncology. It essentially marks the advent of theragnostics and, despite having demonstrated clinical efficacy since its initial application in the 1940s, uncertainty persists in selected cases regarding whether it should be administered [6]. Achieving the goal of maximal therapeutic efficacy while ensuring patient safety—by avoiding both overtreatment and undertreatment—remains a complex and ongoing challenge in clinical practice [7]. Historically, thyroid cancer management often relied on relatively uniform treatment algorithms, with frequent use of radioiodine ablation following surgery across broad patient categories [8]. However, accumulating evidence has supported a more selective and individualized approach, particularly for low-risk disease. Contemporary guidelines increasingly recommend tailoring treatment intensity according to clinicopathologic risk factors, biochemical response, structural findings, and, more recently, molecular characteristics.

In light of the aforementioned challenges, it is important to acknowledge the considerable proliferation of clinical practice guidelines in thyroid cancer over the past two decades. A wide range of scientific societies—including those representing endocrinology, surgery, oncology, and nuclear medicine—have issued numerous guidelines, many of which have been periodically updated. Despite their shared objective of optimizing patient care, these recommendations are

not infrequently divergent, and in some instances even conflicting, thereby contributing to uncertainty in clinical decision-making [9]. The uncertainty and lack of clear consensus concerning the optimal management of low-risk patients—especially in relation to the need for ablation—underscore the pressing need for clinical practice guidelines that are truly applicable in everyday clinical settings and that ensure the delivery of optimal patient care. Therefore, a comprehensive review and synthesis of these guidelines can provide clinicians with a clearer framework for informed decision-making, while highlighting areas of consensus, controversy, and future research needs.

Several influential professional societies have recently issued updated recommendations. In Europe, key guidance has been provided by the European Society for Medical Oncology (ESMO), the European Thyroid Association (ETA), and the joint Society of Nuclear Medicine and Molecular Imaging/European Association of Nuclear Medicine (SNMMI/EANM) nuclear medicine practice guideline. More recently, the 2025 American Thyroid Association (ATA) guidelines introduced additional methodological refinements through a structured dynamic assessment model.

Given the growing complexity of differentiated thyroid cancer management, comparative evaluation of these recommendations is clinically relevant, particularly for nuclear medicine specialists practicing in European healthcare settings. The present review therefore summarizes and compares major contemporary guideline frameworks, focusing on similarities, differences, and their practical implications for risk stratification, radioiodine use, molecular testing, surveillance, and multidisciplinary care.

Methods

A narrative comparative review was performed using major contemporary guideline documents relevant to adult differentiated thyroid cancer management. The primary sources included the ESMO Clinical Practice Guidelines [10], the 2022 ETA Consensus Statement on post-surgical radioiodine therapy [11], the 2022 SNMMI/EANM practice guideline for nuclear medicine evaluation and therapy of differentiated thyroid cancer [12], and the 2025 ATA management guidelines [13].

Guidelines were reviewed comparatively across predefined domains considered most relevant to daily clinical practice and nuclear medicine decision-making: risk stratification systems, indications for postoperative radioiodine administration, molecular testing integration, follow-up strategies, and multidisciplinary applicability. Particular attention was paid to areas of convergence and divergence between European and American recommendations.

In addition, real-world applicability was considered using recently published comparative analysis of differentiated thyroid cancer guideline implementation. The objective was not to

perform a systematic meta-analysis, but rather to provide a clinically oriented synthesis with emphasis on practical interpretation and European relevance.

Results

Contemporary European and international thyroid cancer guidelines demonstrate convergence toward individualized, risk-adapted management of differentiated thyroid cancer while maintaining distinct methodological approaches. The reviewed ESMO, ETA, EANM/SNMMI, and ATA 2025 recommendations emphasize multidisciplinary evaluation, selective radioiodine application, and molecular integration into clinical decision-making.

Risk stratification represents a central area of evolution. All guidance employs dynamic reassessment, though methodological frameworks differ: ETA and EANM emphasize individualized risk-adapted approaches, ESMO follows a broadly risk-stratified framework, while ATA 2025 introduces the structured DATA model (Diagnosis, Assessment, Treatment, Aftercare), facilitating continuous re-stratification throughout the patient journey.

***Table 1**. Key contemporary trends in differentiated thyroid cancer guideline recommendations.*

Trend	ESMO 2019	ETA 2022	EANM/SNMMI 2022	ATA 2025
Risk stratification	Dynamic	Individualized	Risk-adapted	DATA framework
Radioiodine use	Selective	Conservative	Targeted	Risk-based
Molecular testing	BRAF V600E	BRAF/RET	Preoperative integration	Comprehensive
Surveillance	US + Tg	US + Tg	US + Tg	Dynamic reassessment

ESMO: European Society for Medical Oncology, ETA: European Thyroid Association, EANM/SNMMI: European Association of Nuclear Medicine / Society of Nuclear Medicine and Molecular Imaging, ATA: American Thyroid Association, BRAF = B-Raf proto-oncogene, serine/threonine kinase, V600E = Valine-to-Glutamic acid substitution at codon 600, RET: Rearranged during Transfection (RET proto-oncogene), US = Ultrasound, Tg = Thyroglobulin

Radioiodine therapy indications have converged toward conservative application. Low-risk patients rarely require ablation, intermediate-risk cases warrant selective use, while high-risk disease generally supports therapy across all reviewed recommendations. RhTSH preparation protocols are standardized across guidelines, reflecting broad agreement regarding patient preparation before radioiodine administration.

Table 2. Main observations from comparative evaluation of differentiated thyroid cancer guidelines.

Parameter	European Guidelines (ETA/EANM)	ATA Guidelines	Consensus
Low-risk ablation	Rare / generally avoided	Rare / selective	Avoid routine use
Intermediate-risk RAI	Selective use	Selective use	Case-by-case decision
High-risk RAI	Commonly recommended	Commonly recommended	Strong agreement
rhTSH preparation	Standardized	Standardized	Broadly aligned
Follow-up first 2 years	US + Tg every 6-12 months	US + Tg every 6-12 months	Harmonized

ETA: European Thyroid Association, EANM: European Association of Nuclear Medicine, ATA: American Thyroid Association, RAI: Radioactive Iodine, rhTSH: Recombinant Human Thyroid-Stimulating Hormone (recombinant human thyrotropin), US: Ultrasound, Tg: Thyroglobulin.

Nuclear medicine procedures maintain essential roles, although their indications are now more refined. Post-therapy whole-body scanning, dosimetry in patients with high cumulative radioiodine exposure, and FDG-PET/CT in the setting of rising thyroglobulin with negative iodine scans remain widely accepted components of advanced disease assessment. European recommendations place particular emphasis on practical implementation through multidisciplinary collaboration.

Molecular testing integration has accelerated significantly across recent recommendations. Preoperative BRAFV600E assessment is increasingly incorporated in intermediate- and high-risk settings, while RET and NTRK fusions identify patients who may benefit from targeted systemic therapies. ATA 2025 further highlights the incremental value of additional molecular markers, including TERT promoter alterations, for refinement of aggressive disease characterization.

The main differences in risk assessment emphasis between European and American recommendations are outlined in Table 3.

Table 3. Risk stratification comparison: European vs American guidelines.

Risk Factor	European (ETA/EANM)	American (ATA 2025)

Risk Factor	European (ETA/EANM)	American (ATA 2025)
Primary tumor features	Tumor extent and risk-adapted pathologic features	Structured reassessment within DATA framework
Lymph node disease	Integrated into individualized risk assessment	Integrated into dynamic post-treatment assessment
Distant metastases	High-risk feature	High-risk feature
RAI-related assessment	Iodine avidity and post-therapy imaging emphasized	Integrated with biochemical and structural response
Molecular markers	BRAF/RET and selected targeted markers	Broader molecular refinement including TERT context

ETA/EANM: European Thyroid Association / European Association of Nuclear Medicine, ATA: American Thyroid Association, DATA: Diagnosis, Assessment, Treatment, Aftercare, BRAF: B-Raf proto-oncogene, serine/threonine kinase, RET: Rearranged during Transfection (RET proto-oncogene), TERT: Telomerase Reverse Transcriptase.

Surveillance strategies exhibit substantial harmonization among all major recommendations. Neck ultrasound combined with thyroglobulin monitoring every 6-12 months during the first two years, followed by risk-adapted intervals, constitutes a common principle of follow-up. This dynamic monitoring model supports individualized duration and intensity of surveillance according to initial risk category and treatment response.

Comparative analyses of guideline applicability suggest that, despite broad conceptual agreement, real-world implementation differs across healthcare environments. European recommendations appear particularly feasible within European systems because of their emphasis on multidisciplinary practicality, whereas ATA 2025 provides additional methodological refinement through its structured reassessment framework. Overall, the reviewed literature supports precision medicine principles while acknowledging that some transatlantic differences persist and still require clinical judgment in routine practice.

Discussion

The present review illustrates a clear conceptual evolution in differentiated thyroid cancer management, characterized by a shift from standardized therapeutic algorithms toward individualized, risk-stratified approaches. European guidance from ESMO, ETA, and EANM has played a central role in promoting multidisciplinary decision-making and selective application of

nuclear medicine procedures, while ATA 2025 adds methodological refinement through the DATA framework and more explicit dynamic reassessment principles.

A central theme across all reviewed documents is the effort to balance adequate treatment against overtreatment. Earlier management strategies often supported broad use of postoperative radioiodine ablation, whereas contemporary recommendations favor much more selective application, especially in low-risk disease [14]. This evolution reflects growing evidence that excellent outcomes can often be achieved with surgery and surveillance alone in appropriately selected patients [15].

The comparative evaluation of guideline applicability is especially relevant in daily practice. Recent analyses have shown that although methodological quality among guidelines may be high, practical feasibility varies considerably [3]. European recommendations appear particularly well aligned with real-world multidisciplinary care pathways in European healthcare systems, suggesting that implementation value depends not only on scientific rigor but also on clarity, feasibility, and contextual adaptability [16].

For nuclear medicine specialists, these developments are highly significant. Radioiodine remains central in postoperative staging, risk refinement, and treatment of selected patients, but its use is now more nuanced and individualized. Post-therapy scanning, dosimetry in patients with substantial cumulative exposure, and FDG-PET/CT in biochemical persistence with negative iodine imaging illustrate how nuclear medicine is increasingly integrated into precision oncology rather than applied routinely [17].

Molecular diagnostics represent another major area of progress. Incorporation of BRAFV600E, RET, NTRK, and selected additional markers has enhanced risk assessment and expanded therapeutic possibilities, particularly in advanced or radioiodine-refractory disease [18]. At the same time, harmonized surveillance using neck ultrasound and thyroglobulin testing supports a dynamic follow-up strategy that can be adapted according to evolving patient status [19].

Despite broad convergence, relevant differences persist between European and American recommendations, particularly in terminology, structure, and the degree of formalization of dynamic assessment. For this reason, clinical judgment remains essential, especially in intermediate-risk disease where management decisions are often most nuanced. Overall, integration of European practicality with American methodological innovation appears to offer the most balanced framework for contemporary differentiated thyroid cancer care.

Conclusion

Contemporary thyroid cancer guidelines demonstrate substantial evolution toward individualized, risk-adapted management of differentiated thyroid cancer. European recommendations from ESMO, ETA, and EANM/SNMMI provide a practical multidisciplinary framework that emphasizes selective radioiodine use, refined risk stratification, and growing molecular integration, whereas ATA 2025 contributes additional methodological structure through continuous dynamic reassessment.

Nuclear medicine maintains a central role within this evolving framework. Radioiodine therapy, post-therapy imaging, dosimetry, and targeted PET/CT remain essential in selected patients for staging, treatment planning, and surveillance. Current guidance therefore supports a more precise and patient-centered use of these modalities rather than routine application.

Overall, the reviewed literature supports a precision medicine model in which treatment intensity, follow-up, and imaging strategies are adapted to individual risk and response patterns. European guidance appears particularly suitable for implementation in European clinical practice, while ATA 2025 offers complementary refinement. Future research should focus on validation of selective strategies and further harmonization of major international recommendations.

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Nuclear Medicine through the patient's eyes: Diagnosis, Accuracy and Hope

Kaiti Kontopoulou

Distinguished professors,
and scientists of Nuclear Medicine, dear friends and colleagues,

It is a special honor for me, as a representative of a patient association, to be among you today and share a perspective that is perhaps neglected and not often heard at scientific conferences: **the patient's own perspective**.

For scientists, Nuclear Medicine is a dynamic and evolving branch of medical science, with high-tech tools, highly precise imaging methods, and therapeutic applications that open up new doors and opportunities.

As for the patient, Nuclear Medicine is much more. It is **the moment when science meets anxiety, uncertainty, but nonetheless hope**.

A person's first encounter with a Nuclear Medicine examination is often accompanied by strong emotions. There is fear of the results, of the unknown, but also a deep expectation: that technology and knowledge will provide a clear answer.

And indeed, Nuclear Medicine today is one of the most valuable allies in the fight against cancer. Today we are talking more and more about the **precision medicine**.

The **Accuracy of diagnosis**, the ability to detect even the smallest changes in the body that give doctors the ability to design targeted and effective treatments.

For the patient, however, this concept is not just a scientific term. It is the hope that their treatment will be truly tailored to their needs, that they will not be just a number or an incident, but a person with their own unique story.

From the patient's perspective, this precision translates into something very specific: **more secure, less uncertain, and a chance for a better quality of life.**

Nuclear Medicine is making a decisive contribution to this new era. With modern imaging techniques and targeted therapeutic applications, a new reality is being created in oncology: **diagnosis and treatments are becoming increasingly personalized.**

But let me add more to the patients' perspective.

Technology, no matter how advanced, acquires real value when accompanied by **human care**.

For a patient entering the examination room, it is of great importance that they are informed, understood, and feel that the medical team is by their side not only as scientists but also as people.

And here I would like to recognize the significant contribution of Nuclear Medicine professionals, who serve this difficult but essential mission every day.

At the same time, on this same mission, the **patient associations** have an important role.

They work as a connecting bridge between the scientific community and society. They support patients psychologically and practically, but also raise awareness and inform about the possibilities offered by modern medicine.

Collaboration between scientific bodies and patient associations can create a strong support network, where knowledge, experience and human solidarity work together.

Because ultimately, our common goal is one: **To transform scientific progress into real improvement in people's lives.**

Nuclear Medicine shows us that science can see deep inside the human body. While it can also remind us that we must see **the person behind the image**.

Every examination, every result, every treatment decision concerns a life, a family, a set of dreams and expectations.

And that's why, when scientific knowledge is combined with human sensitivity, medicine becomes more than just science. It becomes **an act of hope** .

A thought that perhaps expresses better than any scientific term what patients experience: *The progress of medicine is not measured only by technologies and achievements. It is measured by the lives it illuminates and the hope it gives birth to.*

“And perhaps ultimately this is the most essential message I want to convey today. For the patient, every Nuclear Medicine examination is not just an image on a screen. It is a moment of truth, a moment of anguish, but also a hand that brings hope. Within that image, the organism isn't the only thing getting captured. There’s also a human being whose life requires time, **quality and perspective**. And when science meets **precision**, when knowledge meets **sensitivity**, then something much greater than a diagnosis is born: hope. The hope that medicine advances, not only to cure diseases, but to keep alive the dignity and light of human life”.

"Science is constantly advancing, shedding light, more than ever before, deeper into the mysteries of the human body. For the patient, however, this progress means something very simple and very big at the same time: more life, more hope".

And as Yannis Ritsos writes: *“And if you get tired, never say the road is over. There is always a window somewhere open to the light.”*

This is the light that medicine serves. And this is the light that gives patients the strength to continue.

Science advances with precision and knowledge. But man advances with something even more powerful: hope.

And as Tasos Livaditis writes: *“And if sometimes you don't see the sun, remember that it exists. And for that alone, it's worth continuing.”*

Perhaps this is the deepest mission of medicine: to keep this certainty alive within man.

Radioiodine refractory thyroid cancer; Bridging multidisciplinary synergy

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Abstract

Differentiated thyroid carcinoma (DTC) is the most frequent thyroid malignancy. It consists of papillary (85%), follicular (13%) with subtypes and anaplastic (<2%) thyroid cancer, derived from follicular dedifferentiation.(1) DTC is typically associated with a favorable prognosis.(1) However, a subset of patients progresses to a state of radioiodine (RAI) refractoriness (RAIR), necessitating complex multidisciplinary management.(2) This article explores the diagnostic challenges, prognostic evaluation, and the evolving therapeutic landscape for RAIR-DTC, highlighting the importance of integrated oncology care.

Introduction and Classification

Differentiated thyroid carcinomas (DTCs), which include papillary and follicular carcinomas, are the most prevalent forms of endocrine malignancy and are generally associated with a favourable prognosis when diagnosed and treated at early stages (2). The standard treatment pathway for these patients typically involves thyroidectomy followed by thyroid-stimulating hormone (TSH) suppression and, in selected cases, radioactive iodine (RAI) therapy (2).

While the majority of patients respond well to these conventional treatments, a subset of the population will experience disease recurrence or progression, eventually evolving into a state known as radioiodine-refractory differentiated thyroid cancer (RAIR-DTC) (3). This clinical transformation is often marked by the tumor's biological differentiation, which reduces its ability to trap iodine, thereby rendering further RAI therapy ineffective and significantly complicating long-term management (3).

To address the heterogeneity of these tumors, 2022 World Health Organization (WHO) classification provides an essential diagnostic framework (4). This classification system is critical for clinicians, as it enables the differentiation between well-differentiated cancers and more aggressive entities such as high-grade follicular-derived carcinomas (DHGTC) and poorly differentiated thyroid carcinomas (PDTC) (4).

Understanding these histological distinctions is paramount, as they directly dictate the patient's prognosis, the necessity for more intensive follow-up protocols, and the timing for transitioning to alternative therapeutic strategies. Consequently, the effective management of RAIR-DTC now relies on a deeper biological understanding of these aggressive subtypes to tailor care to the individual's patient disease kinetics (3).

Defining RAI Refractoriness

Radioiodine (RAI) remains the foundational cornerstone of treatment for DTC, serving either as an essential tool for remnant ablation or as a targeted therapy for metastatic disease (5). However, as tumors progress, they often lose the expression of sodium-iodine symporter (NIS), leading to a state of radioiodine refractoriness (RAIR) that portends a poorer prognosis (3).

Clinically, identifying this state is critical, as it necessitates a pivot away from RAI toward more aggressive systemic or local interventions (3).

The formal classification of RAIR-DTC is established when one or more of the following clinical conditions are met: (3)

a) Absence of Iodine Uptake: The primary definition includes the lack of iodine uptake in tumor lesions on a diagnostic RAI scintigraphy scan

b) Heterogeneous Response: Patients may exhibit uptake in some metastatic sites but not in others, or they may show progression of disease despite previously documented uptake

c) Progression Post-Therapy: RAIR is confirmed if the disease show clear evidence of progression within 6 to 12 months following a therapeutic dose of RAI

d) High Cumulative Exposure: The condition is also defined by disease progression that occurs after the patient has received a substantial cumulative RAI dose, typically exceeding 600mCi (22.2GBq)

The diagnosis of RAIR is not merely an imaging finding; it represents a biological transition that requires a prompt reassessment of the patient's entire therapeutic strategy (3).

Diagnostic Approach and Staging

Monitoring patients with RAIR-DTC requires a highly rigorous and comprehensive approach, as the clinical focus shifts from curative intent towards disease control and quality-of-life preservation. The diagnostic framework relies on integrating biochemical monitoring with precise radiological assessments to detect disease progression at the earliest possible stage (6).

The primary diagnostic pillars include the following (3, 6):

Biochemical Surveillance: Regular assessment of serum thyroglobulin (Tg) levels is essential: while an elevated Tg in the setting of negative RAI imaging often serves as the first indicator of RAIR, it necessitates further investigative imaging.

Routine Anatomical Imaging: Standard follow-up protocols utilize chest CT scans, ideally performed every 6 to 12 months to monitor for pulmonary metastatic progression. Neck ultrasounds remain critical for evaluating local or regional lymph node involvement.

Advanced Cross-Sectional Imaging: When neck ultrasound is negative, but serum Tg levels remain elevated (>10ng/ml), further intensive investigation via high resolution CT or MRI of the head, neck and chest is indicated to locate occult disease.

Functional Imaging (^{18}F-FDG-PET/CT): This modality is increasingly valuable in the diagnostic algorithm. It is particularly effective for identifying more aggressive, dedifferentiated tumors that no longer concentrate iodine and are therefore missed by traditional RAI scintigraphy.
Standardized Response Assessment: To maintain consistency in monitoring disease kinetics, the RECIST 1.1 (Response Evaluation Criteria in Solid Tumors) criteria are the standard for categorizing treatment response, allowing clinicians to objectively determine when a therapeutic shift is required.

Clinical Case Example: The Power of Multidisciplinary Management

To illustrate the clinical application of these principles, consider a 60-years-old patient with a history of papillary thyroid carcinoma, a tall cell variant with extrathyroidal extension initially treated with total thyroidectomy and high dose radioactive iodine with positive uptake in the trachea. Six months post-treatment, the patient presented with rising serum thyroglobulin levels (Tg: 10ng/ml) and a presence of pathological lymph nodes in the tracheal region. The patient underwent neck dissection and histology confirmed HGDTC. A second dose of high dose RAI was administered with elevated Tg (>30ng/ml) and there was no radioiodine uptake. At follow up a pulmonary CT demonstrated lung metastases. Subsequent ^{18}F-FDG-PET/CT imaging revealed multiple pulmonary metastases, confirming a diagnosis of RAIR-DTC.

In a multidisciplinary tumor board, the team evaluated the patient's clinical presentation. Given the patient's disease kinetics, the team opted for targeted systemic therapy with TKI therapy. This approach successfully stabilized the patient's disease, highlighting the necessity of coordinated multidisciplinary input.

Therapeutic Strategies: Beyond RAI

The therapeutic landscape for RAIR-DTC has undergone a transformative shift in recent years, moving away from a reflexive reliance on radioiodine toward a sophisticated model of personalized systemic therapy and targeted interventions (6). This evolution reflects our deeper

understanding of the molecular drivers of thyroid cancer and the implementation of precision oncology (6).

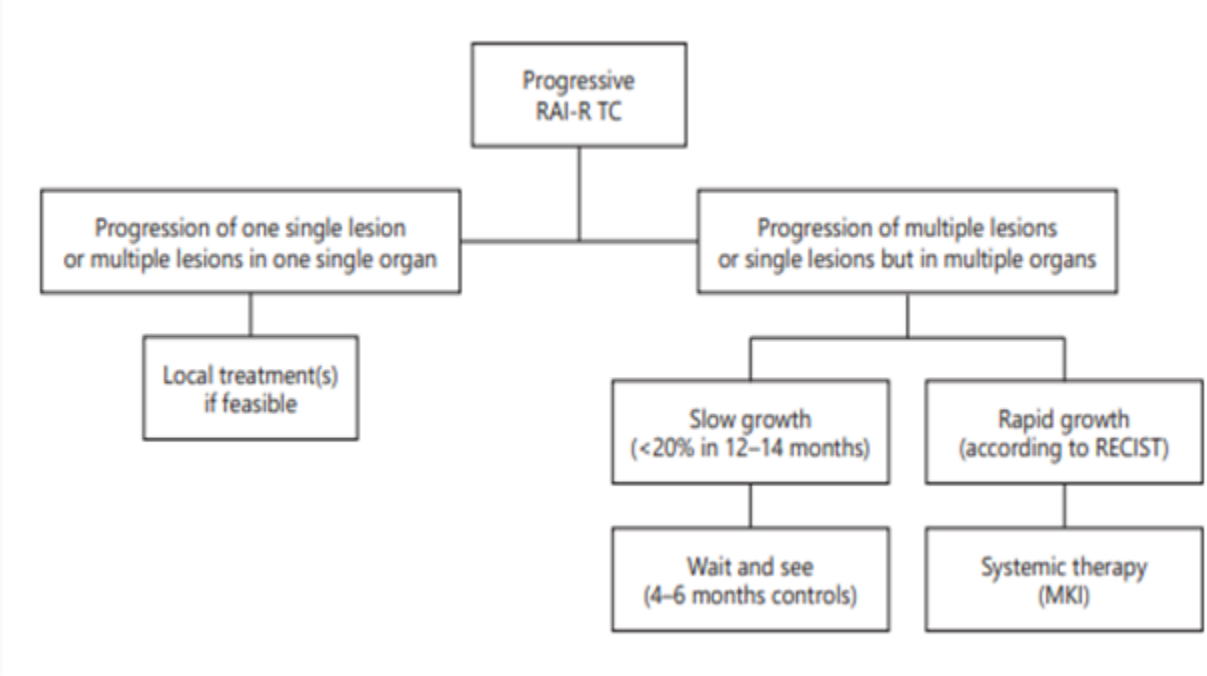

Figure 1. Therapeutic algorithm of RAI refractory DTC (5)

Localized Treatments

For patients presenting with oligometastatic disease or localized recurrence, the therapeutic strategy focuses on local control to manage symptoms, prevent complications, and delay the initiation of systemic therapy (7). When surgical resection is not feasible or causes an unacceptable risk to the patient, alternative local interventions are highly effective. These include external beam radiation therapy (EBRT) for bone metastases to prevent fractures, and thermal ablation techniques such as radiofrequency (RF) or laser ablation for accessible soft tissue lesions (6). Additionally, arterial embolization may be utilized to reduce tumor burden in specific metastatic sites, providing a critical bridge to systemic treatments (6).

Systemic Targeted Therapy

When systemic progression is confirmed, Tyrosine Kinase Inhibitors (TKIs) represent the standard of care (7). Agents such as Lenvatinib and Sorafenib function as cytostatic inhibitors that disrupt the signaling pathways responsible for tumor angiogenesis, cell proliferation, and survival (6). The landmark SELECT clinical trial established the clinical efficacy of Lenvatinib, demonstrating significant improvements in progression-free survival (PFS) for patients with progressive RAIR-DTC (7). While these drugs are potent, they are frequently associated with

toxicities such as hypertension, diarrhea, and fatigue, necessitating careful patient selection and proactive management by multidisciplinary team (7).

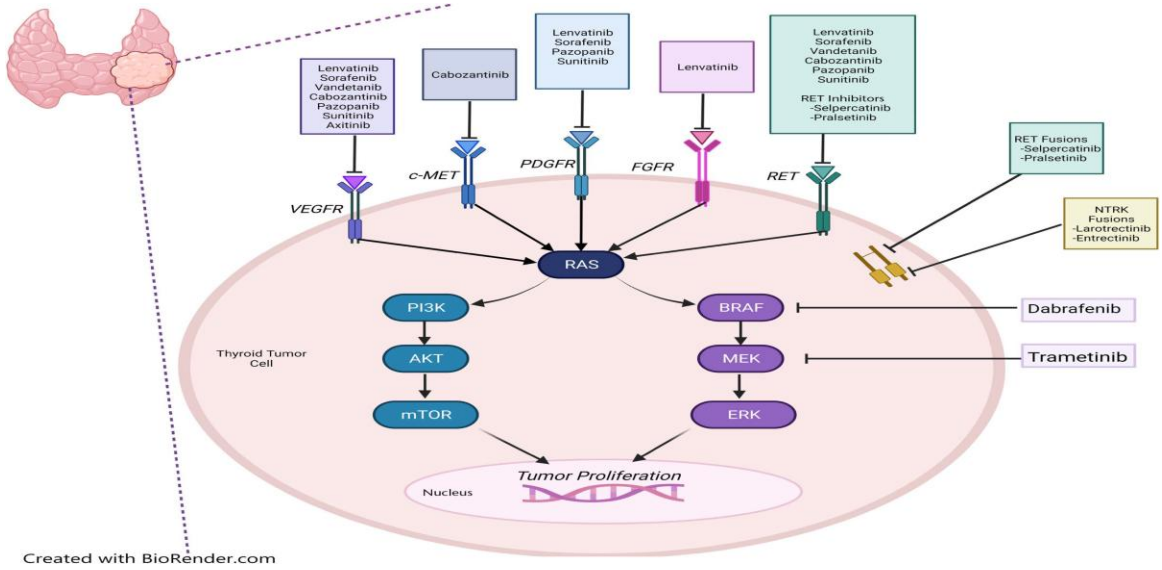

Figure 2. *Spectrum* of TKI selectivity (2).

Table 1*. TKIs Side Effects (6)*

Cardiovascular	Arterial hypertension, Thromboembolism, Cardiac failure, QT prolongation
Skin	Hand foot syndrome, Photophobia
Gastrointestinal	Stomatitis, Weightloss, Nausea, Diarrhea, Hemorrhage,
Renal	Proteinuria, Nephrotic syndrome, Renal failure
Endocrine	Hypothyroidism, Adrenal insufficiency

Actionable Driver Mutations and Precision Oncology

The frontier of RAIR-DTC management lies in tissue-based biomarker testing to identify specific actionable genomic alterations (6). This precision approach allows for the use of highly targeted therapies, which often offer superior efficacy and more favorable safety profiles compared to broad-spectrum TKIs (6). Key therapeutic targets identified through genomic profiling include (6):

Table 2. *Mutations and Targeted Therapies (6).*

Target	Therapeutic Approach
BRAF V600E	**Combination BRAF/MEK inhibitors (e.g. Dabrafenib + Trametinib(8)**

RET fusions	**Selective RET inhibitors (e.g. Selpercatinib, Pralsetinib)**
NTRK fusions	**NTRK inhibitors (e.g. Larotrectinib. Entrectinib)**

Immune Checkpoint Inhibitors (ICIs)

For patients with RAIR-DTC, the combination of ICIs and TKIs represents an evolving and promising therapeutic strategy (6). While standard systemic care often relies on single TKI agent, such as lenvatinib, sorafenib, or cabozatinib, to inhibit tumor angiogenesis and growth, these agents often offer only limited duration of response (9). By pairing a TKI with an ICI (such as the combination of lenvatinib and pembrolizumab), researchers aim to leverage the TKI's ability to modulate the tumor microenvironment potentially making the tumor more "visible" to the immune system, while the ICI works to remove the "brakes" on the patient's own T-cell response (10). Although clinical research is ongoing, this synergic approach is being actively investigated to improve response rates and achieve more durable disease control in patients who have exhausted or progresses on conventional therapies (10).

Multidisciplinary Synergy: The core of Modern Care

The management of RAIR-DTC is inherently complex, involving clinical, biochemical, and psychological considerations that transcend the scope of a single medical specialty. The optimal care of these patients is achieved only through a truly integrated, "team-based" approach.

The Multidisciplinary Team (MDT)

An effective MDT for RAIR-DTC must be composed of experts from diverse disciplines, including (6):

a) Endocrinologists: To manage hormone replacement, TSH suppression, and overall metabolic monitoring.

b) Nuclear Medicine Specialists: To assess RAI uptake status, oversee diagnostic functional imaging, and evaluate patients for potential redifferentiation clinical trials.

c) Surgeons: To determine the feasibility of surgical interventions for local recurrence or symptom palliation.

d) Medical Oncologists: To lead the administration of targeted systemic therapies and manage treatment-related toxicities

e) Radiologists: To interpret complex cross-sectional imaging and provide localized control through radiation strategies.

Collaborative Decision-Making

This synergy ensures that complex treatment decisions –ranging from the precise timing of TKI initiation to determining the threshold for palliative intervention –are made with a holistic view of the patient's disease kinetics (6). The MDT allows for the consideration of factors beyond the tumor itself, such as the patient's performance status, comorbidities, and personal quality of life priorities. Furthermore, this collaborative model creates a structured environment for discussing clinical trial enrollment, which is often a critical option for patients who have exhausted standard of care treatments (6).

Conclusion

The management of radioiodine refractory thyroid cancer has evolved into a sophisticated, biomarker-driven field. While systemic therapies have improved survival for patients with progressive metastatic disease, they carry significant toxicities. The integration of early genomic testing, meticulous monitoring of disease progression, and coordinated multidisciplinary care remains the gold standard for optimizing outcomes in these challenging cases.

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Peptide receptor radionuclide therapy with ^{177}Lu-DOTATATE: A retrospective evaluation of the experience at the Department of Nuclear Medicine at Theageneio Cancer Hospital

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Abstract

Objective: The aim of this retrospective study was to evaluate the clinical characteristics, treatment response and toxicity profile of patients treated with peptide receptor radionuclide therapy (PRRT) using ^{177}Lu-DOTATATE at the Department of Nuclear Medicine at Theageneio Cancer Hospital. **Materials and Methods**: Forty-nine patients with advanced somatostatin receptor-positive neuroendocrine tumors (NETs) and related neoplasms underwent treatment with ^{177}Lu-DOTATATE between January 2022 and January 2026. Demographic, clinical, imaging and therapeutic data were retrospectively analyzed. Response assessment was performed according to RECIST 1.1 criteria. Toxicity evaluation included hematologic, renal and hepatic adverse effects. **Results**: Pancreatic and small intestine NETs represented the most common primary tumors. Liver, lymph node and bone metastases were the predominant metastatic sites. Disease control was achieved in 81.3% of patients, with partial response observed in 27.1% and stable disease in 54.2% of patients, and most individuals completed the planned four treatment cycles. Hematologic toxicity was recorded in a minority of eight cases, while severe renal or hepatic toxicity remained uncommon. **Conclusion**: PRRT with ^{177}Lu-DOTATATE appears to be an effective and generally well-tolerated therapeutic option in patients with advanced NETs, providing high disease control rates with acceptable toxicity.

Keywords: Neuroendocrine Tumor (NET) -Peptide Receptor Radionuclide Therapy (PRRT) -Lutathera -^{177}Lu-DOTATATE -PET/CT - ^{68}Ga-DOTATOC

Introduction

Neuroendocrine neoplasms (NENs) comprise a heterogeneous group of tumors arising from neuroendocrine cells distributed throughout the body, most commonly within the gastroenteropancreatic and bronchopulmonary systems. Although historically considered rare malignancies, the incidence and prevalence of NENs have increased substantially over recent decades, largely due to improvements in diagnostic imaging, endoscopic techniques, pathological classification, and disease awareness [1].The biological behavior of these tumors is highly variable, ranging from indolent well-differentiated lesions to aggressive neoplasms with rapid progression and metastatic dissemination [2, 3]. Tumor grading based on the Ki-67 proliferation index and mitotic activity remains a cornerstone of prognostic stratification and therapeutic decision-making 3.

A hallmark of well-differentiated neuroendocrine tumors is the overexpression of somatostatin receptors (SSTRs), particularly subtype 2 (SSTR2), on the surface of tumor cells 4. This characteristic has enabled the development of a theranostic approach combining molecular imaging and targeted radionuclide therapy. Functional imaging with radiolabeled somatostatin analogues, most commonly ^{68}Ga-DOTATOC, ^{68}Ga-DOTATATE, or ^{68}Ga-DOTANOC positron emission tomography/computed tomography (PET/CT), allows accurate staging, assessment of receptor expression, and selection of suitable candidates for peptide receptor radionuclide therapy (PRRT) [5, 6]. The degree of radiotracer uptake, often assessed using the Krenning score, has been shown to correlate with treatment eligibility and therapeutic efficacy [7].

Peptide receptor radionuclide therapy has emerged as one of the most important systemic treatment options for patients with advanced, unresectable, or metastatic somatostatin receptor-positive neuroendocrine tumors [8]. The therapy is based on the administration of radiolabeled somatostatin analogues that selectively bind to tumor-associated SSTRs and deliver targeted radiation to malignant cells. Among available radionuclides, lutetium-177 (^{177}Lu) has gained widespread acceptance due to its favorable physical characteristics, including medium-energy beta emissions suitable for tumor irradiation and concomitant gamma emissions that permit post-therapy imaging and dosimetric evaluation [9]. The radiopharmaceutical ^{177}Lu-DOTATATE (Lutathera®) has demonstrated significant clinical benefit, including tumor control, symptom improvement, and prolonged progression-free survival, while maintaining an acceptable safety profile [10, 11].

The clinical role of PRRT was firmly established following the publication of the landmark NETTER-1 trial, which demonstrated significantly improved progression-free survival and objective response rates in patients with advanced midgut neuroendocrine tumors treated with ^{177}Lu-DOTATATE in combination with standard-dose somatostatin analog therapy compared with high-dose octreotide LAR alone [10]. Subsequent studies and long-term follow-up analyses confirmed the efficacy and safety of PRRT across a broader spectrum of gastroenteropancreatic

and bronchopulmonary neuroendocrine neoplasms [11]. Consequently, international organizations including the European Neuroendocrine Tumor Society (ENETS), the European Association of Nuclear Medicine (EANM), and the Society of Nuclear Medicine and Molecular Imaging (SNMMI) recommend PRRT as a standard therapeutic option for appropriately selected patients with advanced SSTR-positive disease [6, 9, 12].

Despite the growing body of evidence supporting PRRT, real-world data remain essential for evaluating treatment outcomes in routine clinical practice [11]. Institutional experiences provide valuable information regarding patient selection, imaging characteristics, treatment response, and toxicity profiles in heterogeneous populations that may not be fully represented in prospective clinical trials. Furthermore, published data from Greek centres remain limited. Therefore, the aim of the present study was to retrospectively evaluate the demographic and clinical characteristics, imaging findings, therapeutic response, and safety profile of patients treated with ^{177}Lu-DOTATATE at the Department of Nuclear Medicine of Theageneio Cancer Hospital over a four-year period.

Materials and Methods

Study Design

This retrospective observational study was conducted at the Department of Nuclear Medicine of Theageneio Cancer Hospital, Thessaloniki, Greece. Medical records of patients treated with peptide receptor radionuclide therapy (PRRT) using ^{177}Lu-DOTATATE (Lutathera®) between January 2022 and January 2026 were reviewed. The study aimed to evaluate patient demographics, tumor characteristics, imaging findings, treatment response, and treatment-related toxicity in routine clinical practice. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Population

A total of 49 patients with advanced somatostatin receptor-positive neuroendocrine neoplasms (NENs) and other SSTR-positive tumors were included in the study. Eligible patients had histologically confirmed disease and were considered suitable candidates for PRRT following multidisciplinary evaluation and assessment of somatostatin receptor expression by molecular imaging.

Demographic and clinical data collected included age, sex, body mass index (BMI), primary tumor site, tumor grade, metastatic disease distribution, previous systemic treatments, and interval between initial diagnosis and initiation of PRRT.

Baseline Tumor Characteristics

Tumor grading was based on the Ki-67 proliferation index according to the World Health Organization classification for gastroenteropancreatic and pulmonary neuroendocrine neoplasms 3. Patients were classified as Grade 1 (G1) or Grade 2 (G2) when applicable. Somatostatin receptor expression was assessed using the Krenning score in patients who underwent pre-treatment ^{68}Ga-DOTATOC PET/CT imaging 5.

Metastatic disease was categorized according to the presence of hepatic, lymph node, osseous, peritoneal, and other metastatic sites.

Imaging Evaluation

Pre-treatment molecular imaging was performed using either ^{68}Ga-DOTATOC PET/CT or ^{99m}Tc-Tektrotyd SPECT/CT. Imaging studies were reviewed for assessment of disease extent and somatostatin receptor expression 5.

Whenever possible, a follow-up imaging study using ^{68}Ga-DOTATOC PET/CT was performed before and after completion of PRRT, typically 6 months before to 3 months after treatment. Post-therapy SPECT/CT following the final treatment cycle was also used for treatment evaluation in some patients.

In a subgroup of patients, mainly those with G2 neuroendocrine tumors or tumors with suspected higher metabolic activity, complementary ^{18}F-FDG PET/CT was performed before and after PRRT. ^{18}F-FDG PET/CT findings were analyzed descriptively and were not used as the primary response assessment method.

Treatment Protocol

Patients received PRRT with ^{177}Lu-DOTATATE according to institutional protocols 13. Treatment was generally administered in four cycles at approximately 8-week intervals. Renal protection was provided through co-infusion of amino acid solutions according to standard clinical practice.

Concomitant treatment with long-acting somatostatin analogues was recorded when applicable.

Response Assessment

Treatment response was evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST version 1.1) 14. Patients were classified as having complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD) based on available imaging studies.

Overall disease control rate (DCR) was defined as the proportion of patients achieving complete response, partial response, or stable disease.

Toxicity Assessment

Treatment-related toxicity was assessed through review of laboratory and clinical data. Hematological toxicity was evaluated using hemoglobin, white blood cell, platelet, and

coagulation parameters. Renal and hepatic toxicity were assessed using serum creatinine and liver enzymes.

Treatment discontinuation, transfusion requirements, and clinically significant adverse events were recorded.

Statistical Analysis

Descriptive statistical analysis was performed using frequencies, percentages, means, standard deviations, and medians where appropriate. Continuous variables are presented as mean±standard deviation, while categorical variables are presented as absolute numbers and percentages.

Results

Patient Characteristics

Forty-nine patients with advanced somatostatin receptor-positive neuroendocrine neoplasms underwent treatment with ^{177}Lu-DOTATATE between January 2022 and January 2026. The cohort included 30 males and 19 females, with a mean age of 60.7±12.2 years and a mean body mass index of 27.3±6.3kg/m². The median interval between initial diagnosis and initiation of PRRT was 38 months (IQR: 13–84 months) (Table 1).

Table 1. *Baseline Patient Characteristics.*

Characteristic	Value
Patients, n	49
Male sex, n (%)	30 (61.2)
Female sex, n (%)	19 (38.8)
Age, years (mean±SD)	60.7±12.2
BMI, kg/m² (mean±SD)	27.3±6.3
Time from diagnosis to PRRT, months [median (IQR)]	38 (13-84)

Tumor Characteristics

The most common primary tumor sites were pancreas (16 patients) and small intestine (13 patients), followed by tumors of unknown primary, paragangliomas, lung tumors, colorectal tumors, and medullary thyroid carcinoma (Table 2).

Histological grading was available for 42 patients, including 14 G1 and 28 G2 tumors 3

(Table 3). Somatostatin receptor expression assessment demonstrated a Krenning score of 3 in 12 patients and a Krenning score of 4 in 33 patients 5 (Table 4).

Table 2. *Primary Tumor Distribution.*

Primary tumor site	n (%)
Pancreas	16 (32.7)
Small intestine	13 (26.5)
Unknown primary	8 (16.3)
Paraganglioma	5 (10.2)
Lung	3 (6.1)
Colorectal	3 (6.1)
Medullary thyroid carcinoma	1 (2.1)

Table 3. *Histological Grade.*

Grading	n (%)
G1	14 (33.3)
G2	28 (66.7)

Table 4. *Somatostatin Receptor Expression.*

Krenning score	n (%)
3	12 (26.7)
4	33 (73.3)

Metastatic Disease

Liver metastases were the most frequent metastatic site (33 patients), followed by lymph node (26 patients) and osseous involvement (17 patients). In addition, there were peritoneal, pulmonary, mesenteric, intestinal, adrenal, and intrapelvic metastases (Table 5).

Table 5. *Metastatic sites.*

Metastatic site	n (%)
Liver	33 (67.4)
Lymph node	26 (53.1)
Bone	17 (34.7)
Peritoneum	10 (20.4)
Other	6 (12.2)

Previous systemic treatments

Most patients had received at least one systemic treatment prior to initiation of PRRT. Somatostatin analogues represented the most commonly administered therapy, having been used in 30 patients (61.2%). Other previous systemic treatments included everolimus in 13 patients, chemotherapy, prior PRRT, and tyrosine kinase inhibitors (TKIs) (Table 6).

The majority of patients received maintenance somatostatin analogue therapy between PRRT cycles (25/49, 51%).

Table 6. *Previous systemic treatments.*

Previous systemic treatments	n (%)
Somatostatin analogues	30 (61.2)
Everolimus	13 (26.5)
Chemotherapy	5 (10.2)
PRRT	4 (8.2)
TKIs	3 (6.1)

Imaging Evaluation

Pre-treatment assessment was performed with either ^{68}Ga-DOTATOC PET/CT or ^{99m}Tc-Tektrotyd SPECT/CT.

Thirty-five patients underwent both pre- and post-treatment ^{68}Ga-DOTATOC PET/CT evaluation. Fourteen patients underwent complementary ^{18}F-FDG PET/CT imaging before and after treatment (Table 7). Among the 14 patients who underwent both pre- and post-treatment ^{18}F-FDG PET/CT, 4 had G1 NETs, 9 had G2 NETs, and 1 had a paraganglioma. Among patients with G1 tumors, 3 demonstrated positive ^{18}F-FDG uptake and 1 negative ^{18}F-FDG scan before PRRT, whereas post-treatment imaging showed positive findings in 2 patients and negative findings in 2 patients. In patients with G2 tumors, 5 positive and 4 negative ^{18}F-FDG PET/CT scans were recorded before treatment, compared with 4 positive and 5 negative scans following PRRT. The patient with paraganglioma demonstrated persistent ^{18}F-FDG positivity on both pre- and post-treatment imaging.

Table 7. *Imaging evaluation.*

Pre-treatment Imaging	n (%)
^{68}Ga-DOTATOC PET/CT	45 (91.8)
^{99m}Tc-Tektrotyd SPECT/CT	4 (8.2)
Pre- and post-treatment imaging	
^{68}Ga-DOTATOC PET/CT	35 (71.4)
^{18}F-FDG PET/CT	14 (28.6)

Treatment Response

According to RECIST 1.1 criteria, partial response was observed in 13 patients (27.1%), stable disease in 26 patients (54.2%), and progressive disease in 9 patients (18.7%) [14]. No complete responses were observed (Table 8). The overall disease control rate (DCR) was 81.3%. One patient was excluded from response assessment because only the first treatment cycle had been completed at the time of analysis.

According to tumor grade, no partial responses were observed among patients with G1 NETs, whereas 11 patients achieved stable disease and 3 experienced progressive disease. In contrast, partial response was documented in 12 patients with G2 NETs, while stable disease and progressive disease were observed in 11 and 5 patients, respectively (Table 9).

According to Krenning score, patients with a score of 3 achieved partial response, stable disease, and progressive disease in 2, 9, and 1 cases, respectively. Corresponding findings for patients with a Krenning score of 4 were 10, 15, and 8 cases, respectively (Table 10).

Table 8. *Overall treatment response.*

Response	n (%)
CR	0 (0)
PR	13 (27.1)
SD	26 (54.2)
PD	9 (18.7)

Table 9. *Treatment response according to tumor grade*.

Grade	PR, n (%)	SD, n (%)	PD, n (%)
G1	0 (0)	11 (78.6)	3 (21.4)
G2	12 (42.8)	11 (39.3)	5 (17.9)

Table 10. *Treatment response according to Krenning score.*

Krenning score	PR, n (%)	SD, n (%)	PD, n (%)
3	2 (16.7)	9 (75.0)	1 (8.3)
4	10 (30.3)	15 (45.5)	8 (24.2)

Safety and Toxicity

Forty-three patients (87.8%) completed all four planned treatment cycles. Hematological toxicity was documented in 8 patients (16.3%), while hepatic and renal toxicity were observed in 1 patient each (Table 11). Notably, the patient who developed renal toxicity was already undergoing dialysis. Three patients required blood transfusion support. Treatment discontinuation occurred in 6 patients. One patient experienced carcinoid crisis.

Table 11. *Treatment toxicity.*

Variable	n (%)
Hematological toxicity	8 (16.3)
Hepatic toxicity	1 (2.0)
Renal toxicity	1 (2.0)

Discussion

The present retrospective single-center study evaluated the efficacy and safety of peptide receptor radionuclide therapy (PRRT) with ^{177}Lu-DOTATATE in patients with advanced somatostatin receptor-positive neuroendocrine neoplasms. Treatment was associated with a high disease control rate and an acceptable safety profile, supporting the role of PRRT as an effective therapeutic option in routine clinical practice. Furthermore, the study provides real-world data from a Greek tertiary referral center, contributing to the limited published experience from the region.

The efficacy outcomes observed in our cohort are consistent with previously published evidence. The landmark NETTER-1 trial demonstrated significantly prolonged progression-free survival and improved response rates in patients with advanced midgut neuroendocrine tumors treated with ^{177}Lu-DOTATATE compared with high-dose octreotide LAR 10. Similar findings have been reported in large retrospective series by Kwekkeboom et al. and Brabander et al., which confirmed durable disease control and favorable long-term outcomes following PRRT [8, 11]. Notably, the disease control rate observed in our cohort was comparable to that reported by Brabander et al. (82%), despite the substantially smaller sample size of our study. Although direct comparisons are limited by differences in patient selection, tumor characteristics, and response assessment methods, our results further support the effectiveness of PRRT in a real-world clinical setting.

An interesting finding of the present study was the association between tumor grade and treatment response. Patients with G1 tumors predominantly achieved stable disease, whereas partial responses were observed more frequently among patients with G2 tumors. The predominance of G2 tumors in our cohort likely reflects the characteristics of patients referred for PRRT rather than the overall distribution of neuroendocrine tumor grades. Compared with G1 tumors, G2 NETs generally exhibit a higher proliferative rate and are more likely to demonstrate disease progression requiring systemic treatment, while still retaining sufficient somatostatin receptor expression to benefit from PRRT [3, 12]. This observation may also explain why measurable tumor shrinkage was observed more frequently among G2 tumors in our study. Nevertheless, the relatively small sample size precludes definitive conclusions regarding the

predictive value of histological grade.

Somatostatin receptor expression also appeared to influence treatment outcomes. Most partial responses were observed in patients with a Krenning score of 4, supporting the established role of receptor density in patient selection for PRRT 5-7. At the same time, disease control was also achieved in patients with a Krenning score of 3, suggesting that adequate receptor expression rather than maximal uptake alone may be sufficient to achieve therapeutic benefit. These findings are consistent with current recommendations emphasizing the importance of somatostatin receptor imaging for patient selection [12].

A subgroup of patients underwent complementary ^{18}F-FDG PET/CT imaging before and after treatment, most of whom had histologically confirmed G2 tumors. Although the number of patients undergoing dual-tracer imaging was limited, a small shift from FDG-positive to FDG-negative findings was observed following PRRT. This may reflect a reduction in tumor metabolic activity in responding lesions, supporting the complementary role of ^{18}F-FDG PET/CT in assessing biological response beyond conventional morphologic imaging. The increasing use of dual-tracer imaging has highlighted the importance of evaluating both somatostatin receptor expression and tumor glucose metabolism in neuroendocrine neoplasms [15, 16]. Although the NETPET classification was not formally applied in the present study, ^{18}F-FDG PET/CT provided additional information regarding tumor heterogeneity and biological behavior [15, 16]. Future studies incorporating standardized dual-tracer imaging approaches may further improve patient stratification and therapeutic decision-making.

The safety profile observed in our cohort was consistent with previous reports from both prospective clinical trials and large retrospective series, including studies evaluating long-term treatment-related adverse events, confirming the generally favorable tolerability of ^{177}Lu-DOTATATE [10, 11, 17]. Hematological toxicity represented the most common adverse event, whereas clinically significant renal or hepatic toxicity was uncommon. The low incidence of serious adverse events further supports the safety of PRRT in appropriately selected patients [12].

Several limitations should be acknowledged. First, the retrospective design introduces the possibility of selection and information bias. Second, the study was conducted at a single institution and included a relatively limited number of patients. Third, imaging follow-up and response assessment were not completely uniform across all patients. Finally, progression-free survival and overall survival analyses were not available, limiting the evaluation of long-term clinical outcomes.

Despite these limitations, the study reflects routine clinical practice and includes a heterogeneous patient population representative of patients referred for PRRT in a tertiary oncology center. In addition, detailed information regarding tumor grade, somatostatin receptor expression, imaging findings, treatment response, and toxicity was available for most patients, allowing a comprehensive assessment of treatment outcomes.

Conclusion

PRRT with ^{177}Lu-DOTATATE represents an effective and generally well-tolerated therapeutic option for patients with advanced neuroendocrine tumors. Most patients achieved disease stabilization or partial response, while severe toxicity remained relatively uncommon. The use of ^{68}Ga-DOTATOC PET/CT contributes significantly to appropriate patient selection and response assessment. Furthermore, complementary dual-tracer imaging with ^{68}Ga-DOTATOC PET/CT and ^{18}F-FDG PET/CT may provide additional information regarding tumor biology and treatment response, particularly in patients with G2 neuroendocrine tumors. Larger prospective multicenter studies are needed to further validate these findings.

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Melanoma: from diagnosis to immunotherapy – The journey through molecular medicine

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Abstract

Malignant melanoma is one of the most aggressive skin neoplasms and a major example of progress in modern oncology. The objective of this article is to review the most recent therapeutic data and the transition from diagnosis to modern immunotherapy based on a comprehensive review of the current literature and pivotal clinical trials. The results demonstrate that the profound understanding of the relationship between cancer and the immune system, along with the development of immunotherapies (CTLA-4 and PD-1 inhibitors) and targeted therapies (BRAF/MEK inhibitors), have radically changed the therapeutic approach and patient prognosis. Today, a significant number of patients can achieve long-term disease remission, even in advanced stages. Furthermore, modern molecular medicine has highlighted the importance of biomarkers, while neoadjuvant and adjuvant treatments significantly reduce the risk of relapse. In conclusion, the transition from chemotherapy to targeted and immunological therapies marks a new era in oncology, where treatment personalization and the utilization of the immune system itself constitute the core of the modern oncological strategy.

Keywords: Melanoma -Immunotherapy -Targeted therapy -Molecular medicine -Biomarkers

Introduction

Malignant melanoma represents one of the most aggressive neoplasms of the skin, but also one of the most important examples of progress in modern oncology. The evolution of molecular

biology, the deeper understanding of the relationship between cancer and the immune system, and the development of immunotherapies and targeted therapies have radically changed both the therapeutic approach and the prognosis of patients. Until about fifteen years ago, therapeutic options in metastatic melanoma were limited and overall survival was exceptionally low. Today, a significant percentage of patients can exhibit long-term disease remission, even in advanced stages.

Diagnosis and staging of melanoma are primarily based on histopathological characteristics. Breslow thickness remains the most important prognostic indicator, while the presence of ulceration, mitotic index, and lymph node involvement are also of particular importance. The 8th edition of the TNM staging system incorporated several of these parameters [1]; however, daily clinical experience shows that tumor biology is more complex. Factors such as age, sex, anatomical location, lymphovascular invasion, lymphocytic infiltration, and growth pattern appear to significantly affect prognosis. Furthermore, modern molecular medicine has highlighted the importance of biomarkers such as BRAF and NRAS mutations, gene expression profiles, and circulating tumor DNA (ctDNA), which will likely be further integrated into therapeutic decision-making in the future [2].

Subjects, Material and Methods

This review is based on the comprehensive study of contemporary literature, pivotal phase III clinical trials, and molecular studies evaluating the efficacy of immune checkpoint inhibitors and targeted therapies in patients with cutaneous melanoma.

Results

Melanoma is a tumor with a particularly high mutational burden, mainly due to chronic exposure to ultraviolet radiation [3]. The large number of somatic mutations leads to the generation of neoantigens, which can theoretically be recognized by the immune system [4]. Nevertheless, neoplastic cells develop immune evasion mechanisms, inhibiting T-lymphocyte activity and allowing disease progression. Understanding these mechanisms formed the basis for the development of immune checkpoint inhibitors and marked one of the greatest revolutions in the history of oncology.

The first significant progress was achieved with the development of ipilimumab, a CTLA-4 inhibitor. For the first time, an improvement in overall survival was proven in patients with metastatic melanoma [5, 6]. Subsequently, PD-1 inhibitors, such as nivolumab and

pembrolizumab, offered even higher response rates, a better safety profile, and a longer duration of disease control [7, 8]. Immunotherapy does not directly target the cancer cell; it reactivates the patient's own immune system, allowing T-lymphocytes to recognize and destroy the tumor. The most important advantage of this approach is the potential for prolonged and sustained responses even after treatment discontinuation.

Dual immunotherapy with a combination of anti-CTLA-4 and anti-PD-1 further increased the rates of response and complete remission, especially in high-risk patients or those with brain metastases [7, 8]. However, the increased efficacy is accompanied by greater toxicity. Immune-related adverse events can affect almost any organ, causing dermatitis, colitis, hepatitis, pneumonitis, and endocrinopathies. The early recognition and proper management of these complications are now an integral part of daily clinical practice [9]. Interestingly, several studies have shown that the appearance of immune toxicity correlates with better therapeutic outcomes and prolonged survival, a fact that likely reflects a stronger activation of the immune system.

Parallel to immunotherapy, the progress of molecular biology led to the development of targeted therapies. The MAPK pathway plays a central role in melanoma, through the RAS-RAF-MEK-ERK cascade, which regulates cell proliferation and survival. Mutations of the BRAF gene, primarily V600E, are found in approximately 40-50% of melanoma patients and lead to continuous activation of this pathway. The development of BRAF inhibitors, such as vemurafenib and dabrafenib, constituted a significant milestone, while the addition of MEK inhibitors, such as trametinib and cobimetinib, further improved outcomes and limited resistance mechanisms. Studies such as BRIM-3, COMBI-d, COMBI-v, and coBRIM demonstrated a significant improvement in progression-free survival and overall survival with anti-BRAF/anti-MEK combinations [10]. Targeted therapies offer rapid antitumoral action, high response rates, and quick symptom improvement, which is particularly important in patients with a high tumor burden or a life-threatening clinical presentation. However, their main disadvantage remains the development of acquired resistance, which limits the duration of the therapeutic benefit.

Discussion

The understanding of the interaction between targeted therapies and the immune microenvironment created the theoretical basis for therapeutic combinations. It has been shown that BRAF/MEK inhibitors increase T-lymphocyte infiltration into the tumor, decrease immunosuppressive cytokines, and increase PD-L1 expression, rendering the tumor more sensitive to immunotherapy [11]. The initial results of combinations of immunotherapy and targeted therapies showed increased rates of complete response and prolonged progression-free survival. Nevertheless, they are accompanied by greater toxicity, increased costs, and more difficult management of adverse events. For this reason, the selection of patients who will truly

benefit from such strategies, such as high-risk patients, patients with symptomatic brain metastases, or patients relapsing after adjuvant therapy, is of particular importance.

Significant progress has also been made in the early stages of the disease. Adjuvant and neoadjuvant therapy with anti-PD1 or anti-BRAF/anti-MEK combinations significantly reduces the risk of relapse in high-risk patients following surgical excision [12]. These strategies fundamentally alter the natural history of the disease and significantly increase the chances of long-term disease-free survival.

The modern therapeutic management of melanoma requires a personalized approach. Treatment selection is now based not only on the stage of the disease but also on the molecular profile, tumor burden, presence of brain metastases, general performance status, and patient comorbidities. Management requires close collaboration among medical oncologists, dermatologists, surgeons, radiation oncologists, pathologists, and molecular biologists, confirming that melanoma constitutes an example of multidisciplinary oncological care.

Conclusion

Melanoma is today perhaps the most characteristic example of the successful application of molecular medicine and immunotherapy in clinical practice. The deeper understanding of tumor biology not only improved therapeutic outcomes but entirely changed the way we perceive and treat cancer. The transition from chemotherapy to targeted and immunological therapies marks a new era in oncology, where the personalization of treatment and the utilization of the immune system itself constitute the core of the modern anticancer strategy.

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PET/CT στη σταδιοποίηση, έλεγχο ανταπόκρισης και επανασταδιοποίηση στον καρκίνο του πνεύμονα. Νεότερα δεδομένα στην μοριακή απεικόνιση και κλινικές προεκτάσεις

Ν. Καψωριτάκης

Σύμφωνα με τα πιο πρόσφατα παγκόσμια επιδημιολογικά δεδομένα του International Agency for Research on Cancer (IARC/WHO), ο καρκίνος του πνεύμονα παραμένει η κύρια αιτία θανάτου από κακοήθεια παγκοσμίως, με περισσότερους από 1,8 εκατομμύρια θανάτους ετησίως. Περίπου το 85% των περιπτώσεων καρκίνου του πνεύμονα αφορά τον μη μικροκυτταρικό καρκίνο του πνεύμονα (NSCLC), ενώ το υπόλοιπο 15% τον μικροκυτταρικό καρκίνο του πνεύμονα (SCLC).
Στην Ογκολογία, τα βασικά βήματα για την ορθή διαχείριση των ογκολογικών ασθενών είναι η ακριβής διάγνωση, η σωστή σταδιοποίηση, η επανασταδιοποίηση όπου απαιτείται, καθώς και η πρώιμη εκτίμηση της ανταπόκρισης στη θεραπεία.

Σταδιοποίηση

Η σταδιοποίηση του καρκίνου του πνεύμονα βασίζεται στο σύστημα TNM και αποτελεί τη βάση για την ακριβή εκτίμηση της έκτασης της νόσου και τον καθορισμό της θεραπευτικής στρατηγικής.

Τ σταδιοποίηση

Όσον αφορά την Τ (πρωτοπαθής όγκος) σταδιοποίηση, η αξονική τομογραφία (CT) παραμένει η μέθοδος εκλογής, κυρίως λόγω της ανώτερης χωρικής διακριτικής ικανότητας σε σύγκριση με την μοριακή υβριδική απεικόνιση PET/CT. Η PET/CT παρουσιάζει περιορισμούς στην ακριβή μέτρηση του μεγέθους της βλάβης με μεικτή σύσταση ή στοιχεία θαμβής υάλου (ground-glass opacities), καθώς και λόγω του partial volume effect, το οποίο οδηγεί σε υποεκτίμηση της μεταβολικής δραστηριότητας μικρών βλαβών. Σημαντικό πλεονέκτημα της PET/CT αποτελεί η δυνατότητα διαφοροποίησης περιοχής καρκινικών κυττάρων εντός περιοχών ατελεκτασίας. Οι ατελεκτατικές περιοχές εμφανίζουν συνήθως ήπια πρόσληψη του ραδιοφαρμάκου, γεγονός που επιτρέπει, μέσω της σύντηξης (fusion) ανατομικών και μεταβολικών εικόνων, τη σαφέστερη ανάδειξη του όγκου και τον ακριβέστερο καθορισμό των ορίων του.

Ν σταδιοποίηση

Για την N (λεμφαδενική) σταδιοποίηση, η PET/CT διαδραματίζει πρωτεύοντα ρόλο. Στην κλασική μορφολογική ακτινολογική προσέγγιση, η εκτίμηση της λεμφαδενικής διήθησης βασίζεται κυρίως στο μέγεθος και τα μορφολογικά χαρακτηριστικά των λεμφαδένων. Ωστόσο, είναι γνωστό ότι οι ανατομικές μεταβολές έπονται των μοριακών και μεταβολικών αλλαγών που συμβαίνουν στα καρκινικά κύτταρα, με χρονική καθυστέρηση έως και τρεις μήνες. Η ευαισθησία της CT για την ανίχνευση λεμφαδενικής διήθησης εκτιμάται περίπου στο 60-70%, ενώ της PET/CT ανέρχεται στο 80-90%, καθιστώντας τη μοριακή απεικόνιση ιδιαίτερα αξιόπιστη για τη σταδιοποίηση της νόσου. Παρ' όλα αυτά, θα πρέπει να λαμβάνονται υπόψη τα ψευδώς θετικά αποτελέσματα, τα οποία μπορεί να οφείλονται σε αντιδραστικούς λεμφαδένες (π.χ. μεταφλεγμονώδεις ή σε κοκκιωματώδεις νόσους), καθώς και τα ψευδώς αρνητικά, ιδιαίτερα σε περιπτώσεις μικρομεταστάσεων ή μικρών όγκων.

Μ σταδιοποίηση

Η υβριδική μοριακή απεικόνιση PET/CT κατέχει κεντρικό ρόλο και στην M (μεταστατική) σταδιοποίηση. Ως ολοσωματική απεικονιστική μέθοδος υψηλής ευαισθησίας, έχει ενσωματωθεί στον διαγνωστικό αλγόριθμο πολλών κακοηθειών, συμπεριλαμβανομένου του καρκίνου του πνεύμονα, για την ανίχνευση απομακρυσμένων μεταστάσεων. Ειδικότερα, παρουσιάζει υψηλή ευαισθησία στην ανίχνευση οστικών μεταστάσεων, τόσο οστεολυτικών όσο και οστεοβλαστικών, καθώς και μεταστάσεων στα επινεφρίδια. Ωστόσο, η χρήση του 18F-FDG εμφανίζει περιορισμούς στην εκτίμηση μεταστατικής νόσου στο εγκεφαλικό παρέγχυμα, λόγω της υψηλής φυσιολογικής πρόσληψης του ραδιοφαρμάκου από τον εγκέφαλο. Για τον λόγο αυτό, η μαγνητική τομογραφία (MRI) αποτελεί απαραίτητο συμπληρωματικό έλεγχο για την αξιόπιστη αξιολόγηση εγκεφαλικών μεταστάσεων.

Επανασταδιοποίηση και εκτίμηση ανταπόκρισης στην θεραπεία

Η επανασταδιοποίηση και η αξιολόγηση της θεραπευτικής ανταπόκρισης αποτελούν σημαντικά βήματα στη διαχείριση ασθενών με καρκίνο του πνεύμονα, ιδίως στη εποχή της ιατρικής ακριβείας η οποία βασίζεται σε στοχευμένες θεραπειες και ανοσοθεραπεία. Οι θεραπευτικές αυτές προσεγγίσεις συχνά συνοδεύονται από μεταθεραπευτικές και φλεγμονώδεις αλλοιώσεις, οι οποίες μπορεί να οδηγήσουν σε ψευδώς θετικά απεικονιστικά ευρήματα.

Οι συμβατικές ανατομικές απεικονιστικές μέθοδοι, όπως η αξονική τομογραφία (CT), παρουσιάζουν περιορισμούς στη διαφοροδιάγνωση μεταξύ υπολειπόμενης ενεργής νόσου και μεταθεραπευτικών ή μετεγχειρητικών αλλοιώσεων. Αντιθέτως, οι μεταβολικές και μοριακές μεταβολές σε κυτταρικό επίπεδο δύνανται να προηγούνται των ανατομικών αλλαγών έως και τρεις μήνες μετά την έναρξη της θεραπείας, καθιστώντας την υβριδική απεικόνιση PET/CT ιδιαίτερα κατάλληλη για την εκτίμηση της ενεργότητας, της υπολειπόμενης νόσου και της υποτροπής.

Κριτήρια εκτίμησης ανταπόκρισης

Παραδοσιακά, η εκτίμηση της ανταπόκρισης στην θεραπεία βασζεται στα κριτήρια RECIST (Response Evaluation Criteria in Solid Tumors), τα οποία στηρίζονται αποκλειστικά σε ανατομικές μεταβολές του μεγέθους των βλαβών μέσω της CT. Ωστόσο, τα κριτήρια αυτά εμφανίζουν περιορισμούς, ιδιαίτερα σε θεραπείες που δεν οδηγούν άμεσα σε μείωση του όγκου αλλά σε μεταβολικές μοριακές αλλαγές.

Τα τελευταία χρόνια, αναδεικνύονται τα κριτήρια PERCIST (PET Response Criteria in Solid Tumors), τα οποία βασίζονται στη μοριακή απεικόνιση PET. Τα κριτήρια αυτά εκτός από την ποιοτική εκτίμηση της ενεργότητας και την ποσοτική εκτίμηση της μεταβολικής δραστηριότητας των βλαβών, χρησιμοποιώντας παραμέτρους όπως το SUL (standardized uptake value normalized to lean body mass), το οποίο θεωρείται πιο αξιόπιστο από το SUV, καθώς εξαιρεί την επίδραση του λιπώδους ιστού.

Επιπλέον, σύγχρονες προσεγγίσεις ενσωματώνουν και άλλες ποσοτικές παραμέτρους, όπως το metabolic tumor volume (MTV) και το total lesion glycolysis (TLG), δείκτες για μια πιο ολοκληρωμένη εκτίμηση του συνολικού μεταβολικού φορτίου της νόσου.

Η ανοσοθεραπεία έχει πλέον καθιερωθεί ως βασική θεραπευτική επιλογή στον καρκίνο του πνεύμονα. Ωστόσο, η ερμηνεία των απεικονιστικών ευρημάτων είναι δύσκολη λόγω του φαινομένου της ψευδοπρόοδου (pseudoprogression). Η ψευδοπρόοδος οφείλεται σε διήθηση της νεοπλασματικής περιοχής από φλεγμονώδη κύτταρα, οδηγώντας σε αύξηση του μεγέθους της βλάβης και αυξημένη πρόσληψη ^{18}F-FDG.

Επιπλέον, ανοσοσχετιζόμενες ανεπιθύμητες ενέργειες (immune-related adverse events) μπορεί να εκδηλωθούν με αυξημένη μεταβολική δραστηριότητα σε διάφορα όργανα, όπως στον θυρεοειδή (θυρεοειδίτιδα), στους πνεύμονες (πνευμονίτιδα) και στο παχύ έντερο (κολίτιδα), γεγονός που μπορεί να ερμηνευτεί ψευδώς ως πρόοδος νόσου (ψευδοπρόοδος).

Για την αντιμετώπιση των περιορισμών αυτών, έχουν προταθεί τροποποιημένα κριτήρια εκτίμησης ανταπόκρισης σε ασθενείς υπό ανοσοθεραπεία, όπως τα iPERCIST. Τα κριτήρια αυτά βρίσκονται ακόμη υπό αξιολόγηση, αλλά φαίνεται ότι βελτιώνουν την ακρίβεια της εκτίμησης της ανταπόκρισης. Τα iPERCIST κριτήρια ενσωματώνουνν ποσοτικούς δείκτες όπως το SULpeak, το MTV και το TLG.

PET/CT στην Ακτινοθεραπεία

Η υβριδική μοριακή απεικόνιση PET/CT αποτελεί κρίσιμο εργαλείο στον ακριβή σχεδιασμό της ακτινοθεραπείας, επιτρέποντας τον ακριβέστερο καθορισμό των όγκων-στόχων, όπως το gross tumor volume (GTV) και το metabolic tumor volume (MTV), διακρίνοντας την ενεργό νόσο από τους παρακείμενους φυσιολογικούς ιστούς.

Η προσέγγιση αυτή οδηγεί σε βελτιστοποίηση της κατανομής της δόσης ακτινοβολίας, επιτρέποντας την εξατομίκευση της θεραπείας και τη μέγιστη δυνατή προστασία των υγιών

ιστών. Επιπλέον, συμβάλλει στη μείωση της γεωγραφικής αστοχίας (geographic miss) και στην ακριβέστερη στόχευση περιοχών με υψηλή μεταβολική δραστηριότητα.

Επιπλέον η απεικονιστική μέθοδος PET/CT αποτελεί πολύτιμο εργαλείο για την εκτίμηση της ανταπόκρισης, αλλά συνοδεύεται από απεικονιστικές παγίδες (pitfalls) οι οποίες που μπορεί να οδηγήσουν σε ψευδώς θετικά και ψευδώς αρνητικά αποτελέσματα. Τα ψευδώς θετικά ευρήματα σχετίζονται με φλεγμονώδεις αντιδράσεις, όπως η ακτινική πνευμονίτιδα, η μετακτινική ίνωση με ήπια πρόσληψη του FDG, η ανοσολογική ενεργοποίηση ή λοίμωξη στην ακτινοβολημένη περιοχή, καταστάσεις που μπορούν να μιμηθούν υποτροπή ή υπολειπόμενη νόσο.

Τα ψευδώς αρνητικά μπορεί να εμφανιστούν σε μικρή υπολειπόμενη νόσο με χαμηλή ενεργότητα, σε όγκους χαμηλού γλυκαιμικού δείκτη, σε μεταβολική καταστολή μετά τη θεραπεία ή υπεργλυκαιμία.

Το προτεινόμενο χρονικό διάστημα εκτίμησης της ανταπόκρισης με PET/CT μετα από ΑΚΘ ορίζεται στις 8–12 εβδομάδες προς αποφυγή ψευδών ευρημάτων. Συνιστάται σύγκριση με κλασσική απεικόνιση, αρχικό PET/CT πριν την έναρξη της ΑΚΘ, συναξιολόγηση του πεδίου ακτινοβόλησης, καθώς και επανάληψη απεικόνισης ή βιοψία σε αμφίβολες περιπτώσεις.

Συμπέρασμα

Η υβριδική απεικόνιση PET/CT αποτελεί θεμελιώδες εργαλείο στη σύγχρονη ογκολογία, διαδραματίζοντας καθοριστικό ρόλο στη σταδιοποίηση, τον θεραπευτικό σχεδιασμό και την εκτίμηση της ανταπόκρισης στην θεραπεία εκτιμώντας την βιολογική συμπεριφορά της νόσου. Πέραν της ποιοτικής αξιολόγησης, η ποσοτική ανάλυση της PET μέσω εξειδικευμένων δεικτών, όπως το standardized uptake value (SUV), το SUL, το metabolic tumor volume (MTV) και το total lesion glycolysis (TLG), προσφέρει σημαντικές πληροφορίες για την εκτίμηση της επιθετικότητας της νόσου και την παρακολούθηση της θεραπευτικής ανταπόκρισης. Οι παράμετροι αυτές συμβάλλουν ουσιαστικά στην εξατομίκευση της θεραπείας, ενισχύοντας την εφαρμογή της ιατρικής ακριβείας.

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Molecular imaging of TTR amyloidosis: New data

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Abstract

Transthyretin cardiac amyloidosis (ATTR-CM) is a recognized cause of heart failure that results from age-related or hereditary transthyretin misfolding and systemic amyloid deposition. It is characterized by clinical heterogeneity and may affect the heart among peripheral and autonomous nervous system, gastrointestinal tract, kidneys and eyes. Technetium-99m bone-avid scintigraphy with standardized planar and SPECT/CT protocols, interpreted using Perugini grading and heart-to-contralateral lung ratios after exclusion of light-chain amyloidosis, enables highly sensitive, non-invasive diagnosis of ATTR-CM and early detection in at-risk individuals. This narrative review synthesizes recent data on molecular imaging, emphasizing the central role of nuclear medicine physicians in applying multimodality diagnostic algorithms, recognizing typical and equivocal scan patterns. It further explores emerging roles for quantitative SPECT/CT and amyloid PET tracers in monitoring response to disease-modifying therapies, including tetramer stabilizers (tafamidis, acoramidis), RNA interference silencers (vutrisiran, patisiran), and investigational fibril-targeting antibodies and gene-editing strategies, underscoring a shift from purely diagnostic imaging toward dynamic treatment monitoring in ATTR-CM.

Introduction

Transthyretin (TTR) amyloidosis is a systemic disorder characterized by the extracellular accumulation of misfolded TTR protein fibrils in multiple organs, most notably the heart and peripheral nervous system [1].

There are two forms of the disease: the most common is wild-type ATTR (ATTRwt), which results from age-related misfolding of the normal TTR protein and mainly affects older men, and variant ATTR (ATTRv), which is a hereditary form caused by over 120 pathogenic mutations in the TTR gene [1]. TTR mutations exhibit distinct geographic and ethnic distributions and are inherited in an autosomal-dominant manner, with Val30Met, Val122Ile and Glu89Gln being the most prevalent variants worldwide. Considerable phenotypic heterogeneity exists among patients with different TTR mutations [2].

Cardiac involvement is dominant in ATTRwt and leads to a restrictive cardiomyopathy with progressive heart failure. ATTRv may additionally manifest as a sensorimotor or autonomic polyneuropathy.

For many years, Transthyretin Amyloid Cardiomyopathy (ATTR-CM) was considered a rare and untreatable disease, with diagnosis often delayed and based solely on histology. The introduction of highly sensitive scintigraphy using bone-avid technetium-99m tracers has revolutionized its diagnosis, allowing a noninvasive method without the need for tissue biopsy [3]. Concurrently, the approval of tafamidis in 2019, followed by acoramidis in 2024 and vutrisiran in 2025, has shaped a rapidly evolving therapeutic landscape [4, 5].

This review examines the ATTR-CM with emphasis on the diagnostic value and practical application of bone scintigraphy.

Subjects, Material and Methods

The present narrative review was conducted by critically appraising and integrating data from contemporary peer-reviewed articles, expert consensus statements, and educational reviews focusing on cardiac amyloidosis, with particular emphasis on molecular imaging. Priority was given to articles published from 2016 onwards, including sources comprised original studies, consensus documents, and systematic reviews published in peer-reviewed journals through March 2026. The identification of relevant sources was conducted using the following search terms: amyloidosis; cardiac amyloid imaging; transthyretin; bone scintigraphy; treatment; tafamidis.

Results

Etiology and clinical manifestations

Transthyretin normally forms stable tetramers through hydrophobic interactions. Genetic mutations (ATTRv) or age-related stress can destabilize these structures, causing them to

dissociate into monomers that misfold and aggregate into amyloid fibrils. These fibrils deposit in the heart, leading to increased wall thickness, diastolic and, in advanced disease, systolic dysfunction, as well as conduction abnormalities and atrial fibrillation [1].

Amyloid can also accumulate in peripheral nerves, ligaments, carpal tunnel, spine, eyes, and kidneys. In neuropathic ATTRv, this causes progressive sensorimotor polyneuropathy with autonomic dysfunction [6]. Notably, carpal tunnel syndrome may appear years before cardiac symptoms and can serve as an early warning sign [7].

Wild-type transthyretin amyloidosis predominantly affects men older than 60 years, whereas hereditary ATTR may present at a younger age depending on the specific TTR mutation. Its hallmark is heart failure with preserved ejection fraction (HFpEF), manifesting as exertional dyspnea, fatigue, and peripheral edema. Electrocardiography (ECG) may show low voltage disproportionate to increased wall thickness, although this is not universal. Common associated features include atrial fibrillation, conduction abnormalities, and an apical-sparing pattern on strain imaging [1].

Key clinical “red flags” include bilateral carpal tunnel syndrome, lumbar spinal stenosis, spontaneous biceps tendon rupture, unexplained hypertrophic or restrictive cardiomyopathy, aortic stenosis in older patients, and HFpEF that is refractory to standard therapy. In ATTRv, the presence of sensorimotor or autonomic neuropathy and a suggestive family history should prompt genetic testing [1].

Diagnostic algorithm

According to the ASNC/AHA/ASE/EANM/HFSA/ISA/SCMR/SNMMI expert consensus by Dorbala et al. (2021), the diagnostic algorithm for cardiac amyloidosis is a stepwise, multimodality approach that begins when clinical symptoms raise suspicion of the disease. Suspicion triggers two parallel work-ups: cardiac involvement is investigated through ECG, echocardiography, cardiac magnetic resonance (CMR), bone-avid scintigraphy (^{99m}Tc-PYP/DPD/HMDP), and biomarkers (NT-proBNP, troponin), alongside evaluation for systemic amyloidosis through serum and urine immunofixation, serum free light chain assay, immunoglobulin analysis, and tissue biopsy (endomyocardial, fat pad, bone marrow, or other site) with Congo red staining. Because biomarkers and imaging features are non-specific in isolation, confirming the amyloidosis subtype is essential: Immunoglobulin light chain amyloidosis (AL) requires demonstration of light-chain fibrils in tissue by mass spectrometry or immunohistochemistry, while ATTR can be diagnosed non-invasively by grade 2 or 3 myocardial uptake on bone scintigraphy only once a monoclonal plasma cell process has been excluded – otherwise endomyocardial biopsy is still required. Once ATTR is confirmed, genetic testing for TTR mutations distinguishes wild-type (ATTRwt) from hereditary (ATTRv) disease [8].

Nuclear medicine-based diagnosis

Cardiac nuclear scintigraphy with bone-avid radiotracers is the only imaging method capable of accurately diagnosing ATTR-CM without the need for invasive endomyocardial biopsy, and it becomes especially relevant when serum and urine tests for AL amyloidosis are negative. Three technetium-99m (^{99m}Tc)-labeled phosphate-based bone-avid radiopharmaceuticals are used to detect cardiac ATTR: hydroxymethylene diphosphonate (HMDP), pyrophosphate (PYP), and 3,3-diphosphono-1,2-propanodicarboxylic acid (DPD), all of which show overall equivalent diagnostic accuracy. ^{99m}Tc-DPD and ^{99m}Tc-HMDP are most often used in Europe, while ^{99m}Tc-PYP is the predominant tracer available in the United States, Canada, and Japan. The exact molecular mechanism by which these bone-seeking tracers concentrate in amyloid-laden myocardium is not fully characterized. [9] However, it is thought to involve tracer binding to microcalcifications within or surrounding amyloid deposits. Histopathological studies suggest that these microcalcifications are more abundant in ATTR-CM than in AL amyloidosis, which may contribute to the preferential myocardial uptake observed in ATTR. Moreover, tracer uptake appears to depend on both the type and abundance of amyloid fibrils, with a preferential association with type A fibrils [10.]

Scintigraphic interpretation relies on quantifying the intensity of myocardial radiotracer uptake. This is performed by visual analysis, comparing myocardial uptake to rib uptake on planar or single-photon emission computed tomography (SPECT) images, and by calculating the heart-to-contralateral lung (H/CL) ratio. The Perugini visual scoring system, applied to the planar image obtained 3 hours post-injection, grades cardiac uptake from 0 to 3: grade 0 = no cardiac uptake; grade 1 = mild uptake (less than bone); grade 2 = uptake similar in intensity to rib bone uptake; and grade 3 = substantial cardiac uptake with weak or absent bone signal. Diagnostic criteria for a positive planar scintigraphy include a Perugini score ≥2. Semiquantitative assessment using the heart-to-contralateral chest (H/CL) ratio was included as a diagnostic criterion in guidelines for ATTR-CM, with an H/CL ratio >1.3 at 1 hour or ≥1.5 at 3 hours considered positive. However, the use of H/CL is progressively being phased out, with greater emphasis now placed on visual grading [11].

SPECT -with or without computed tomography (CT)- is recommended by all national and international societies because it provides a more accurate assessment of myocardial versus blood-pool uptake and helps reduce false positives [9].

In a large multicenter study of 1217 patients, bone scintigraphy with a Perugini grade 2 or 3 demonstrated >99% sensitivity for ATTR-CM, with a specificity of 82–86% — most false positives arising from AL amyloidosis, in which grade 1 or 2 uptake can also be seen in 10–30% of cases, while grade 3 is only rarely observed [12]. When monoclonal protein screening (serum free light chains, serum and urine immunofixation electrophoresis) is negative, specificity rises to 100%. The incidental discovery of cardiac uptake on bone scintigraphy performed for non-cardiac reasons can also lead to early diagnosis of previously unsuspected ATTR-CM [13].

Amyloid-binding positron emission tomography (PET) agents originally developed for Alzheimer disease, as well as novel peptide tracers, extend molecular imaging beyond the heart

and beyond bone-tracer limitations. ^{11}C-Pittsburgh compound B (PiB), ^{18}F-florbetaben, and ^{18}F-florbetapir, have demonstrated utility in the detection of cardiac amyloidosis. However, tracer uptake is observed in both transthyretin and light-chain amyloidosis, thereby limiting their specificity for amyloid subtype differentiation. PET imaging offers distinct advantages, including the ability to concurrently visualize systemic amyloid distribution and to provide quantitative assessment of amyloid burden as well as therapeutic response [9].

Furthermore, PET findings exhibit strong concordance with established imaging modalities such as echocardiography, cardiac magnetic resonance, and bone scintigraphy. Specifically, myocardial tracer retention shows a positive correlation with apical sparing and increased wall thickness, and a negative correlation with tricuspid annular plane systolic excursion (TAPSE) and left ventricular end-diastolic volume. PET demonstrates approximately 94% agreement with CMR in assessing the extent of myocardial involvement, while DPD scintigraphy findings are consistent with PET results in the majority of patients [9].

Treatment response monitoring

The emergence of disease-modifying therapies has made non-invasive assessment of treatment response a central goal of nuclear molecular imaging in cardiac amyloidosis. For TTR-CM, management focuses on stabilizing the TTR tetramer and reducing its production, with tafamidis and several additional drugs are under investigation. The standard follow-up scheme for TTR-CM combines six-monthly clinical visits with NT-proBNP and troponin testing, ECG, annual echocardiography and 24-hour Holter monitoring, supplemented by cardiac magnetic resonance and speckle-tracking echocardiography, which have shown value in monitoring tafamidis outcomes [13].

Bone scintigraphy adds a quantitative imaging dimension to this follow-up, although its role is still being exploratory. Visual Perugini grading is relatively insensitive to therapy-induced change because grade 3 is defined by "mild/absent bone uptake" and is therefore confounded by surrounding soft-tissue uptake – meaning that even when amyloid burden falls, the visual grade often remains unchanged [13].

Quantitative SPECT/CT, through Standardized Uptake Value (SUV) max, SUVpeak, retention index, and especially myocardial-to-blood pool or myocardial-to-soft-tissue ratios, can provide more granular estimates of tracer uptake and, in illustrative tafamidis-treated cases, demonstrate reductions in myocardial SUV despite unchanged Perugini scores, suggesting sensitivity to therapy-related changes in amyloid burden or fibril composition [13]. Studies by Papathanasiou et al. (2023) and Vijayakumar et al. (2024), suggest that scintigraphic parameters may detect treatment-related changes earlier than conventional biomarkers and echocardiographic measures. However, these changes may reflect alterations in amyloid fibril structure rather than a true reduction in amyloid burden [14, 15]. In previous work, our group introduced the AHEPA Index as a potential quantitative marker of treatment response on planar

scintigraphy. Preliminary findings were encouraging, although further validation in larger cohorts is needed [16].

While PET cannot yet reliably distinguish AL from ATTR, early studies indicate that changes in tracer retention may reflect treatment response, supporting their development as quantitative tools for serial amyloid load assessment [17, 8].

Disease-modifying therapies

TTR-CM treatment has evolved significantly from primarily supportive care to include several disease-modifying therapies. The main treatment approaches target different steps in the disease process: stabilizing the TTR protein to prevent breakdown into amyloid fibrils, silencing production of TTR in the liver, and removing existing amyloid deposits [18].

Tafamidis (first-line tetramer stabilizer) is the established standard for symptomatic ATTR-CM (NYHA I-III), reducing all-cause mortality, cardiovascular hospitalizations, and functional decline in ATTR-ACT, with sustained benefit in the long-term extension. Earlier treatment and less advanced NYHA class clearly correlate with greater benefit [18, 4].

Acoramidis is a newer, potent TTR stabilizer designed to mimic the super-stabilizing Thr119Met variant, achieving near-complete TTR stabilization and improving a hierarchical composite of death, CV hospitalizations, NT-proBNP, and 6-minute walk in ATTRibute-CM; it is FDA (Food and Drug Administration) approved for ATTR-CM [4].

Vutrisiran, a subcutaneous RNA interference agent, in HELIOS-B reduced the composite of all-cause death and recurrent CV events by 28% and also improved functional and Quality-of-life (QOL) endpoints, with consistent benefit in tafamidis-naïve patients and a safety profile without infusion reactions. It is already approved for ATTRv polyneuropathy and is a leading candidate as an alternative or add-on to stabilizers in ATTR-CM, especially in more advanced NYHA class III where tafamidis benefit is attenuated [18].

Patisiran showed favorable effects on LV wall thickness, strain, NT-proBNP and a ~50% reduction in all-cause hospitalization/mortality in the ATTR-CM subgroup of APOLLO, and in APOLLO-B it attenuated decline in 6MWT; however, it did not significantly reduce hard clinical events in APOLLO-B and was not approved for the cardiomyopathy indication [4].

Ongoing investigation targets novel mechanisms, including monoclonal antibodies directed against amyloid fibrils (notably NI006, which aim to remove pre-formed fibrils), gene editing strategies using CRISPR-Cas9 (NTLA-2001) to permanently silence TTR production in the liver, and combination therapy approaches pairing a stabilizer or silencer with an anti-fibril agent to both prevent new deposition and accelerate clearance of existing amyloid [18].

Discussion

The transformation of ATTR-CM from an underdiagnosed, untreatable condition to a recognizable, manageable disease has been driven in large part by the widespread adoption of Tc-99m bone scintigraphy. Nuclear medicine physicians occupy a critical position in this pathway: not only in performing and interpreting bone scans, but in applying the diagnostic algorithm correctly, ensuring hematological exclusion of AL amyloidosis, and communicating graded and quantified results to referring clinicians [7].

Clinicians should be aware of the principal limitations of bone scintigraphy in ATTR-CM. The inability to differentiate ATTRwt from ATTRv on imaging alone mandates genetic testing in every confirmed case. Grade 1 uptake presents a particular diagnostic challenge: a substantial proportion of patients with grade 1 scans and a monoclonal protein will be found to have AL amyloidosis on biopsy, underscoring the importance of tissue confirmation in this subgroup. [13] Identifying whether amyloid is AL or ATTR is critically important as it is inextricably linked to patients' clinical management and prognosis.

The incremental value of SPECT/CT over planar imaging alone deserves emphasis. SPECT/CT reduces the contribution of blood-pool activity and extracardiac structures to the myocardial region of interest, improving specificity and providing the three-dimensional anatomical localization needed for accurate semi-quantitative and quantitative analysis [9].

The potential of nuclear imaging to serve as a monitoring tool during disease-modifying therapy is an active area of investigation. Serial reductions in SPECT-derived SUV parameters during tafamidis therapy have been reported, and the H/CL ratio has been shown to decrease significantly with treatment. Whether these changes predict clinical outcomes independently of established biomarkers such as NT-proBNP and troponin T remains to be established in larger, prospective trials with long-term follow-up [13].

Unlike bone scintigraphy, which primarily exploits tracer interactions with the amyloid-associated tissue microenvironment, amyloid-targeted PET tracers bind directly to amyloid fibrils, providing a potentially more specific molecular imaging approach to amyloid deposition. In this context, ^{18}F-florbetaben PET is being investigated as a tool for differentiating AL from ATTR cardiac amyloidosis through the assessment of myocardial and multi-organ amyloid involvement. Recent studies, including the work of Sprauel et al. (2026), suggest that quantitative and extracardiac PET parameters may contribute to the discrimination of AL and ATTR amyloidosis [19]. These findings highlight the potential of amyloid PET not only for detecting and characterizing amyloid burden, but also, in the future, for disease monitoring and treatment response assessment across amyloid subtypes.

The natural history of ATTR may be conceptualized as an "iceberg," with the disease evolving silently over years and becoming clinically and thus diagnostically apparent, only at more advanced stages. This raises the question of whether scintigraphy could contribute to the detection of the "hidden," subclinical phase of the disease, before it becomes clinically manifest.

Bone scintigraphy can be positive in genotype carriers and in patients with minimal hypertrophy, supporting its use as a screening tool in at-risk populations [17, 8]. This may be explained by the ability of scintigraphy to detect amyloid deposition up to 5 years before clinical disease manifestation, preceding detectable structural or functional cardiac abnormalities and changes in conventional biomarkers [20].

The potential role of cardiac amyloidosis scintigraphy as a screening tool is also being investigated in selected high-risk populations, such as patients with aortic stenosis or carpal tunnel syndrome. However, its use for screening the general population is not currently justified [21].

From a therapeutic perspective, the nuclear medicine physician should be familiar with the mechanisms and clinical evidence underpinning current therapies, as imaging findings may inform treatment eligibility and monitoring. The availability of three approved disease-modifying drugs with distinct mechanisms and administration routes (daily oral tafamidis, daily oral acoramidis, and quarterly subcutaneous vutrisiran) offers clinicians and patients meaningful choice, though cost-effectiveness and access remain significant barriers in many healthcare systems [18, 4].

Conclusion

Bone-avid tracer scintigraphy has transformed the diagnostic landscape of transthyretin cardiac amyloidosis (ATTR-CM), enabling early, non-invasive disease detection. Beyond diagnosis, its potential role in treatment monitoring and targeted screening is increasingly being explored. ATTR amyloidosis is no longer an invariably fatal and untreatable disease; it is increasingly a condition that can be detected earlier and treated effectively. We are moving from an era of disease recognition to one of active disease modification, with scintigraphy playing an important role in this transition.

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New radiopharmaceuticals in clinical applications, imaging and therapy – Updates in global situation

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Introduction

Traditional radiolabeling is insufficient foe the complies chemical space we are working with today. Efficient labeling of diverse heteroaromatic chemical space is where the radiochemical innovations begin. Rapid growth using nuclear medicine for personalized medicine and support drug discovery efforts, is putting unprecedented demand on radiochemistry manufacturing. New methods for rapid selection of a lead tracer, identification of labeling precursor and novel approaches for rapid radiosynthesis optimization, are required.

Challenges with these new approaches: organic synthesis: making precursors become a significant bottleneck, use-friendliness: requires a significant amount of focused work, adaptation and adoption: refine and generalize workflows, open-source, user friendly software tools, expansion: to other conditions, radionuclides and reaction manifolds.

Materials

Imaging probes:

1. With F-18 for multiple imaging e.g inflammation, breast cancer, adenocarcinoma, brain metastasis, neuroblastoma, tau imaging, glioblastoma, melanoma and prostate cancer with FAPI.
2. With Ga-68 for metastatic kidney carcinoma, new target for prostate cancer OncoACP3, FAPIs for thyroid cancer and liver carcinoma.
3. With Ga-68 and Cu-64 in tumors expressing nectin like breast and cancer and urothial carcinoma.
4. With Cu-64/61 for sarcoma and gastro-intestinal and prostate cancer and NETs
5. With C-11 with many compounds for brain imaging
6. With Zr-89 for multiple myeloma, Zircaix (as a target) for kidney cancer

7. With Tc-99m for SPECT with new compounds for prostate cancer, for bone imaging and for pulmonary diseases. The numbers show that the radiopharmaceuticals for PET in clinical practices are more than the radiopharmaceuticals for SPECT. The pharmaceutical R&D for PET imaging is constantly increasing.

Radiopharmaceuticals for therapy:

A. With b-emitters,

1. With Lu-177 in arthritis, thyroid cancer with FAPI, for sarcoma and prostate cancer.

2. With Tr-161 in pancreatic cancer, in prostate and breast cancer and in hematological malignancies.

B. With a-emitters,

3. Ac-225 for NET and prostate cancer.

4. With Pb-212 with PSMA for prostate cancer.

5. With At-111 for thyroid cancer.

6. With Y-86 with FAPI for targeting Eph2.

7. With Bi-213 for reduction of amyloid plaques.

Results

For the labeling of therapeutic pharmaceuticals isotopes like Lu-177, Tr-161, Ac-225 and At-211 are needed. Their production cannot cover their demand. To cover the market, target development for the production, the processing and the recycling is needed.

TAT therapy can become a routine establishing RPT absorbed dose-effect relationships. It can be used a) in multitargeted pan-cancers with pre targeting opportunities and b) in combination treatments to confront the biological complexities, tumor and microenviromental vulnerabilities.

The theranostic era has evolved through the approved therapies Lu-177 DOTATE (NETs) and Lu-177 PSMA-617 (Prostate Ca) providing proven survival and quality of life benefits. In the pipeline are next generation targets like FAP, CAIX (now phase II trails), others GPCR, DLL3, IGFR1 and LAT. In order to establish a secure environment in the therapies, infrastructure needs should be met like therapy wards with shielding and safety protocols, secure isotope supply and waste management and logistics for short half-life radionuclides.

Conclusions

Barriers for theranostics are heterogenious and context-dependent, varying significally across countries, continents and healthcare systems. These include, limited access to radionuclide production facilities, infrastructure gaps, gaps in dosimetry and treatment

personalization tools, regulatory handlers, workforce shortage, inadequate reimbursements structures, high investments costs and geopolitical discrepancies.

The interventions to overcome the barriers for theranostics are education and training, quality management, investments in R&D and radiopharmacy infrastructure, security of supply, increasing access by bridging the communication gap between the promoting physicians, advocacy and international collaboration,

In near 2040 the global radiopharamaceutical market is expected to grew significantly driven by the rising cancer incidences and chronic diseases, the expanding geriatric population, the increasing adoption of nuclear medicine in diagnostics and therapy and the technological advancements in imaging modalities.

In order for the Nuclear Medicine to become a global public good, international, coordinated, multidisciplinary and equity-focused efforts are needed:

A. Scalable infrastructure models

- Human resources: Capacity building – Education & Training
- Facility Modernisation: Digital PET, Hybrid Imaging & Cyclotron Units
- Centralized GMP Radiopharmacies supporting satellite hospitals {radiopharmacy infrastructure}
- Regional production centers to overcome isotope shortages

B. Digital transformation (AI)

- AI –driven image analysis and predictive dosimetry, Harmonisations of SOP's
- Workflow optimization in high-volume clinics

C. Expanding theranostic targets: FAP, CXCR4, integrins – ensuring readiness of facilities to adopt them

D. Resilient isotope supply chains: partneships between research reactors, cyclotrons and industry

E. Sustainability: radiopharmacy practices, cost effective implementation for low- and middle income countries.