Published in final edited form as:

Biomed Pharmacother. 2017 November ; 95: 469–476. doi:10.1016/j.biopha.2017.08.079.

The role of radionuclide probes for monitoring anti-tumor drugs efficacy: A brief review

Renata Salgado Fernandes^{#a}, Carolina de Aguiar Ferreira^{#b}, Daniel Cristian Ferreira Soares^c, Anna Margherita Maffione^d, Danyelle M. Townsend^e, Domenico Rubello^{d,*}, and André Luís Branco de Barros^{a,**}

^aLaboratório de radioisótopos, Departamento de análises Clínicas, Universidade Federal de Minas Gerais (UFMG), Avenida Presidente Antônio Carlos, 6627, Belo Horizonte, Minas Gerais, Brazil

^bDepartment of Biomedical Engineering, University of Wisconsin-Madison, Madison, WI, 53705, USA

^cLaboratório de Bioengenharia, Universidade Federal de Itajubá (UNIFEI), Rua Irmã Ivone Drumond, 200, Itabira, Minas Gerais, Brazil

^dDepartment of Nuclear Medicine, Radiology, Medical Physics and Clinical Pathology, Santa Maria della Misericordia Hospital, Rovigo, Italy

^eDepartment of Drug Discovery and Pharmaceutical Sciences, Medical University of South Carolina, USA

[#] These authors contributed equally to this work.

Abstract

Despite recent advances in the development of new therapeutic agents and diagnostic imaging modalities, cancer is still one of the main causes of death worldwide. A better understanding of the molecular signature of cancer has promoted the development of a new generation of anti-cancer drugs and diagnostic agents that specifically target molecular components such as genes, ligands, receptors and signaling pathways. However, intrinsic heterogeneity of tumors has hampered the overall success of target therapies even among patients with similar tumor types but unpredictable different responses to therapy. In this sense, post-treatment response monitoring becomes indispensable and nuclear medicine imaging modalities could provide the tools for an early indication of therapeutic efficacy. Herein, we briefly discuss the current role of PET and SPECT imaging in monitoring cancer therapy together with an update on the current radiolabeled probes that are currently investigated for tumor therapy response assessment.

Keywords

Anti-tumor efficacy; Therapeutic monitoring; Radiolabeled probes; Therapy response

*Corresponding author at: Nuclear Medicine, Radiology, Medical Physics and Clinical Pathology, Santa Maria della Misericordia Hospital, Via Tre Martiri 140, 45100 Rovigo, Italy. **Corresponding author at: Faculty of Pharmacy, Federal University of Minas Gerais, Av. Antônio Carlos, 6627, 31270-901, Belo Horizonte, Minas Gerais, Brazil, domenico.rubello@libero.it (D. Rubello), brancodebarros@yahoo.com.br (A.L.B. de Barros).

1. Introduction

Cancer remains a major public health problem, accounting for 1 in each 6 deaths worldwide. The most common types of cancer are lung, colorectum, and prostate in men and lung, breast, and colorectum in women. In the United States alone, upwards of 600,920 cancer-related deaths are estimated for 2017 [1]. Over the last three decades, significant progress has been made in the anti-cancer field to develop new drugs with higher specificity, efficacy and reduced toxicity. In parallel, early diagnosis is recognized as essential for positive clinical outcomes and the field of nuclear medicine has developed probes for early detection and post-treatment monitoring. Consequently, active monitoring of the tumor response to treatment rises as an interesting tool that can be leveraged for personalized medicine [2]. Currently, the response to treatment is usually assessed by measuring the tumor size with computed tomography (CT) or magnetic resonance imaging (MRI), regardless of the fact that tumor shrinkage usually occur several weeks or months after treatment or it may not occur at all with certain therapies, even when patients show positive responses to treatment [3].

Better tools for monitoring response at earlier stages of treatment are urgently needed, the result of which could have several benefits such as reduced side effects as a result of unnecessary chemotherapy and the ability to spare medical costs [4]. Furthermore, detecting and predicting tumor response is essential for improving the ability to tailor individual therapies and rapidly evaluate novel anti-cancer strategies. Markers of response could include, e.g. changes in metabolism or receptor expression associated with tumor cell death or inhibition of proliferation, whereas predictors of response might include the expression of hormone receptors, which predict response to anti-hormonal treatment, or the presence of tumor hypoxia, which can affect the effectiveness of radiotherapy [2].

In this context, molecular imaging has become an indispensable tool to determine the efficiency of tumor therapy regimens. Single-photon emission computed tomography (SPECT) and Positron emission tomography (PET) imaging approaches are the main techniques utilized and possess advantages over other imaging modalities, including high sensitivity and specificity, precise quantification, and almost no limit to tissue penetration [5,6]. Additionally, in contrast to MRI or CT, nuclear medicine imaging techniques allows the possibility to investigate not only tissues' morphological characteristics but also tumor cells' function and the recording of substantial information on tumor metabolism [7]. The most commonly used isotopes for imaging purposes are technetium-99m, fluorine-18, copper-64, gallium-68, and indium-111 [8], and their characteristics and clinical use are described in the following topics.

Molecular imaging offers a unique ability to monitor tumor characteristics in addition to size. Specifically, novel radiopharmaceuticals can be leveraged to identify and monitor tumor characteristics that can distinguish it from other tissues and from other stages of disease. More specifically, several tumor features, such as vascularization, hypoxia, glycolysis, overexpression of some receptors and tumor-cell proliferation might be used and explored as targets for radiolabeled molecules or nanoparticles.

In this review, we briefly discuss the current role of PET and SPECT imaging in monitoring cancer therapy, describe the main isotopes used by these techniques, and provide an update, focused on preclinical settings, on new imaging probes that holds the potential to determine and monitor tumor response to treatment.

2. Different radioisotopes for imaging

2.1. Gamma emitter isotopes

Technetium-99 m (^{99m}Tc) is one of the most abundantly used radionuclides in nuclear medicine due to its favorable properties that include a single 140 keV gamma photon emission and short half-life (6.02 h). In addition, this radioisotope is readily obtained in the form of pertechnetate directly from $^{99}\text{Mo}/^{99m}\text{Tc}$ generators on elution with physiologic saline [9]. The versatile chemistry of Technetium-99 m has been exploited to yield a plethora of different complexes used with success in nuclear medicine investigations through SPECT imaging. For example, imaging with ^{99m}Tc -(methylene) diphosphonate is the best method to detect skeletal metastases in cancer patients, with a lower radiation burden if compared to CT. In addition to initial staging patients, diphosphonate scintigraphy is widely employed to re-stage advance disease during or after treatment. ^{99m}Tc -labeled hydrazinonicotinyl-Tyr3-octreotide (EDDA/HYNIC-TOC) is commonly used for the management of neuroendocrine tumors (NET) [10–12]. Although the ^{68}Ga -DOTA-somatostatin analogue PET/CT is now the recommended standard method for imaging, staging and restaging most types of NET [13,14], the ^{99m}Tc -labeled platform represents a good alternative to Gallium-68 radiotracers where PET/CT or Gallium-68 generators are not available [15].

^{99m}Tc -methoxyisobutylisonitrile (^{99m}Tc -MIBI) was one of the first tracers used in breast cancer patients prior to PET imaging [16,17]. Novikov and co-workers (2015) investigated the potential role of ^{99m}Tc -MIBI in early stages to monitor and predict breast cancer response to neoadjuvant chemotherapy (NAC) [18]. Despite its high predictive value, at present this radiopharmaceutical is not routinely used in this clinical setting.

Several other radioisotopes have been used for SPECT imaging, both at clinical and pre-clinical settings such as ^{67}Ga , ^{186}Re , ^{201}Tl , ^{131}I , ^{123}I and ^{111}In . For example, ^{123}I and ^{131}I are currently used in the diagnosis and treatment of thyroid cancer while ^{111}In is commonly used for labeling Octreoscan, a somatostatin analogue available in the market for scintigraphic localization of primary and metastatic NET overexpressing somatostatin receptors [19]. In addition, some isotopes may have non-oncologic indications, such as ^{67}Ga [20] that is used to investigate chronic granulomatous diseases as sarcoidosis and ^{201}Tl , used as a perfusion agent to study coronary artery disease evaluation [21].

2.2. Positron emitter isotopes

The radioisotope Fluorine-18 (^{18}F) has gained considerable attention due to its nuclear and physical characteristics suitable for PET imaging, including a half-life of 109.7 min and positron emission with low energy (max. 0.635 MeV) and ratio around 97%. Fluorine has favorable chemistry due to its high electronegativity, ability to establish stable bonds with carbon atoms and to act, in many cases, as bioisostere with hydrogen and oxygen [22,23].

The glucose analogue 2-[^{18}F] fluoro-2-deoxy-D-glucose (FDG) is a clinically well-established PET tracer used in diagnosis and management of various malignancies. Independent studies have demonstrated that a reduction in FDG uptake is noted in patients that respond relative to those who do not [24–26]. In addition, increased FDG uptake after treatment is often associated with a high risk for early recurrence and poor prognosis [2]. Janssen and coworkers [27] evaluated metabolic responses of rectal cancer patients with PET/CT scans, in which FDG uptake was significantly reduced in tumor areas only 1 week after chemoradiotherapy, demonstrating the feasibility of a very early response assessment.

Another fluorinated PET radiotracer, 3'-deoxy-3'-fluorothymidine (^{18}F -FLT), is a nucleoside analogue that, after being taken up by the cell, is phosphorylated by thymidine kinase 1 into ^{18}F FLT monophosphate, causing intracellular sequestration of radioactivity. Thymidine kinase 1 is a principal enzyme in the salvage pathway of DNA synthesis. Therefore, FLT allows a non-invasive assessment of tumor proliferation as well as early response to chemotherapy by PET [28]. The role for FLT PET imaging in oncology is in the identification of resistant tumor subvolumes and the possibility to monitor early treatment response rather than in tumor staging [2]. ^{18}F FLT has been used to monitor response to treatment in several types of cancer, such as glioblastoma [29], lung [30] and breast cancer [31]. Despite promising studies, FLT does not play a significant role in clinical setting. This is in part due to its relatively lower uptake in comparison with FDG, affecting the detection and its sensitivity. However, FLT can have advantages over FDG regarding monitoring response to treatment such as better imaging of brain tumors, increased sensitivity to therapies that have higher effect on cell division than on glucose uptake (cytostatic therapies) and possibly lower uptake due to inflammatory response [32]. These features implicate the need to modify analogues with more favorable uptake.

Copper-64 (^{64}Cu) radioisotopes are also important medical radionuclides due to its physical characteristics such as half-life of 12.7 h, beta negative decay with energy of 190.2 KeV as well as positron and gamma emission with $E_{\text{average}} = 280.2 \text{ KeV}$; $E_{\text{max}} = 660 \text{ KeV}$ and 1346 KeV [33]. These characteristics enable this radionuclide to be used both in PET imaging and for radionuclide radiotherapy. Copper radioisotopes can be found in two different oxidation states, Cu^{+1} and Cu^{+2} , that permits its conjugation into different molecules, constituting radiopharmaceuticals for PET imaging of cancer. The well-established coordination chemistry of copper radioisotopes allows for its reaction with a wide variety of chelator agents that can be further linked to antibodies, peptides, proteins and nanostructured nanomaterials [34].

Fujibayashi et al. [35] developed a neutral lipophilic complex dia-cetyl-2,3-bisN4-methyl-3-thiosemicarbazone (^{64}Cu -ATSM) that have interesting hypoxia-selective properties. This is important clinically as it is well known that hypoxia is correlated to tumor aggressiveness, resistance to radiotherapy and chemotherapy, increased risk of invasion and metastasis and poor prognosis [28]. Thus the ability to quantifying the extent of hypoxic tissue within a mass may be important to develop a therapeutic platform with greater success rates. A similar compound, ^{64}Cu -diacetyl-bis ethylthiosemicarbazone (^{64}Cu -ATSE), has a wider tissue-oxygenation level specificity than ^{64}Cu -ATSM and, in clinical trials, have provided

images of tumor hypoxia that improved the clinical outcome of patients submitted to external beam radiotherapy [36].

Another PET tracer that is available for imaging regions of hypoxia, is the 2-nitroimidazole derivative [^{18}F]-fluoromisonidazole (^{18}F -FMISO). In hypoxic cells FMISO maintains the extra electron because of O_2 shortage and therefore is not cleared from the cells [37]. ^{18}F FMISO has been explored for its ability to predict therapeutic response. Several parameters derived from FMISO PET and MR imaging were found to be the most significant predictors of survival such as hypoxia volume, hypoxia surface area, and tumor-to-blood uptake ratio [38,39].

Gallium-68 (^{68}Ga) is one the earliest discovered positron-emitting radioisotope to be applied in nuclear medicine. In the early 1960s, Gottschalk and co-workers initialized the clinical use of ^{68}Ga aiming to investigate processes related to central nervous system [40]. The Germanium-68/gallium-68 generator has been investigated since 1970's and constituted an important advance in clinical applications since it does not require the use of cyclotron accelerators, allowing imaging with a reduced cost. The use of labeled peptides, particularly somatostatin analogues, are used in the diagnosis and therapy monitoring of tumors expressing somatostatin receptors (SSTR), mainly neuroendocrine tumors (NET) [41].

Chelator-conjugated somatostatin analogues have been developed more recently which include, DOTATATE, DOTANOC and DOTATOC [42–44]. ^{68}Ga -DOTATATE was recently approved by the US Food and Drug Administration as an imaging agent for the detection of NET [45]. ^{68}Ga -DOTATATE PET has proved a significantly higher sensitivity in detecting primary and metastatic NET than the traditional ^{111}In -pen-tetreotide SPECT, especially for the gastro-entero-pancreatic NETs. Recently, Walker et al. [46] have evaluated the potential of ^{68}Ga -DOTATATE for diagnosis of indeterminate pulmonary nodules (IPN) showing an equivalent accuracy but better specificity of ^{68}Ga -DOTATATE with the one of ^{18}F FDG in the diagnosis of non-neuroendocrine lung cancer.

2.3. Considerations for diagnostic imaging

Among nuclear medicine procedures, scintigraphy is the most established modality within imaging techniques since is widely available in most hospitals. However, the most important advantages of PET imaging over SPECT is the capacity for greater spatial resolution and sensitivity (by approximately two to three orders of magnitude), the ability to detect and record a higher percentage of the emitted events, which leads to improved image quality, improved temporal resolution and the possibility of performing shorter scans. In the recent years, the molecular imaging field has tended toward the use of PET imaging not only because of its sensitive advantage but also due to the increasing availability of PET imaging isotopes and its radiolabeling methods optimization [47]. A great number of PET isotopes have been increasingly used in the last years, ranging from short-lived types such as ^{15}O , ^{11}C , ^{13}N , ^{82}Rb to radioisotopes with longer half-lives, such as ^{76}Br , ^{86}Y , ^{89}Zr , and ^{124}I [48–50].

3. New radiolabeled probes for monitoring cancer therapy

3.1. Molecules

Molecular imaging has become an indispensable tool with the potential to revolutionize the medical community, not only for diagnostic purposes but also for therapeutic strategies, especially considering the ability to leverage these tools for personalized care. Active monitoring of tumor response to treatment is essential for a rapid evaluation that can be titrated to improve a patients' quality of life [3,51]. Several tracers have been employed for biological imaging that are important for cancer staging, treatment selection, and response monitoring. Also, regardless of the treatment of choice, several tumor characteristics, such as vascularity, hypoxia, glycolysis rate and tumor-cell proliferation have been identified to have prognostic and response monitoring potential [39]. In the recent years, new imaging probes with potential for diagnosis and monitoring cancer therapy have been developed from tumor receptors and/or biomarkers, and are summarized in Table 1.

Stammes and co-workers [52] reported a near-infrared fluorescent (NIRF) carboxylated cyanine dye (HQ4) that also possess strong necrosis avidity properties that can be employed to determine the efficacy of chemotherapy by monitoring therapy-induced tumor necrosis. For an optimal whole body imaging, HQ4 was functionalized with DTPA and radiolabeled with ^{111}In for SPECT images. SPECT and biodistribution studies were used in preclinical mice models of breast cancer following cyclophosphamide treatment. These studies showed a higher amount of radioactivity in chemotherapy-treated tumors compared to untreated controls (Fig. 1). The radiotracer [^{111}In]DTPA-HQ4, therefore, has been shown to have the potential to be clinically translated for diagnostic-prognostic purposes and to predict early treatment outcome of anticancer treatments.

An increased apoptotic index of tumor cells during treatment in preclinical and clinical studies represents a good prognostic indicator. As such, noninvasive imaging of apoptosis provides a potentially valuable approach for evaluating early tumor response in therapies. In this sense, Luo et al. [3] validated the feasibility of $^{99\text{m}}\text{Tc}$ -duramycin as a potential apoptosis probe for monitoring tumor response to paclitaxel in breast cancer xenografts. Biodistribution studies and SPECT images showed a higher tumor uptake for the treated group that could be related to increasing apoptosis ratio. Target-to-nontarget ratio (tumor-to-muscle ratio) was two-fold increased for the group treated with pacli-taxel, which suggests that $^{99\text{m}}\text{Tc}$ -duramycin may serve as a potential apoptosis imaging probe [3].

Epidermal growth factor receptor mutant III (EGFRvIII) is exclusively expressed in tumors. This featured provides an opportunity for the development of an imaging approach for early detection, diagnosis and prognosis of patients with EGFRvIII positive tumors. Liu et al. [53] developed a nuclear molecular imaging probe by labeling a novel anti-EGFRvIII monoclonal antibody, 4G1, with iodine-125 and evaluating its potential to detect EGFRvIII expression in glioblastoma xenograft models by SPECT imaging. SPECT/CT and bio distribution studies, using tumor-bearing BALB/c nude mice, showed higher tumor uptake in models that express EGFRvIII when compared to the wild-type (Fig. 2). The results suggest that the radiolabeled 4G1 mAb is a promising probe to detect EGFRvIII expression *in vivo* by nuclear medicine imaging.

Angiogenesis is essential for the growth and metastasis of solid tumors. Tumors are unable to grow beyond 1–2 mm³ in size without the neovasculature providing oxygen and nutrients [54]. Radiolabeled RGD (arginyl-glycyl-aspartic acid) peptides allow specific and noninvasive *in vivo* imaging of integrin $\alpha_v\beta_3$ expression, a receptor overexpressed in the early stages of angiogenesis. Capitalizing on this feature, Shi et al. [55] used a radiolabeled 3PRGD2, a novel PEGylated RGD dimer probe, to monitor the efficacy of Endostar antiangiogenic therapy. ⁶⁸Ga-3PRGD2 PET imaging was performed in Endostar treated/untreated Lewis Lung Carcinoma (LLC) mice on days 3, 7, 14, and 21 post-treatment. PET image showed changes in tumor uptake after antiangiogenic therapy earlier than ¹⁸F FDG metabolic response used as a control group. This could be related to the Endostar inhibition of the newly formed vascular endothelial cells, leading to the decrease of integrin expression, with consequent decrease of tumor uptake. Hence, ⁶⁸Ga-3PRGD2 is a promising platform that merits further development.

Terry and co-workers [51] evaluated head and neck squamous cell carcinoma (HNSCC) xenograft models to determine whether ¹¹¹In-RGD2 can monitor responses to antiangiogenic or radiation therapy at early stages. The results showed that treatment of mice with bevacizumab, sorafenib, or radiotherapy was effective in inhibiting tumor growth. However, in antiangiogenic therapy, the radiotracer could not detect any changes in tumor uptake. Otherwise, in irradiation experiments, ¹¹¹In-RGD2 proved to be a good, early, and sensitive tool to monitor changes in angiogenesis.

The exposition of phosphatidylserine (PS) from the cell membrane is associated with most cell death programs. This feature makes PS an attractive target for imaging overall cell death response in patients following drug treatment. To this end, Wang and co-workers [56] evaluated a macrocycle coordination complexes with cyclic polyamine labeled with carbon-11 (¹¹C-CyclenZn2) as a new PET probe for cell death imaging. Kunming mice were subcutaneously inoculated with S-180 fibrosarcoma cells. The treatment group received a single dose of cyclophosphamide. PET images showed that the tumor-to-muscle ratios for the treated group were significantly higher than for non-treated mice, due to the induced apoptosis. ¹¹C-CyclenZn2 is, therefore, a promising PET tracer for noninvasively monitoring tumor cell death following anti-cancer chemotherapy.

Among transmembrane receptors, HER2 is particularly important and one of the most highly characterized, particularly in breast cancer patients. HER2-positive primary tumors are associated with high mortality rates among patients. Zhang et al. [57] evaluated SPECT imaging of ^{99m}Tc-peptide-Z_{HER2:342}, an affibody molecule with high affinity for HER2, for monitoring the therapeutic response to trastuzumab in nude mice bearing HER2-positive SKOV-3 xenografts. Imaging was performed before treatment as well as 8 and 15 days after administration of the therapeutic agent. SPECT images showed no difference in tumor uptake between trastuzumab-treated and control group before treatment. However, there was a significant decrease in target-to-nontarget ratios in trastuzumab-treated mice on day 8 and 15, when compared with mice of the control group. The early response to trastuzumab in mice bearing SKOV-3 xenografts was successfully monitored by SPECT imaging using ^{99m}Tc-peptide-Z_{HER2:342}. Collectively, these studies clearly demonstrate the feasibility of

radiolabeled small molecules as a platform for the early noninvasive imaging to better evaluate treatment response using PET and SPECT in preclinical and clinical studies.

3.2. Nanoparticles

Biomedical imaging using nanoparticles (NPs) can provide or enhance the distinction of normal from diseased tissue, whether that be tumor margins for image guided surgery, sentinel lymph node (SLN) drainage in metastatic cancer, or even identifying sites of inflammation. Nanoparticles are structures that are nanometers in size and have an unusually large available surface area per unit of volume NPs have been extensively studied for biological applications since their small size allow extravasation from endothelial cell while also being able to carry a relatively high amount of therapeutic and/or diagnostic agents [65].

Their biggest advantage relies on a key factor: multifunctionality. NPs can be synthesized from different materials and can be designed to have different chemical compositions, surface chemical characteristics, structural components, shapes and sizes which expands its functional capabilities as potentially effective versatile tools for tumor detection and treatment [66]. In addition to being engineered with receptor specific ligands that can allow a preferential accumulation of the NPs in the diseased tissue, NPs are unique in a sense of also being to accumulate at tumor tissues by exploiting the anatomical differences between normal and diseased tissues through the enhanced permeability and retention (EPR) effect. The EPR effect is based on the fact that the tumor vasculature is leaky and allow NPs penetration while the lymphatic drainage is not efficient, resulting in a prolonged retention of the nanosystems in tumor tissues [67].

More than 40 nanomedicines have already been approved for clinical use and experimental nanotechnologies have the potential to revolutionize diagnosis and care [68]. NPs have also emerged as clinically relevant platforms not only for therapeutic agents, but also for radiotracers. This recently developed expansion of nanomedicine branch is referred to as “radionanomedicine”, which relies on the labeling of radionuclides onto nanomaterials for use both in diagnosis and therapy [69].

In biomedical imaging, NPs can provide or enhance the distinction of normal from diseased tissue, whether that be tumor margins for image guided surgery, sentinel lymph node (SLN) drainage in metastatic cancer, or even identifying sites of inflammation [70]. In this context, radiolabeled nanoparticles as theranostic agents have been widely used and summarized in recent review articles [71–75]. However, the use of radiolabeled NPs in monitoring tumor therapy efficacy has not been well explored and, to the best of our knowledge, only a few reports have been published to date.

Variability of patient response to nanotherapy-based treatments is still a concern in the clinical settings and it is believed to result from unpredictable tumor permeability and drug clearance heterogeneity [76]. Utilizing inclusion criteria, Perez-Medina et al.[77] developed a PET nanoreporter able to predict therapeutic outcome in individual subjects. The nanoreporter (^{89}Zr -NRep) consisted of a pegylated liposome labeled with Zirconium-89, using desferrioxamine B (DFO) as a chelator, and presented highly similar physicochemical

characteristics (size exclusion chromatography retention time, dynamic light scattering size measurements and zeta potential) as the clinically approved anti-cancer liposomal formulation Doxil® [78], indicated for the treatment of Recurrent Ovarian Cancer, Multiple Myeloma nad AIDS-related Kaposi's sarcoma. The rationale behind this study was that the liposomal nanoreporter could be co-injected with the already largely used Doxil® and correlate with its tumor uptake, thereby predicting its therapeutic outcome. In fact, after intravenous co-injection of Doxil (20 mg kg⁻¹) and ⁸⁹Zr-NRep (1 mCi kg⁻¹) in 4T1 tumor-bearing mice, they demonstrated a strong correlation between DOX and ⁸⁹Zr in circulation ($r = 0.96$, $p * 0.0001$), as well as between the DOX and ⁸⁹Zr-NRep at 6, 24 and 47 h after co-administration of both compounds ($n = 24$). Furthermore, they reported a strong correlation ($r = 0.97$, $p * 0.01$) between uptake values determined by PET (24 h post-injection) and DOX levels in tumors. These studies suggest that ⁸⁹Zr-NRepPET-derived uptake can serve as an inclusion criterion of treatment efficacy and indicator as it predicted therapeutic outcome.

In the prior section it was highlighted that the imaging of apoptosis can allow non-invasive assessment of disease states and response to therapeutic intervention for a variety of diseases, including cancer, as anti-tumor drugs often lead to apoptosis [79]. Zhang et al. [80] synthesized a PEG coated, core cross-linked polymeric micelles (CCPM), conjugated with annexin A5. This is a targeting ligand for the specific binding and detection of phosphatidylserine (PS) a component of the cell membrane that externalizes to the outer surface in the early stage of apoptosis. The micelles were dually labeled with near-infrared fluorescence fluorophore and ¹¹¹In and the effect of apoptosis was evaluated in EL4 lymphoma bearing mice following cyclophosphamide and etoposide treatment. The biodistribution of ¹¹¹In-labeled Annexin AD-CCPM was studied and the results are represented in Fig. 3. ¹¹¹In-la-beled micelles showed significantly higher uptake in the tumors of the treated mice (8.01%ID/g) when compared with the tumors of the untreated mice (3.2%ID/g) ($p * 0.001$). In addition, the tumor-to-blood ratios were 2.2 in the untreated group versus 4.1 in the treated group, while the tumor-to-muscle ratios were 14.8 and 38.8 in the untreated group and treated groups respectively, demonstrating that this platform could be used to apoptosis as a function of the anti-tumor therapeutic effect.

The complexity and heterogeneity of tumors make it clear that careful patient selection is required to identify those most likely to benefit from a given nanotherapy. Ideally, patients that are targeted to receive nanoparticle-based chemotherapeutics, should be evaluated individually for tumor accumulation and the treatment selection should be based accordingly. In this sense, radiolabeled nanoparticles could serve as an invaluable tool to predict the bio distribution of drug delivery systems as well as to individualize and optimize cancer therapy during the treatment period. More importantly, nanoparticles could also serve as instruments for mapping intra-tumoral deposition and drug release. This is especially important given the intra-tumoural distribution of nanoparticles is not homogeneous but is affected by factors such as interstitial fluid pressure (IFP), blood flow, diffusion and stroma thickness [81]. As a result, the central core of tumors, which are often hypoxic and necrotic, tend to show decreased NP accumulation. On the practical side, this can lead to the development of nanomedicines with comparable tumor uptakes resulting in different treatment outcomes because of differences in intra-tumoral distribution. Understanding and

overcoming the heterogeneity in tumor distribution is key to future success. During treatment, changes in the tumor microenvironment, including vascularization, can affect NP uptake [82]. The role of concurrent therapy is another factor to consider, as an example pharmacologic agents affecting blood pressure and vascular permeability may alter nanoparticle delivery and heterogeneity within the tumor. In addition, other therapeutic modalities may influence blood vessels and endothelial cells within solid tumors [82]. These factors may limit NPs ability to monitor drug therapy. Treatment itself influences the tumor microenvironment. When tumor cells become necrotic or apoptotic, the area becomes less angiogenic and hypoxic. As such, the vasculature can become leaky and compromise NP accumulation through EPR. Ideally radiolabeled NPs can be targeted to tumor — specific markers and potentially revolutionize not only cancer diagnosis and therapy, but also treatment monitoring.

4. Conclusion and future perspectives

The role of molecular imaging in cancer diagnosis, therapy and monitoring is continually evolving. Based on the information provided in this review, SPECT and PET imaging agents, including those that target non-specific tumor properties such as metabolism, cellular proliferation and apoptosis, can be used for therapeutic response monitoring, for early identification of non-responders, for which the strategy should be changed, and potentially as prognostic and adjunct agents for individualized care. In addition, non-invasive techniques for imaging tissue function that can give an early evidence of therapeutic response can be used as indicators of drug efficacy and as predictors of the most effective therapy at an early stage of treatment in the clinical settings, which is a valuable tool for improving the outcome. For that, therapeutic interventions response assessment should provide feedback that can guide follow-up regimens. The rationale is a rapid response prediction after each cycle of treatment, so that timely adjustments can be made long before the conventional endpoints. This has been successfully explored with radiolabeled small molecules but has rarely been demonstrated with the use of nanoparticles, probably owing to their relatively large sizes and limited access to intracellular targets, making them suboptimal or even inadequate for the task. As the case may be, nanoparticles, in accordance to Chen et al. [67] can find applications in sensing a change in the tumor microenvironment that is relevant to progression in therapy and this needs to be more in depth explored.

Acknowledgments

The authors would like to thank CNPq (Conselho Nacional de Desenvolvimento Científico e Tecnológico) and FAPEMIG (Fundo de Amparo a Pesquisa do Estado de Minas Gerais) for their financial support.

References

- [1]. Siegel RL, Miller KD, Jemal A, Cancer statistics, CA Cancer J. Clin 67 (2017) (2017) 7–30, 10.3322/caac.21387. [PubMed: 28055103]
- [2]. Brindle K, New approaches for imaging tumour responses to treatment, Nat. Rev. Cancer 8 (2008) 94–107. [PubMed: 18202697]
- [3]. Luo R, Niu L, Qiu F, Fang W, Fu T, Zhao M, Zhang Y-J, Hua Z-C, Li X-F, Wang F, Monitoring apoptosis of breast cancer xenograft after paclitaxel treatment with ^{99m}Tc-labeled duramycin SPECT/CT, Mol. Imaging 15 (2016).

- [4]. Liang J, Chen Y, Huang Z, Zhao Y, He L, Early chemotherapy response evaluation in tumors by ^{99m}Tc-DTPA-DG, *Cancer Biother. Radiopharm* 23 (2008) 363–370, 10.1089/cbr.2007.0446. [PubMed: 18593369]
- [5]. Fernandes RS, Dos Santos Ferreira D, de Aguiar Ferreira C, Giammarile F, Rubello D, de Barros ALB, Development of imaging probes for bone cancer in animal models. A systematic review, *Biomed. Pharmacother* 83 (2016) 1253–1264. [PubMed: 27565848]
- [6]. de Barros A, Tsourkas A, Saboury B, Cardoso V, Alavi A, Emerging role of radiolabeled nanoparticles as an effective diagnostic technique, *EJNMMI Res.* 2 (2012) 39, 10.1186/2191-219X-2-39. [PubMed: 22809406]
- [7]. Bauerle T, Semmler W, Imaging response to systemic therapy for bone metastases, *Eur. Radiol* 19 (2009) 2495–2507. [PubMed: 19468736]
- [8]. Kurdziel KA, Ravizzini G, Croft BY, Tatum JL, Choyke PL, Kobayashi H, The evolving role of nuclear molecular imaging in cancer, *Expert Opin. Med. Diagn* 2 (2008) 829–842, 10.1517/17530059.2.7.829. [PubMed: 19122861]
- [9]. Banerjee S, Pillai MR, Ramamoorthy N, Evolution of Tc-99 m in diagnostic radiopharmaceuticals, *Semin. Nucl. Med* 31 (2001) 260–277. [PubMed: 11710769]
- [10]. Czepczynski R, Gryczynska M, Ruchala M, ^{99m}Tc-EDDA/HYNIC-TOC in the diagnosis of differentiated thyroid carcinoma refractory to radioiodine treatment, *Nucl. Med. Rev. Cent. East. Eur* 19 (2016) 67–73. [PubMed: 27479883]
- [11]. Artiko V, Afgan A, Petrovic J, Radovic B, Petrovic N, Vlajkovic M, Sobic-Saranovic D, Obradovic V, Evaluation of neuroendocrine tumors with ^{99m}Tc-EDDA/HYNIC TOC, *Nucl. Med. Rev. Cent. East. Eur* 19 (2016) 99–103. [PubMed: 27479786]
- [12]. Sergieva S, Robev B, Dimcheva M, Fakirova A, Hristoskova R, Clinical application of SPECT-CT with ^{99m}Tc-Tektrotyd in bronchial and thymic neuroendocrine tumors (NETs), *Nucl. Med. Rev. Cent. East. Eur* 19 (2016) 81–87. [PubMed: 27479885]
- [13]. Sundin A, Arnold R, Baudin E, Cwikla JB, Eriksson B, Fanti S, ENETS consensus guidelines for the standards of care in neuroendocrine tumors: radiological, nuclear medicine and hybrid imaging, *Neuroendocrinology* (2017), 10.1159/000471879 (in press).
- [14]. Bozkurt MF, Virgolini I, Balogova S, Beheshti M, Rubello D, Decristoforo C, Guideline for PET/CT imaging of neuroendocrine neoplasms with ⁶⁸Ga-DOTA-conjugated somatostatin receptor targeting peptides and ¹⁸F-DOPA, *Eur. J. Nucl. Med. Mol. Imaging* 44 (2017) 1588–1601. [PubMed: 28547177]
- [15]. Trogrlic M, Tezak S, ^{99m}Tc-EDDA/HYNIC-TOC in management of patients with head and neck somatostatin receptor positive tumors, *Nucl. Med. Rev. Cent. East. Eur* 19 (2016) 74–80. [PubMed: 27479884]
- [16]. O'Connor MK, Morrow MMB, Hunt KN, Boughey JC, Wahner-Roedler DL, Connors AL, Rhodes DJ, Hruska CB, Comparison of Tc-99m maraciclalide and Tc-99m sestamibi molecular breast imaging in patients with suspected breast cancer, *EJNMMI Res.* 7 (2017) 5. [PubMed: 28091980]
- [17]. Ma Q, Chen B, Gao S, Ji T, Wen Q, Song Y, Zhu L, Xu Z, Liu L, ^{99m}Tc-3P4-RGD2 scintimammography in the assessment of breast lesions: comparative study with ^{99m}Tc-MIBI, *PLoS One* 9 (2014) 1–7, 10.1371/journal.pone.0108349.
- [18]. Novikov SN, Kanaev SV, Petr KV, Tatyana SY, Elena TA, Ludmila JA, Nikolay ID, Zhanna BV, Pavel KI, Technetium-99 m methoxyisobutylisonitrile scintimammography for monitoring and early prediction of breast cancer response to neoadjuvant chemotherapy, *Nucl. Med. Commun* 36 (2015) 795–801. [PubMed: 26011586]
- [19]. van der Lely AJ, de Herder WW, Krenning EP, Kwekkeboom DJ, Octreoscan radioreceptor imaging, *Endocrine* 20 (2003) 307–311. [PubMed: 12721512]
- [20]. Beaumont D, Herry JY, Sapene M, Bourguet P, Larzul JJ, de Labarthe B, Gallium-67 in the evaluation of sarcoidosis: correlations with serum angiotensin-converting enzyme and bronchoalveolar lavage, *Thorax* 37 (1) (1982) 11–18. [PubMed: 6280330]
- [21]. Steien S, Aaseth J, Thallium-201 as an agent for myocardial imaging studies, *Analyst* 120 (1995) 779–781. [PubMed: 7741228]

- [22]. Park BK, Kitteringham NR, Effects of fluorine substitution on drug metabolism: pharmacological and toxicological implications, *Drug Metab. Rev* 26 (1994) 605–643. [PubMed: 7924905]
- [23]. Jacobson O, Kiesewetter DO, Chen X, Fluorine-18 radiochemistry, labeling strategies and synthetic routes, *Bioconjug. Chem* 26 (2015) 1–18; [PubMed: 25473848]
- [24]. Weber WA, Ott K, Becker K, Dittler HJ, Helmberger H, Avril NE, Meisetschlager G, Busch R, Siewert JR, Schwaiger M, Fink U, Prediction of response to preoperative chemotherapy in adenocarcinomas of the esophagogastric junction by metabolic imaging, *J. Clin. Oncol* 19 (2001) 3058–3065. [PubMed: 11408502]
- [25]. Weber WA, Petersen V, Schmidt B, Tyndale-Hines L, Link T, Peschel C, Schwaiger M, Positron emission tomography in non-small-cell lung cancer: prediction of response to chemotherapy by quantitative assessment of glucose use, *J. Clin. Oncol* 21 (2003) 2651–2657. [PubMed: 12860940]
- [26]. Schelling M, Avril N, Nahrig J, Kuhn W, Romer W, Sattler D, Werner M, Dose J, Janicke F, Graeff H, Schwaiger M, Positron emission tomography using [(18)F]Fluorodeoxyglucose for monitoring primary chemotherapy in breast cancer, *J. Clin. Oncol* 18 (2000) 1689–1695. [PubMed: 10764429]
- [27]. Janssen MHM, Ollers MC, van Stiphout RGPM, Buijsen J, van den Bogaard J, de Ruyscher D, Lambin P, Lammering G, Evaluation of early metabolic responses in rectal cancer during combined radiochemotherapy or radiotherapy alone: sequential FDG-PET-CT findings, *Radiother. Oncol* 94 (2010) 151–155. [PubMed: 20116114]
- [28]. Teng FF, Meng X, Sun X-D, Yu JM, New strategy for monitoring targeted therapy: molecular imaging, *Int. J. Nanomed* 8 (2013) 3703–3713.
- [29]. Schiepers C, Dahlbom M, Chen W, Cloughesy T, Czernin J, Phelps ME, Huang S, Kinetics of 3'-deoxy-3'-18F-fluorothymidine during treatment monitoring of recurrent high-grade glioma, *J. Nucl. Med* 51 (2010) 720–727 [PubMed: 20395318]
- [30]. Mileschkin L, Hicks RJ, Hughes BGM, Mitchell PLR, Charu V, Gitlitz BJ, Macfarlane D, Solomon B, Amler LC, Yu W, Pirzkall A, Fine BM, Changes in 18F-fluorodeoxyglucose and 18F-fluorodeoxythymidine positron emission tomography imaging in patients with non-small cell lung cancer treated with erlotinib, *Clin. Cancer Res* 17 (2011) 3304–3315. [PubMed: 21364032]
- [31]. Humbert O, Cochet A, Coudert B, Berriolo-Riedinger A, Kanoun S, Brunotte F, Fumoleau P, Role of positron emission tomography for the monitoring of response to therapy in breast cancer, *Oncologist* 20 (2015) 94–104. [PubMed: 25561512]
- [32]. Gambhir SS, Molecular imaging of cancer with positron emission tomography, *Nat. Rev. Cancer* 2 (2002) 683–693. [PubMed: 12209157]
- [33]. Asabella AN, Cascini GL, Altini C, Paparella D, Notaristefano A, Rubini G, The copper radioisotopes: a systematic review with special interest to 64 Cu, *BioMed Res. Int* 2014 (2014) 1–9.
- [34]. Niccoli Asabella A, Cascini GL, Altini C, Paparella D, Notaristefano A, Rubini G, The copper radioisotopes: a systematic review with special interest to 64Cu, *Biomed Res. Int* 2014 (2014) 786463. [PubMed: 24895611]
- [35]. Fujibayashi Y, Taniuchi H, Yonekura Y, Ohtani H, Konishi J, Yokoyama A, Copper-62-ATSM: a new hypoxia imaging agent with high membrane permeability and low redox potential, *J. Nucl. Med* 38 (1997) 1155–1160. [PubMed: 9225812]
- [36]. Bourgeois M, Rajerison H, Guerard F, Mougins-Degraef M, Barbet J, Michel N, Cherel M, Faivre-Chauvet A, Gustin J-F, Contribution of [164Cu]-ATSM PET in molecular imaging of tumour hypoxia compared to classical [18F] – MISO – a selected review, *Nucl. Med. Rev* 14 (2011) 90–95.
- [37]. Lee ST, Scott AM, Hypoxia positron emission tomography imaging with 18f-fluoromisonidazole, *Semin. Nucl. Med* 37 (2007) 451–461. [PubMed: 17920352]
- [38]. Kobayashi H, Hirata K, Yamaguchi S, Terasaka S, Shiga T, Houkin K, Usefulness of FMISO—PET for glioma analysis, *Neurol. Med. Chir. (Tokyo)* 53 (2013) 773–778. [PubMed: 24172591]

- [39]. Bussink J, Kaanders JHAM, van der Graaf WTA, Oyen WJG, PET-CT for radiotherapy treatment planning and response monitoring in solid tumors, *Nat. Rev. Clin. Oncol* 8 (2011) 233–242. [PubMed: 21263464]
- [40]. Banerjee SR, Pomper MG, Clinical applications of gallium-68, *Appl. Radiat. Isot. Incl. Data Instrum. Methods Use Agric. Ind. Med* 76 (2013) 2–13.
- [41]. Al-Nahhas A, Win Z, Szyszko T, Singh A, Nanni C, Fanti S, Rubello D, Gallium-68 PET: a new frontier in receptor cancer imaging, *Anticancer Res.* 27 (2017) 4087–4094
- [42]. Yamaga LYI, Cunha ML, Campos Neto GC, Garcia MRT, Yang JH, Camacho CP, Wagner J, Funari MBG, 68Ga-DOTATATE PET/CT in recurrent medullary thyroid carcinoma: a lesion-by-lesion comparison with 111In-octreotide SPECT/CT and conventional imaging, *Eur. J. Nucl. Med. Mol. Imaging* 44 (2017) 1588–1601. [PubMed: 28547177]
- [43]. Deroose CM, Hindie E, Kebebew E, Goichot B, Pacak K, Taieb D, Imperiale A, Molecular imaging of gastroenteropancreatic neuroendocrine tumors: current status and future directions, *J. Nucl. Med* 57 (2016) 1949–1956. [PubMed: 27811124]
- [44]. Sawicki LM, Deuschl C, Beiderwellen K, Ruhlmann V, Poeppel TD, Heusch P, Lahner H, Fuhrer D, Bockisch A, Herrmann K, Forsting M, Antoch G, Umutlu L, Evaluation of 68Ga-DOTATOC PET/MRI for whole-body staging of neuroendocrine tumours in comparison with 68Ga-DOTATOC PET/CT, *Eur. Radiol* (2017), 10.1007/s00330-017-4803-2.
- [45]. Barrio M, Czernin J, Fanti S, Ambrosini V, Binse I, Du L, Eiber M, Herrmann K, Fendler WP, The impact of somatostatin receptor-directed PET/CT on the management of patients with neuroendocrine tumor: a systematic review and meta-analysis, *J. Nucl. Med* 58 (2017) 756–761. [PubMed: 28082438]
- [46]. Walker R, Deppen S, Smith G, Shi C, Lehman J, Clanton J, Moore B, Burns R, Grogan EL, Massion PP, 68Ga-DOTATATE PET/CT imaging of indeterminate pulmonary nodules and lung cancer, *PLoS One* 12 (2017) e0171301. [PubMed: 28182730]
- [47]. de C, Ferreira A, Fuscaldi LL, Townsend DM, Rubello D, de Barros ALB, Radiolabeled bombesin derivatives for preclinical oncological imaging, *Biomed. Pharmacother* 87 (2017) 58–72. [PubMed: 28040598]
- [48]. Conti M, Eriksson L, Physics of pure and non-pure positron emitters for PET: a review and a discussion, *EJNMMI Phys.* 3 (2016), 10.1186/s40658-016-0144-5.
- [49]. Mcquade P, McCarthy DW, Welch MJ, 11 Metal Radionuclides for PET Imaging, (2003), pp. 251–264.
- [50]. Deri MA, Zeglis BM, Francesconi LC, Lewis JS, PET imaging with (89)Zr: from radiochemistry to the clinic, *Nucl. Med. Biol* 40 (2013) 3–14. [PubMed: 22998840]
- [51]. Terry SYA, Abiraj K, Lok J, Gerrits D, Franssen GM, Oyen WJG, Boerman OC, Can 111In-RGD2 monitor response to therapy in head and neck tumor xenografts? *J. Nucl. Med* 55 (2014) 1849–1855. [PubMed: 25349221]
- [52]. Stammes MA, Knol-Blankevoort VT, Cruz LJ, Feitsma HRIJ, Mezzanotte L, Cordfunke RA, Sinisi R, Dubikovskaya EA, Maeda A, DaCosta RS, Bierau K, Chan A, Kaijzel EL, Snoeks TJA, van Beek ER, Lowik CWGM, Pre-clinical evaluation of a cyanine-based SPECT probe for multimodal tumor necrosis imaging, *Mol. Imaging Biol* 18 (2016) 905–915. [PubMed: 27277828]
- [53]. Liu X, Dong C, Shi J, Ma T, Jin Z, Jia B, Liu Z, Shen L, Wang F, Radiolabeled novel mAb 4G1 for immunoSPECT imaging of EGFRvIII expression in preclinical glioblastoma xenografts, *Oncotarget* 8 (2017) 6364–6375. [PubMed: 28031526]
- [54]. Chua TC, Yao P, Akther J, Morris DL, Impact of tumor angiogenesis in peritoneal mesothelioma after radical cytoreduction and hyperthermic intraperitoneal chemotherapy, *Pathol. Oncol. Res* 16 (2010) 217–222. [PubMed: 19789996]
- [55]. Shi J, Jin Z, Liu X, Fan D, Sun Y, Zhao H, Zhu Z, Liu Z, Jia B, Wang F, PET imaging of neovascularization with (68)Ga-3PRGD2 for assessing tumor early response to Endostar antiangiogenic therapy, *Mol. Pharm* 11 (2014) 3915–3922. [PubMed: 25158145]
- [56]. Wang H, Wu Z, Li S, Hu K, Tang G, Synthesis and evaluation of a radiolabeled bis-zinc(II)-cyclen complex as a potential probe for in vivo imaging of cell death, *Apoptosis* 22 (2017) 585–595. [PubMed: 28084570]

- [57]. Zhang J, Zhao X, Wang S, Wang N, Han J, Jia L, Ren X, Monitoring therapeutic response of human ovarian cancer to trastuzumab by SPECT imaging with (99m)Tc-peptide-Z(HER2:342), Nucl. Med. Biol 42 (2015) 541–546. [PubMed: 25735223]
- [58]. Liu Y, Jin X, Lan X, Lang J, Wen Q, An R, SPECT imaging of colorectal cancer by targeting CD133 receptor with 99mTc-labeled monoclonal antibody, Q. J. Nucl. Med. Mol. Imaging (2016), <http://www.ncbi.nlm.nih.gov/pubmed/27387378>.
- [59]. Hernández-Agudo E, Mondejar T, Soto-Montenegro ML, Megías D, Mouron S, Sanchez J, Hidalgo M, Lopez-Casas PP, Mulero F, Desco M, Quintela-Fandino M, Monitoring vascular normalization induced by antiangiogenic treatment with 18F-fluoromisonidazole-PET, Mol. Oncol 10 (2016) 704–718. [PubMed: 26778791]
- [60]. Larimer BM, Wehrenberg-Klee E, Caraballo A, Mahmood U, Quantitative CD3 PET imaging predicts tumor growth response to anti-CTLA-4 therapy, J. Nucl. Med 57 (2016) 1607–1611. [PubMed: 27230929]
- [61]. Beaino W, Nedrow JR, Anderson CJ, Evaluation of (68)Ga- and (177)Lu-DOTA-PEG4-LLP2A for VLA-4-targeted PET imaging and treatment of metastatic melanoma, Mol. Pharm 12 (2015) 1929–1938, 10.1021/mp5006917. [PubMed: 25919487]
- [62]. Khurana H, Meena VK, Prakash S, Chuttani K, Chadha N, Jaswal A, Dhawan DK, Mishra AK, Hazari PP, Preclinical evaluation of a potential GSH ester based PET/SPECT imaging probe DT(GSHMe)(2) to detect gamma glutamyl transferase over expressing tumors, PLoS One 10 (2015) e0134281. [PubMed: 26221728]
- [63]. Piert M, Shao X, Raffel DM, Davenport MS, Montgomery J, Kunju L, Hockley BG, Siddiqui J, Scott PJH, Chinnaiyan A, Rajendiran T, Preclinical evaluation of 11C-sarcosine as a substrate of proton-coupled amino acid transporters and first human application in prostate cancer, J. Nucl. Med (2017), 10.2967/jnumed.116.173179.
- [64]. Aung W, Tsuji AB, Sudo H, Sugyo A, Furukawa T, Ukai Y, Kurosawa Y, Saga T, Immunotargeting of integrin $\alpha 6 \beta 4$ for single-photon emission computed tomography and near-infrared fluorescence imaging in a pancreatic cancer model, Mol. Imaging 15 (2016)
- [65]. Lammers T, Aime S, Hennink WE, Storm G, Kiessling F, Theranostic nanomedicine, Acc. Chem. Res 44 (2011) 1029–1038. [PubMed: 21545096]
- [66]. Bhandare N, Narayana A, Nuclear Medicine & Radiation Therapy Applications of Nanotechnology in Cancer: A Literature Review of Imaging and Treatment, (2014), 10.4172/2155-9619.1000195.
- [67]. Parveen S, Misra R, Sahoo SK, Nanoparticles: a boon to drug delivery, therapeutics, diagnostics and imaging, Nanomedicine 8 (2012) 147–166. [PubMed: 21703993]
- [68]. Peer D, Karp JM, Hong S, Farokhzad OC, Margalit R, Langer R, Nanocarriers as an emerging platform for cancer therapy, Nat. Nano 2 (2007) 751–760.
- [69]. Lee DS, Im HJ, Lee YS, Radionanomedicine: widened perspectives of molecular theragnosis, Nanomed. Nanotechnol. Biol. Med 11 (2015) 795–810.
- [70]. Pratt EC, Shaffer TM, Grimm J, Nanoparticles and radiotracers: advances toward radionanomedicine, Wiley Interdiscip. Rev. Nanomed. Nanobiotechnol 8 (2016) 872–890. [PubMed: 27006133]
- [71]. Goel S, Chen F, Ehlerding EB, Cai W, Intrinsically radiolabeled nanoparticles: an emerging paradigm, Small 10 (2014) 3825–3830. [PubMed: 24978934]
- [72]. Ferro-Flores G, Ocampo-Garcia BE, Santos-Cuevas CL, Morales-Avila E, Azorín-Vega E, Multifunctional radiolabeled nanoparticles for targeted therapy, Curr. Med. Chem 21 (2014) 124–138. [PubMed: 23992338]
- [73]. Choi H, Lee Y, Hwang DW, Lee DS, Access O, Translational radionanomedicine: a clinical perspective, Radionanomed. Facil 8 (2016) 71–84.
- [74]. Morales-Avila E, Ferro-Flores G, Ocampo-Garcia BE, Gomez-Oliván LM, Engineered multifunctional RGD-gold nanoparticles for the detection of tumour-specific $\alpha(v)\beta(3)$ expression: chemical characterisation and ecotoxicological risk assessment, J. Biomed. Nanotechnol 8 (6) (2012) 991–999. [PubMed: 23030007]
- [75]. Xing Y, Zhao J, Conti PS, Chen K, Radiolabeled nanoparticles for multimodality tumor imaging, Theranostics 4 (2014) 290–306. [PubMed: 24505237]

- [76]. Prabhakar U, Maeda H, Jain RK, Sevick-Muraca EM, Zamboni W, Farokhzad OC, Barry ST, Gabizon A, Grodzinski P, Blakey DC, Challenges and key considerations of the enhanced permeability and retention effect for nanomedicine drug delivery in oncology, *Cancer Res.* 73 (2013) 2412–2417. [PubMed: 23423979]
- [77]. Pérez-Medina C, Abdel-Atti D, Tang J, Zhao Y, Fayad ZA, Lewis JS, Mulder WJM, Reiner T, Nanoreporter PET predicts the efficacy of anti-cancer nanotherapy, *Nat. Commun* 7 (2016) 11838. [PubMed: 27319780]
- [78]. Barenholz Y, Doxil(R)-the first FDA-approved nano-drug: lessons learned, *J. Control. Release* 160 (2012) 117–134. [PubMed: 22484195]
- [79]. Gerl R, Vaux DL, Apoptosis in the development and treatment of cancer, *Carcinogenesis* 26 (2005) 263. [PubMed: 15375012]
- [80]. Zhang R, Lu W, Wen X, Huang M, Zhou M, Liang D, Li C, Annexin A5-conjugated polymeric micelles for dual SPECT and optical detection of apoptosis, *J. Nucl. Med* 52 (2011) 958–964. [PubMed: 21571801]
- [81]. Chen H, Zhang W, Zhu G, Xie J, Chen X, Rethinking cancer nanotheranostics, *Nat. Rev. Mater* 2 (2017) 17024. [PubMed: 29075517]
- [82]. Andresen TL, Petersen AL, Hansen AE, Henriksen JR, Chapter 7 - Contribution of Nuclear Medicine to Cancer Nanotheranostics, *Nanotheranostics for Personalized Medicine*, (2017), pp. 147–190, 10.1142/9789814713535_0007.

Fig. 1.

Optical and SPECT imaging of [^{111}In]DTPAHQA in (a) control and (b) chemotherapy-treated MCF-7 tumor-bearing mice. Chemotherapy group received a single i.p. injection of cyclophosphamide (265 mg/kg) followed by i.v. injection of [^{111}In] DTPA-HQA 72 h later. Images were acquired 24 h after probe injection. Reproduced with permission from [52].

Fig. 2. SPECT/CT images of F98_{npEGFRvIII} and F98_{npEGFR} (wild-type) tumor-bearing mice at 4 and 24 h post-injection. ¹²⁵I-4G1 uptakes in F98_{npEGFRvIII} tumors were significantly higher than that in F98_{npEGFR} tumors at each time point. The arrows indicate the F98_{npEGFRvIII} and F98_{npEGFR} tumors. Reproduced with permission from [53].

Fig. 3.

Representative Dual SPECT/CT images of EL4 lymphoma apoptosis with ^{111}In -labeled annexin A5-CCPM in A) non-treated mouse and E) treated mouse. Representative fluorescence molecular tomographic images of B) non-treated mouse and F) treated mouse. Representative autoradiographs of excised tumors of C) non-treated group and G) treated group. Fluorescence images of the same slides used in autoradiographic studies in D) non-treated group and H) treated group. This research was originally published in JNM. R. Zhang, W. Lu, X. Wen, M. Huang, M. Zhou, D. Liang, C. Li, "Annexin A5-Conjugated Polymeric Micelles for Dual SPECT and Optical Detection of Apoptosis" J. Nucl. Med. 52 (2011) 958–964. The Society of Nuclear Medicine and Molecular Imaging, Inc © [80].

Table 1

Novel probes with potential for diagnosis and monitoring cancer therapy efficacy.

Imaging probe	Isotope	Targeting	Tumor type	Ref
Monoclonal antibody - SHNH-AC133	^{99m} Tc	CD133 expression	Cancer steam cells	[58]
Misonidazole	¹⁸ F	Hypoxia	Breast and pancreas	[59]
p-isothiocyanatobenzyl-deferoxamine-CD3	⁸⁹ Zr	Lymphocyte T cells (CD3)	Colon	[60]
DOTA-PEG4-LLP2A	⁶⁸ Ga/ ¹⁷⁷ Lu	Very late antigen-4 (VLA-4)	Malignant melanoma	[61]
DT (GSHMe) ₂ - Homobivalent peptide system	^{99m} Tc/ ⁶⁸ Ga	Gamma Glutamyl Transferase (GGT)	Ehrlich Ascites tumor (EAT)	[62]
Sarcosine	¹¹ C	Proton-coupled amino acid transporters (PAT)	Prostate	[63]
Human anti- $\alpha_6\beta_4$ monoclonal antibody (IgG1)	¹¹¹ In	$\alpha_6\beta_4$ integrin	Pancreas	[64]