Journal of Nuclear Medicine, published on July 3, 2020 as doi:10.2967/jnumed.119.236943

SPECT/CT - standing on the shoulders of giants, it is time to reach for the sky!

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Running title: SPECT/CT: State of the Art

Disclosure of Interest: OI is a consultant for General Electric Healthcare. No other potential conflicts of interest relevant to this article exist.

ABSTRACT

Twenty years ago single photon emission computed tomography/x-ray computed tomography (SPECT/CT) became commercially available, combining the strengths of both techniques: the diagnostic sensitivity of SPECT and the anatomic detail of CT. Other benefits initially included attenuation correction of SPECT reconstructions, ultimately evolving to correction techniques that would enable absolute tracer uptake quantification. Recent developments in SPECT hardware include solid state digital systems with higher sensitivity and resolution, using novel collimator designs based on tungsten. Similar advances in CT technology have been introduced in hybrid SPECT/CT systems, replacing low-end X-ray tubes, with high-end multislice CTs equipped with iterative reconstruction and metal artefact reduction algorithms, and dual-energy capabilities. More recently, the design of whole-body SPECT/CT systems has taken another major leap with the introduction of a ring-shaped gantry equipped with multiple movable detectors surrounding the patient. These exciting developments have fueled efforts to develop novel SPECT radiopharmaceuticals, creating new chelators and prosthetic groups for radiolabeling. Innovative SPECT radionuclide pairs have now become available for radiolabeling with the potential for use as theranostic agents. The growth of precision medicine and the associated need for accurate radionuclide treatment dosimetry will likely drive the use of SPECT/CT in the near future. In addition, expanding clinical applications of SPECT/CT in other areas such as orthopedics, offer exciting opportunities. While it is true that the SPECT/CT ecosystem has seen a number of challenges during its development over the past two decades, it is now a feature-rich and mature tool ready for clinical prime time.

NOTEWORTHY

- Current state-of-the-art hybrid SPECT/CT devices offer significant improvements in SPECT spatial resolution and sensitivity, accurate absolute tracer uptake quantification comparable with PET/CT, together with many advanced CT features (pages 9 and 11).
- Technical progress is driving renewed interest in SPECT radiopharmaceutical development, with promising recent advances in chemistry and labeling methods (page 15).
- More widespread use of radionuclide therapies and theranostics requires robust patient dosimetry and is one of the driving applications of SPECT/CT use (page 8).
- Rigorous standardization of SPECT/CT is the next priority to achieve reproducible, consistent and accurate quantification (page 13).
- Further multicenter, large scale, prospective studies are needed to provide evidence-based data on the clinical value of SPECT/CT (page 19).

INTRODUCTION

Mark Twain is famously supposed to have said that history does not repeat itself, but it does often rhyme. With some adaptation, this can be said of the introduction of hybrid imaging modalities in nuclear medicine, in particular when comparing single photon emission computed tomography/x-ray computed tomography (SPECT/CT) with positron emission tomography/x-ray computed tomography (PET/CT). Both were developed based on the premise that adding CT capabilities to the gamma or PET camera would not only solve the problem of correcting for signal attenuation, it would also open up the possibility of a one-stop shop of functional and anatomic imaging.

Under the hybrid paradigm, the combined result exceeds the sum of its parts by the synergy in individual strengths of the techniques (the diagnostic sensitivity for SPECT and anatomic detail for CT) while overcoming their mutually exclusive limitations (the diagnostic specificity for SPECT and sensitivity for CT). Despite these similarities, the speed at which both hybrid techniques were embraced in clinical practice, generated literature evidence, and impacted patient care has varied considerably. The significant differences in acceptance and implementation of the two hybrid modalities have sparked lively and contentious debates, assuming a winner-takes-all scenario (*1*).

While in the sprint to market success PET/CT has been victorious, we will argue that in the marathon of progress in hybrid imaging, SPECT/CT has become an effective, versatile, and mature modality 20 years after its commercial introduction (*2,3*). Its contribution to clinical progress in a wide spectrum of specialties was recently extensively reviewed (*4*). Instead, this paper will cover the SPECT/CT ecosystem by analyzing the lessons learned during its development and reviewing recent emerging applications,

progress in physics/engineering and radiopharmacy/chemistry that will collectively drive its future (Figure 1).

PIONEERING EARLY YEARS

The origins of SPECT, CT and the ultimate construction of the first integrated SPECT/CT devices have been reviewed in detail elsewhere, recognizing the tremendous academic efforts lying at its foundation (*5*). In particular, the pivotal work by Bruce H. Hasegawa and colleagues at the University of California San Francisco merits special attention (*6*). The first commercially available SPECT/CT devices used low performance X-ray tubes mounted on the same gantry as the SPECT detectors. This resulted in slow CT image acquisitions (up to 10 minutes), limiting throughput and increasing the risk of motion artefacts, with suboptimal anatomic detail (*7*). Nonetheless, the improvements in SPECT quantification by virtue of attenuation correction and improved localization of areas of increased tracer uptake generated great enthusiasm. In particular, cardiac and oncological imaging studies benefitted from the more reliable quantification and localization, respectively, as seen in the early published literature (Figure 2A).

Subsequently, attenuation correction was recommended for routine clinical use, followed by broader professional procedural guidance for SPECT/CT (*8*). It also quickly became clear that major differences existed in the implementation of these techniques between vendors and systems, leading to conflicting results in clinical use (*9*). At that time, the market had yet to decide which SPECT/CT design would ultimately prevail. This uncertainty fueled skepticism against the use of insufficiently validated and poorly standardized methods and contributed in part to a slow adoption of SPECT/CT in clinical practice (*10*). This was compounded by the rapid take-off of PET/CT which had the

advantage of being intrinsically quantitative and, in addition, was less prone to variation between vendors – or so it was perceived. It was a wake-up call that every innovation needs careful validation and standardization before clinical implementation, a lesson that reverberates even today (*11*).

IF A LITTLE IS GREAT, IS MORE BETTER?

Despite the clear anticipated advantages of SPECT/CT imaging, its clinical implementation was hampered by difficulties in defining key clinical areas of benefit. In the beginning it had been anticipated that only a fraction of patients would require a SPECT/CT acquisition, making the incorporation of high-end CT systems hard to justify from a cost-to-benefit perspective. As a result, striking the balance between image quality, price, and safeguarding patient throughput, all critical issues from a marketing point of view, proved difficult. Also, high-end CT capabilities were considered unnecessary given the low SPECT resolution and concerns regarding the CT-related additional radiation burden (*12*). On top of this, the flexibility in terms of mechanical design enabling detector movement, supported target organs/regions, and isotope energies demanded from SPECT systems remained higher compared to PET/CT. In essence, SPECT/CT devices had to offer familiarity and continuity to users in the clinical field on a level not demanded by early PET/CT systems. This required considerable trade-offs in gantry and collimator designs to maintain as much of this flexibility as possible, delaying major breakthroughs in improving SPECT resolution.

Even with its limited CT capabilities, the first generation SPECT/CT devices quickly produced exciting results in clinical practice (*13*). From 2004 onwards, the introduction of multislice CT demonstrated the incremental benefits of better CT image quality (*14*). 64-

slice CT capabilities emerged on high-end or dedicated SPECT/CT systems in 2006, mainly targeting cardiac applications (*15*). In practice however, most users continued to use limited-capability CT until the end of the first decade of SPECT/CT. A lack of clinical imaging guidelines defining what indications would benefit from hybrid SPECT/CT prolonged this situation.

This evolution was much easier for PET/CT, which at that time was – and arguably still remains – highly focused on whole-body acquisitions using a single photon energy in a homogeneous, mostly oncology, clinical setting. In contrast with SPECT, attenuation correction is required for virtually all PET studies and CT enabled fast and robust correction methods. Indeed, PET/CT devices with 64-slice CT systems were commercially available from 2005 and quickly ended the era of PET-only cameras. These superior CT capabilities also impacted non-oncological indications and caused a shift in cardiac imaging from SPECT/CT to PET/CT, an evolution that would prove difficult to reverse (Figure 2B).

The nuclear medicine community has struggled considerably in defining the appropriate type of CT required for SPECT/CT, leading to the appearance of confusing terminology such as “low-dose” or “high-dose” and “non-diagnostic” or “diagnostic” CT acquisition protocols. Each of these terms is associated with perceived positive or negative connotations concerning radiation exposure and clinical value. This ambiguity has needlessly complicated defining the clinical role of SPECT/CT. With the benefit of hindsight, SPECT/CT could have profited from a different paradigm, where the appropriate CT acquisition parameters are tailored according to the specific disease or diagnostic question (Figure 3) (*16*). Considerable effort will be required to harmonize

clinical practice in this respect, with recent guidelines for bone SPECT/CT being a very good initial attempt to define broad region-specific CT acquisition parameters (*17*).

COMING OF AGE AND READY FOR PRIME TIME!

High Level Features Coming Together

From approximately 2010 onwards, high-end multislice CT variants are part of all SPECT/CT portfolios. At the same time, iterative reconstruction techniques for CT were gradually introduced, reducing ionizing radiation doses up to 80% without loss of image quality and solving in part one of the initial barriers in the implementation of SPECT/CT (*18*). Around 2013, SPECT/CT as a hybrid modality had come of age, available with a full set of technical capabilities (enabling correction for attenuation, scatter, partial volume, and motion). This brought the potential for robust absolute quantification to clinical practice (Figure 4), with reported accuracies for ^{99m}Tc imaging to within ±5% of the true radionuclide concentration (*19,20*). Ironically, this technological progress was briefly overshadowed by a global ^{99m}Tc shortage that created doubt on the viability of SPECT/CT once more, as further discussed below.

Precision Medicine as Breakthrough Application

A renewed interest in radionuclide treatments using ^{90}Y and ^{177}Lu in oncology under the paradigm of precision medicine (popularized in nuclear medicine using the term theranostics) strongly relies on molecular tumor characterization and individualized treatment planning. While ^{90}Y has been one of the main radionuclides used for therapy, it has recently been surpassed by ^{177}Lu in theranostics applications. Its separate gamma and beta decay modes allow for imaging of the activity distribution and calculating the

dose distribution. It has now been recognized that individualized dosimetry is favored over fixed, or patient weight or body surface area based administered activities. This requires absolute activity measurements in order to deliver target doses that are as high as safely attainable and is only possible after correcting for degrading physical phenomena, such as photon scatter, photon attenuation, partial volume effect and detector dead time (*21*). Increasingly accurate correction techniques and iterative reconstruction methods have improved the capabilities of modern SPECT/CT systems to achieve high level quantitative images, comparable to PET/CT.

Tools to process an image in activity per unit volume have now become available, with acceptable accuracies in most organs and moderate-sized tumors. The *in vivo* accuracy of solid-state SPECT/CT quantification of ^{177}Lu-PSMA was recently reported to be within 20%, with challenges remaining in quantifying smaller structures (*22*). It is expected that quantification and dosimetry applications will drive further applications of SPECT/CT, as seen in literature citations today (Figure 2A).

Leveraging the Full Diagnostic Power of SPECT/CT

The improved capabilities of the embedded CT systems are benefitting the use of SPECT/CT in for example bone disease (Figure 2A). In addition, the novel multimodal SPECT reconstruction techniques can improve image resolution and have shown benefit in assessing uptake in small osseous structures (*23*). The availability of metal artefact reduction algorithms to reduce the degradation of CT images caused by photon-deprivation and beam-hardening artefacts have further improved the image quality of SPECT/CT. Another enhancement now available on SPECT/CT is dual-energy CT, which uses virtual monochromatic reconstructions for high-energy photons (140 keV) that are

less susceptible to metal artifacts (*24*). These breakthroughs have improved amongst others the assessment of painful arthroplasties, a diagnostic challenge increasing in prevalence due to changes in demographics. Moreover, SPECT/CT is less susceptible to image degrading artefacts in cases after arthroplasty compared to MRI, even with the recent improvements in MRI metal artefact reducing sequences technology.

The painful total knee arthroplasty (TKA) has been a successful model for developing the clinical application of high-end bone SPECT/CT. Consistent and relevant impact on patient management has been demonstrated with the potential for healthcare cost-savings, making SPECT/CT part of the routine diagnostic algorithm for patients with pain after primary TKA according to some leading groups (*25,26*). Exciting results are emerging in other post-operative skeletal settings including the spine, hip, and hand/foot pain as well (*27-29*). Further progress will require novel radiopharmaceuticals offering improved pharmacokinetics (e.g. next generation radiobisphosphonates) or visualizing specific causes such as infection (e.g. ^{99m}Tc-UBI-29-4), as further discussed below.

Despite the once grey-sky scenarios predicted by some for SPECT/CT imaging, current trends show a strong growth in the acceptance of state-of-the-art SPECT/CT devices. Recent data from Europe show a 22% increase in the number of installed SPECT/CT scanners in France from 2015 to 2018, with similar data from the UK and Germany available (*30*). While SPECT/CT has come of age and is a reliable hybrid imaging modality ready for prime time, some unique challenges will need to be addressed. In particular regarding the use of SPECT/CT in young patients (e.g. for the assessment of low back pain) which requires even more attention to exposure to ionizing

radiation and regional issues with reimbursement pending further evidence of cost-effectiveness.

PROGRESS IN PHYSICS AND ENGINEERING

Innovation in Detector and Collimator Design

Over the last few years, digital solid-state SPECT detector technology has become commercially available. Cadmium-Zinc-Telluride (CZT) detectors have excellent count sensitivity, system resolution, and energy resolution, enabling significant reductions in administered activities or acquisition time, as well as facilitating dynamic SPECT. Their superior energy resolution also facilitates dual-isotope imaging through improved separation of the photon peaks in the detected energy spectrum. The higher stopping power on the other hand allows for thinner detectors and a higher imaging resolution, in the order of 2.5 mm or even sub-mm range for preclinical systems (*31*). While these capabilities have been known for many years, issues such as slow and small crystal growth and crystalline defects hampered its cost-effective large-scale production, which have been solved only recently (*32*).

CZT itself is not a prerequisite of higher resolution systems and has intrinsic detector efficiencies similar to traditional systems. Yet, the smaller footprint and lighter weight of these detectors facilitated the construction of gantry designs optimized for specific anatomic regions, focusing primarily on cardiac imaging. The improved spatial resolution and sensitivity with novel detector arrangements in CZT cardiac cameras (*33*) were facilitated by the introduction of more sophisticated reconstruction algorithms (e.g.

Bayesian reconstruction) that could incorporate prior information about the expected characteristics of the image (*34*). For example, in one comparison between two dedicated cardiac CZT SPECT systems and conventional dual-head Anger camera, both the central spatial resolution (6.7-8.6 *versus* 15.0-15.3 mm) and count sensitivity on cardiac phantom images (460-850 *versus* 130 counts s^{-1} MBq^{-1}) were superior with the CZT systems (*33*). At present this technology is being incorporated into general-purpose dual- and multi-head SPECT/CT system designs (Figure 4) (*35,36*). Most importantly, reducing image acquisition times or lowering the injected radionuclide activity are now possible for cardiac studies (*37*) and are being explored for a wider range of nuclear medicine studies.

The availability of compact detectors with higher intrinsic spatial resolution, enabled the implementation of novel collimator designs in the clinic (*37,38*). This has been made possible by the use of tungsten and 3D printing techniques, delivering higher stopping power, smaller collimator bores, and septal thickness. These new materials make new collimator geometries possible that until now have been beyond reach or impractical to implement on a large scale. Examples include minifying multiple-pinhole collimators (allowing more projections per detector) and (multiple-slit) slit-slat collimators (combining the advantages of pinhole and parallel-hole collimators). Both these approaches may be the basis for developing fully stationary detector systems, which could represent the next revolution in SPECT gantry design. The resulting clinical SPECT images achieve resolutions down to 3 mm, with exciting preliminary clinical data in brain and cardiac imaging (*39*). However, the technique has not yet been implemented in hybrid SPECT/CT system designs.

The Next Major Leap Forward

A true paradigm shift in SPECT/CT design was unveiled in 2017, when the first 360° ring shaped gantry was introduced, equipped with 12 CZT-based elongated detectors that can move in- and outwards to come as close to the patient as possible. These detectors are equipped with novel tungsten parallel-hole collimators and move in a swiveling motion to provide a unique scanning geometry (*35*). While the clinical experience with this new device is still limited and the additional cost associated with this new design remains to be justified, preliminary results in bone imaging show that a whole-body SPECT acquisition of 20 minutes offers significant improvements in sharpness and contrast and can replace current bone scanning protocols (*40*). It is also signaling an important and inevitable milestone in nuclear medicine practice: the end of the planar imaging era. Indeed, now is the time to let go of the paradigm of the hybrid gamma camera as the jack of all trades, master of none.

Need for Standardization

The recent technological progress has created considerable variability among the available SPECT/CT systems, not only with respect to their physical designs, but also the algorithms used for image correction and reconstruction. Such discrepancies may result in inconsistent or inaccurate results, limiting reproducibility as seen early on with PET (*41*). Only rigorous standardization provided the solution to achieve reproducible, consistent and accurate quantification. This required a common quality control and quality assurance standard, as outlined in protocols by North American and European professional societies and groups (*42,43*).

Multiple collaborative groups have started ambitious projects aimed at standardizing quantitative SPECT/CT and creating protocols to determine the accuracy and uncertainties of specific dosimetry platforms (*11,44*). However, these have been hampered by a tendency to sacrifice user control of application settings and transparency in closed-source workstation solutions using proprietary algorithms in favor of easy-to-use interfaces. Other issues that complicate standardization are the increasing design differences between systems, defining the acceptable minimum level of image quality, and for the purpose of image quantification, validating the use of (often small) phantoms as accurate surrogates of patient geometry.

These observations should prompt a call-to-action from major professional societies and international bodies such as the SNMMI, EANM and IAEA, to launch initiatives to support the standardization of SPECT/CT quantification. Indeed, standardization and traceability are key requirements to harness the full potential of theranostic applications and provide truly individualized and high-quality patient care.

INNOVATIONS AND CHALLENGES IN SPECT RADIOPHARMACEUTICAL DEVELOPMENT

Strength and Challenges of SPECT Radionuclides

Improvements in SPECT/CT technology alone are not enough, as further adoption of the technique is critically linked to the development of novel SPECT radiopharmaceuticals. These remain highly attractive tools for imaging both in clinical practice as well as in preclinical research. A multitude of single-photon emitters are available (e.g. ^{99m}Tc, ^{111}In, ^{123}I) with longer half-lives than commonly used PET

radionuclides, facilitating their distribution to more remote locations. Also, SPECT tracers are relatively inexpensive, often available at a tenth of the cost of PET agents. Today, ^{99m}Tc is used in approximately 85% of all nuclear medicine diagnostic procedures, accounting for 30 million examinations worldwide every year (*45*). However, its production depends on the use of highly enriched uranium targets in nuclear research reactors, making the global supply chain complicated and particularly vulnerable to reactor shutdowns. First in 2009, and then in 2012 and 2013, (un)planned shutdowns have caused extended global shortages. To safeguard future supply, providers have been encouraged to recover their full costs in order to support the transition to low enriched uranium targets and investments in sufficient production and reserve capacity in case of unplanned outages. At the same time alternative or supplementary production technologies are also being developed, including neutron activation of ^{98}Mo targets in research reactors, ^{99}Mo production with linear accelerators, and direct production of ^{99m}Tc on cyclotrons (*46*).

Beyond ^{99m}Tc, SPECT radionuclides with an extended half-life (i.e. ^{111}In and ^{123}I) enable the use of lengthier and more complex radiolabeling procedures, as well as longer imaging protocols. A typical example is infection imaging using ^{111}In-labeled white blood cells, which benefits from delayed acquisitions to improve specificity (*47*). A unique strength of SPECT is dual-isotope imaging which enables simultaneous detection of tracer distribution in space and over time, in a single imaging session, thus reducing acquisition times (and therefore patient discomfort), image artefacts and quantitation errors due to patient motion. This approach is particularly well-suited for the study of interconnected functional, metabolic, chemical and biological processes. This

methodology was recently used to study Takotsubo cardiomyopathy showing that dual-isotope SPECT with the perfusion tracer ^{99m}Tc-MIBI and the fatty-acid metabolism imaging agent ^{123}I-BMIPP combined with cardiac CT could visualize the typical changes in both processes caused by vasospasms in the distal left anterior descending (LAD) coronary artery (*48*).

Innovation in SPECT Tracers for Imaging and Treatment

Therapeutic drug development is targeting ever more specific pathways or processes using small-molecule inhibitors or monoclonal antibodies. Ideally, tracer development can mirror these versatile approaches to derive predictive diagnostic radiopharmaceuticals or to exploit the highly specific targeting properties of these compounds to produce radionuclide therapies.

The small-molecule PSMA inhibitor radiotracers have become an important class of compounds in the management of prostate cancer. One of the first developed compounds of this class was the radioiodinated (^{123}I) tracer MIP-1095, which has successfully been used for targeted tumor therapy (*49*). Uniquely, MIP-1095 can be used as a theranostic agent for SPECT (^{123}I) and radionuclide therapy (^{131}I). In addition, the ^{99m}Tc-analogue MIP-1404 (also known as ^{99m}Tc-trofolastat), prepared using the technetium tricarbonyl core, has been proposed for SPECT/CT imaging with good tumor targeting ability and favorable biodistribution, and has recently entered a phase 3 study to support possible market introduction (*50*).

For developing monoclonal antibody or peptide-based imaging agents, nonmetallic radionuclides, such as ^{123}I, have been frequently labeled using direct electrophilic

aromatic substitution on histidine or tyrosine amino acid residues. Unfortunately, this requires labeling conditions that are often too harsh for antibodies and may damage their structure and affinity. This has been recently overcome by the introduction of reactive prosthetic groups, such as the novel radioiodinated BODIPY dual functional agent, allowing labeling under milder conditions. Proof-of-concept data demonstrated successful SPECT imaging with ^{123}I-trastuzumab of HER2-positive tumors (*51*).

For metallic SPECT radionuclides such as ^{99m}Tc and ^{111}In, bifunctional chelating groups have been the cornerstone for labeling antibodies and peptides. The versatile chemistry of ^{99m}Tc with its stable and readily accessible oxidation states is characterized by chemically robust core structures that can be exploited as platforms for radiopharmaceutical design. One such well-known approach uses the ^{99m}Tc(V)-organohydrazino (HYNIC) core to derivatize a wide range of different targeting molecules (*52*). A promising example is the development of ^{99m}Tc-duramycin as a SPECT tracer for apoptosis, enabling imaging of the induction of cell death early after chemotherapy and radiotherapy. Providing a very early read-out of treatment effect, it could potentially be used to tailor cancer treatments more quickly, sparing toxicity and cost in non-responding patients (*53*). Another interesting target in oncology and cardiovascular medicine is angiogenesis, with ^{99m}Tc-HYNIC-D(RGD) or ^{99m}Tc-maraciclatide integrin $\alpha_v\beta_3$ imaging demonstrating the ability to visualize tumors and treatment response in cancer models (*54*). Integrin imaging has also been used to visualize inflamed atherosclerotic plaques with the potential to non-invasively identify high-risk plaques in patients (*55*). Finally, the expression of the c-MET receptor in non-small cell lung cancer could recently be demonstrated with ^{99m}Tc-HYNIC-cMBP SPECT,

providing essential information on a signaling pathway that contributes to cancer progression and may mediate acquired resistance to epidermal growth factor receptor-targeted therapy (*56*). A multitude of SPECT/CT applications and their potential advantages can be envisioned, targeting a wide range of important predictive tumor patterns aiding treatment selection and available in convenient kit formulations.

A drawback of the HYNIC platform is that its chemistry is often complex, hampering clinical translation because of regulatory issues. A possible solution is the introduction of the organometallic $[^{99m}Tc(CO)_3]^+$ core. It is a very versatile building block and the immediate water-soluble precursor $[^{99m}Tc(CO)_3(H_2O)_3]^+$ can be easily obtained from homemade or commercially available kits. A major advantage of labelling with the ^{99m}Tc-tricarbonyl core is the very wide variety of ligands which bind very efficiently to Tc(I) forming highly robust complexes. Recently, fibroblast activating protein (FAP) inhibitors were successfully labelled using this method, enabling SPECT/CT imaging of cancer-associated fibroblasts, present in many malignancies. As FAP is typically not expressed in healthy tissues, it may represent an important target for theranostic applications (*57*).

Nanobodies have also proven to be particularly suited for ^{99m}Tc-labeling via tricarbonyl chemistry, with many exciting possible applications including the non-invasive quantification of immune checkpoint (PD-L1) expression in tumors to guide immunotherapy (*58*).

Progress is also being made in improving surrogate radionuclides used for pre-therapy SPECT/CT imaging and dosimetry studies. While ^{111}In is still frequently used for this purpose, its chemistry is slightly different from that of the radiolanthanides typically coordinated in these ligands (e.g. ^{177}Lu). This may introduce errors in assessing the tissue

distribution and could be solved by using the radiolanthanide ^{155}Tb (*59*). The administration of ^{155}Tb alongside a therapeutic terbium isotope, such as ^{149}Tb or ^{161}Tb, would represent the ideal theranostic pair because of the identical chemical properties. Similarly, the cyclotron produced SPECT radioisotope ^{203}Pb is attracting attention as the imaging surrogate for the therapeutic ^{212}Pb, as both can be directly imaged using SPECT/CT (*60*). These new diagnostic/therapeutic pairs may greatly facilitate the calculation of the dosimetry of alpha- and beta-emitter labeled radiopharmaceuticals. It is clear that recent innovations in radiopharmaceutical and chemistry techniques have created a promising and versatile landscape of powerful labeling methods that show great opportunity to develop the next generation of SPECT/CT radiopharmaceuticals.

CONCLUSIONS

The last 20 years have witnessed a paradigm shift with the introduction of SPECT/CT as hybrid imaging modality in nuclear medicine. The development of SPECT/CT has often been bench-marked against that of PET/CT. However, the appropriate use of SPECT/CT needs to consider a variety of options in the clinical setting including availability of various radionuclides, the need to image one or more body regions using optimized acquisition modes, and adherence to appropriate use criteria for the multitude of oncological and non-oncological indications. These inherent differences between the two modalities renders such comparisons meaningless as a way to value the relative success of both techniques. The SPECT/CT ecosystem has seen its challenges, but has emerged over the past two decades as a feature-rich and mature tool ready for clinical prime time, owing to innovations in physics and engineering as well as in radiopharmacy and chemistry. Nevertheless, additional efforts should be made to standardize the quantitative results of contemporary SPECT/CT technology. Furthermore, a continued research effort is required to value its clinical benefit and assess its cost-effectiveness. Proof of benefit in economic and humanistic outcomes is critical in order to gain widespread adoption of SPECT/CT.

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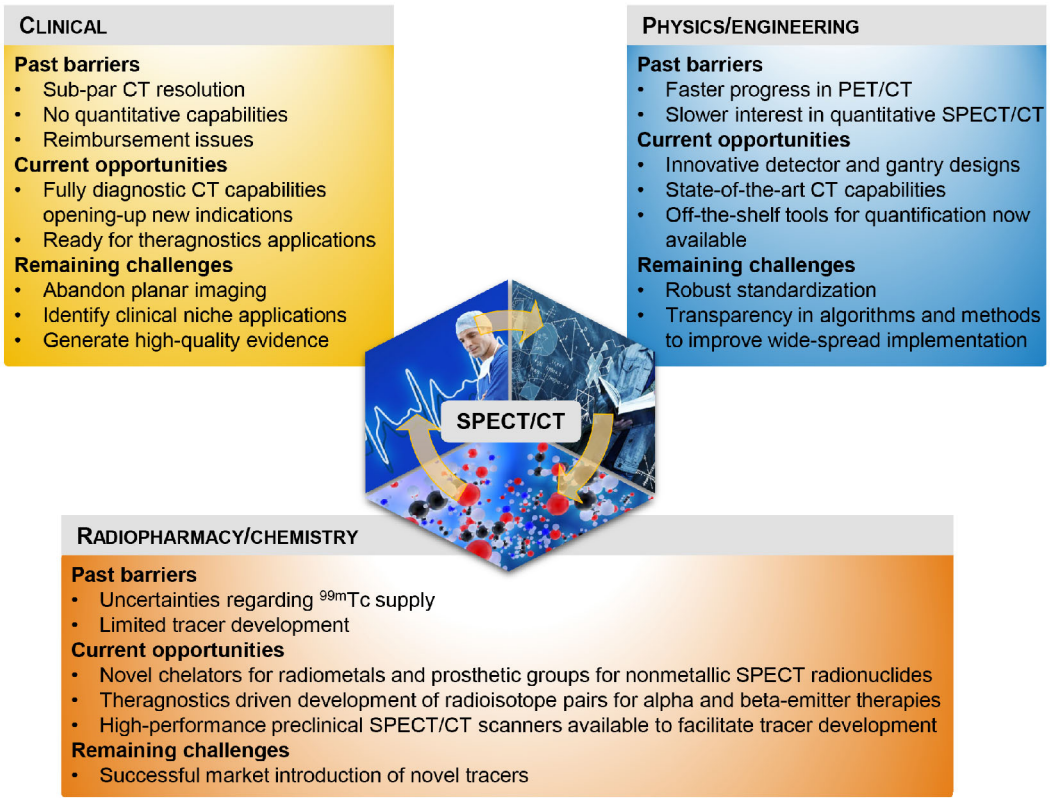

Figure 1. Summary of past barriers, current opportunities, and remaining challenges in developing the SPECT/CT ecosystem, covering the clinical, physics/engineering, and radiopharmacy/chemistry fields.

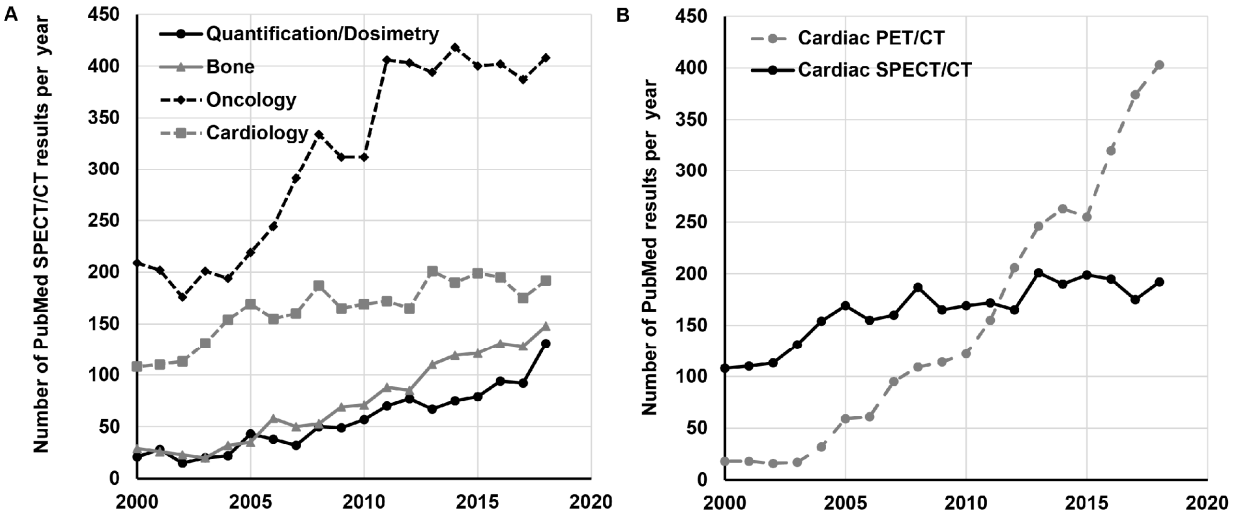

Figure 2. Total number of PubMed citations per year (range: 2000-2018) as measure of interest, A) using the keyword SPECT/CT for selected subspecialty topics, and B) comparison of annual number of publications in cardiology using the keywords SPECT/CT or PET/CT.

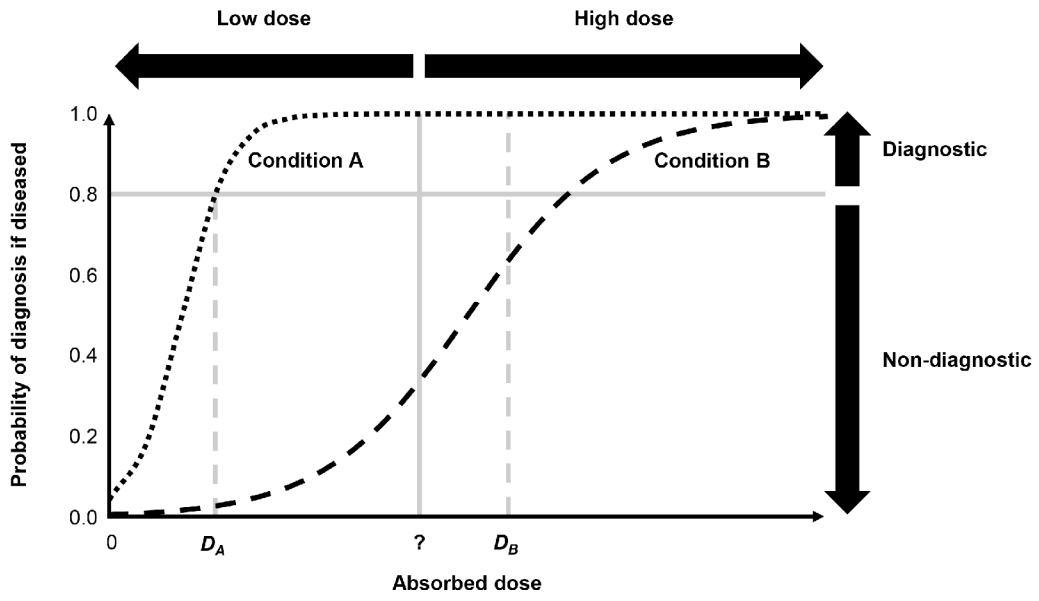

Figure 3. Illustration of the relative value and confusing nature of terminology such as “low-dose” or “high-dose” and “non-diagnostic” or “diagnostic” CT acquisition protocols, assuming that sensitivity is a function of image quality and thus absorbed dose. A specific CT acquisition protocol resulting in an exposure D_B can be considered both “diagnostic” and “non-diagnostic” depending on the condition of interest. Conversely, for condition A (e.g. fracture) “low-dose” (D_A) acquisition settings may result in adequate sensitivity and be considered “diagnostic”, whereas for condition B (e.g. prosthetic loosening) “high-dose” (D_B) settings are required to obtain the same diagnostic threshold.

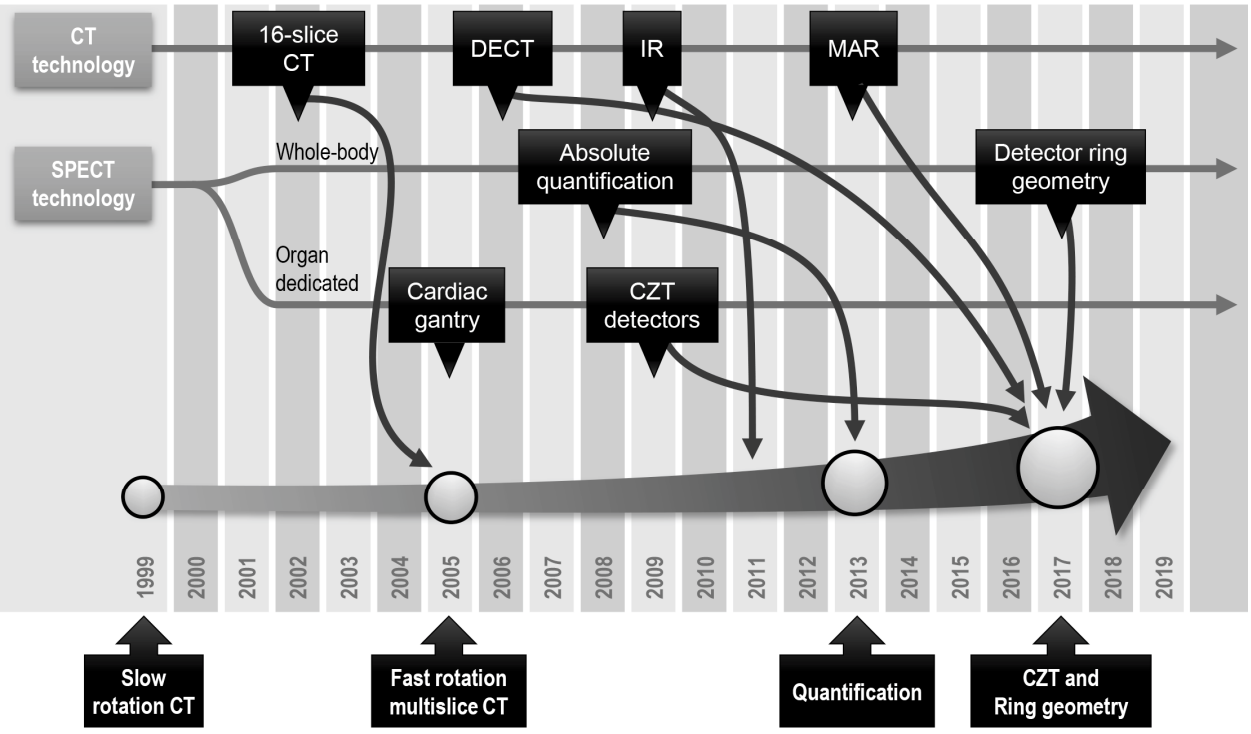

Figure 4. Summary of approximate time of introduction of milestones in whole-body SPECT/CT technology, showing incorporation of subsequent innovations in CT and SPECT technology. While some novel CT technologies were quickly incorporated into SPECT/CT systems (e.g. iterative reconstruction), others showed significant delays in their translation into hybrid scanners. For SPECT innovations, it is interesting to note the parallel development of dedicated cardiac gantry designs that saw earlier introduction of breakthroughs, such as CZT detectors, compared to whole-body capable devices.

Abbreviations: DECT=dual energy computed tomography; IR=iterative reconstruction; MAR=metal artefact reduction; CZT=cadmium-zinc-telluride