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It all began with the development of the gamma camera by Hal Anger in 1957. It ushered into clinical medicine a novel methodology for the diagnosis and characterization of normal and abnormal metabolic processes. Using selected, gamma-emitting radionuclides injected into the body, an imaging study is performed to display their distribution based on the physiology and or pathophysiology of various organs.

The next several decades yielded only minor technical changes to Anger’s basic design, until the arrival of SPECT/CT in 2004. This concatenation of two inherently disparate technical approaches to imaging is as natural a combination as the joining of chocolate and peanut butter, or the consumption of ice cream on a hot summer day.

While the current SPECT/CT technology may or may not be the end of this evolutionary imaging pathway, it is certainly the step of the staircase upon which we stand and practice today.

This excellent series of articles by Dr. Partha Ghosh, reviews the clinical utility of this technological, hybrid-imaging device to assist in the diagnosis and characterization of malignant and non-malignant disease. It highlights the continued utility that this modality has, even in this day of ever more sophisticated and fashionable technologies. It provides the ability to continue to be of immense clinical practicality on a day-to-day basis. The various sections of this publication deal with the utility in different cancers, citing relevant literature references for additional information. They also demonstrate that the most evolved version of this technology, SPECT combined with diagnostic CT, clearly provides improved accuracy and efficacy compared to the use of non-diagnostic CT.

Diagnostic and therapeutic implications of SPECT/CT, as well as its ability to affect the management of many diseases, are clearly delineated in these articles. We are presented with a cogent argument for the continuing value that SPECT/CT has to offer in the daily practice of molecular imaging, and specifics on how to continue to make this a valuable tool to deliver personalized medicine to our patients, today and into the future.

Is this the last evolutionary step for this technology? I do not know for sure, but I personally doubt it. As it stands, like the tale of the white rabbit, the journey for diagnostic SPECT•CT is far from over.

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Molecular Imaging
Imaging modalities are commonly differentiated as providing functional or molecular information or anatomical detail. Nuclear medicine, molecular imaging (MI); falls in the first category and provides limited information about the anatomical location of molecular abnormalities. Computed Tomography (CT), well known for its great anatomical detail, has been used to complement molecular data for diagnosis, as well as for planning, monitoring and evaluation of therapy. Many papers have shown that the interpretation of molecular images is improved when it is coregistered with the anatomical images from a CT system.

At first, the coregistration of the MI and CT datasets took place with fusion software. However, the registration of the two scans obtained at different times, on different imaging systems, and under different situations, limited the accuracy to the range of 5-7 mm. To overcome these problems, there have been attempts to better control the environment of the MI and CT scans and to minimize the time between them. These included a system with a gamma camera and a CT scanner, in one room, that shared a patient bed to quickly transport the patient between the two gantries.

In 1999, a gantry-mounted X-ray tube that rotated along with the nuclear medicine detectors was announced as a solution for attenuation correction and anatomical mapping. The technology is still available today. The maximum rotation speed of this system is 20 seconds per rotation, which is adequate for SPECT, but does not compare to state-of-the-art sub-second CT. As a result, the CT acquisition takes minutes, instead of seconds. The X-ray tube is a 2.5 mA fixed anode tube similar to a dental X-ray system, and the image quality is severely limited. Some refer to this technology as SPECT/CT, although the term “non-diagnostic CT” has been introduced to differentiate this technology from more recent implementations of the SPECT/CT concept.

In 2004, under the premise that diagnosis is the primary goal of diagnostic imaging, Siemens announced an integrated SPECT•CT system based on multislice spiral CT offering full diagnostic CT capabilities. The new product family, from Siemens, was called Symbia® TruePoint SPECT•CT, where SPECT and CT rotate on two tightly integrated but independent rings. The minimum CT rotation time is 0.5 seconds, which translates into CT scans in a matter of seconds, a standard in any state-of-the-art stand-alone CT.

The benefits of the Symbia diagnostic SPECT•CT were first demonstrated by the University of Michigan at the 2005 ASNC annual meeting and included improved accuracy of the CT-based attenuation map and increased specificity and sensitivity of myocardial perfusion imaging. Soon after, an impressive improvement in diagnostic confidence for oncology was reported by the University of Erlangen.

For the purposes of this paper, a diagnostic SPECT•CT system is one which is able to perform fast spiral CT with full diagnostic capabilities. One of the consequences is that it can be used for SPECT, SPECT•CT, and CT, which may result in a significant economical benefit. Without a doubt, the consequences in the clinical arena are the most exciting. Novel applications, such as parathyroid surgical planning, become standard protocol in many centers. Radiotracers that were developed in the 1980’s and 1990’s, but were dismissed due to poor anatomical detail, are now being revisited. Specialties, that would rarely refer patients to the nuclear medicine department, now line up for a diagnostic SPECT•CT. Sick and restless patients can benefit from a one-stop workup with higher clinical value and lower dose.

The focus of this paper is the improved clinical outcomes and diagnostic confidence that is provided by diagnostic SPECT•CT. Clinical confidence translates into conclusive reports that will better serve referring clinicians and patients, the ultimate goal of diagnostic imaging.
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Myocardial Perfusion Imaging

Attenuation correction of myocardial perfusion SPECT, using integrated CT, is a well established procedure. Numerous studies have demonstrated the advantage of CT-based attenuation correction (CT AC) for improved image quality and higher sensitivity and specificity of myocardial perfusion studies, especially in overweight patients and in women. CT generates high-quality attenuation maps due to higher photon flux.

One study\(^2\) used SPECT/CT with low-dose, slow, non-diagnostic CT for myocardial perfusion imaging with attenuation correction using CT-based attenuation maps. A comparison of SPECT myocardial perfusion was performed with quantitative, myocardial perfusion PET using \(^{13}\)NH\(_3\) to evaluate the efficacy of slow, low-dose, CT-based attenuation correction. The study included 23 obese patients (BMI of 28.5 +/- 4.2 kg/m\(^2\)). There were lower uptakes in the inferior, inferoseptal and inferolateral walls in the non-attenuation corrected (NAC) images compared to the attenuation corrected (AC) images in almost all patients. When compared to PET perfusion, the NAC studies showed underestimation of regional perfusion in the mid and basal inferolateral segment. On the other hand, the perfusion was overestimated in the apex, as well as the apical and mid anterior and anterolateral segments. AC studies showed significant normalization and correction of perfusion patterns in the inferior and inferolateral segments. However, some amount of overestimation of the apex and anterolateral wall persisted, even with CT AC, although it was less pronounced. According to the author, the overestimation of perfusion by NAC SPECT and, in a less-pronounced way, by CT AC is related to the non-uniform thickening of the left ventricle. Left ventricular thickening substantially decreases along the longitudinal axis from the apex to the basal segments, and the partial volume effects may lead to accentuation and overestimation of the apical uptake in the SPECT studies. The papillary muscles located in the anterolateral wall may also contribute to the overestimation of regional perfusion in the anterolateral segment. This study demonstrated the adequacy of attenuation correction with low-dose CT although visual and quantitative differences in uptake in the lateral wall between SPECT and PET persisted even with CT AC.

Artifacts of CT attenuation correction, related to misregistration between CT and SPECT datasets prior to the correction, have been the subject of major studies. Misregistration may lead to artificial creation of defects in SPECT, which may be interpreted as ischemia or infarction, and require careful consideration. Misregistration between SPECT and CT can be related to respiratory motion, motion of the heart on its axes during the cardiac cycle, as well as left ventricular wall motion in systole and diastole. A phantom study\(^2\) ascertained that cardiac translation (motion of the heart during respiration not completely synchronized with the diaphragm) mismatch was the biggest contributor to the misregistration, but changing overlap between the heart and liver, lung expansion due to diaphragm contraction, as well as lung expansion due to chest wall motion during respiration, all contributed to the misregistration. The authors recommended attenuation correction at various phases of the respiratory cycle for optimum accuracy. However, in routine clinical practice, accurate correction for all sources of misregistration may be difficult. The argument in favor of a slow, low-dose, poor-resolution CT is that due to the long CT rotation, there is an averaging-out of the cardiac motion, which can lead to improved coregistration between the SPECT and the CT.

This theory, however, has been put to the test, and several studies have measured the degree of misregistration between SPECT and slow CT and have tried to correct for the misregistration using software realignment tools to improve the CT AC process. One study\(^2\,^3\) analyzed 27 patients who were normal on the non-attenuation-corrected SPECT images but exhibited a clinically relevant defect in the slow CT attenuation correction images. Thus, it was assumed that misregistration between the SPECT and slow, non-diagnostic CT was instrumental in creating the defect seen on CT AC images. In 2 extremely obese patients, quantification of misalignment was not possible since a part of the body contour was outside the transaxial field of view of the non-diagnostic CT scanner. For 25 patients, the mean misalignment in the y-direction (antero-posterior) was 1.3 +/- 0.4 pixels. In the z-direction (supero-inferior), there was misalignment in 8 patients.

In 15 patients, manual correction of the misalignment in the y-direction led to smaller and less intense defects. In six patients, manual coregistration and correction of the misalignment returned the defects to normal. However, manual correction could not change the defect size and intensity in four patients. In these four patients, the mismatch in the y-direction was less than one pixel (seven mm), but there was also a coincident mismatch in the craniocaudal or z-direction. From this study, it can be extrapolated that a combination of antero-posterior and cranio-caudal motion can cause misregistration, which may be very difficult to correct even after manual realignment of SPECT and CT, and that z-direction motion contributes to most of the persistent defects. In a slow CT, the cranio-caudal motion does not average out, and this may cause artifacts related to attenuation correction, which should be kept in mind while interpreting scans. The authors state in this context that “this misalignment is much more difficult to detect and correct. Most obviously, the body outline cannot serve as a reference and there are no internal landmarks easily discernible in both CT and SPECT.” The authors also comment that artifacts in the apical and anterior walls in attenuation-corrected images may be related to an underestimation of the attenuation effects of the anterior chest wall, and the case of misalignment and the overestimation of the attenuation effect of the liver and diaphragm may be related to overcorrection.

Another study, addressing similar concerns\(^2\,^4\), included 105 patients who underwent myocardial perfusion SPECT/CT using low-resolution, slow, non-diagnostic CT. Nine patients refused CT due to claustrophobia, and 10 had CT studies with significant
artifacts – motion, metal and beam hardening – and were excluded from the final evaluation of misregistration. The mean recorded maximal misregistration was 8.6 mm +/- 3.8 mm. This equaled 1.25 +/- 0.55 pixels. 36 percent of the studies showed less than one pixel misalignment, 57 percent showed one to two pixel misalignment and seven percent of the studies showed greater than two pixel misalignment. For manual re-registration in 88 percent of patients, the CT had to be shifted in the x-, y- as well as in z-directions, thus delineating misregistration in all three planes. There was a major change in the perfusion pattern in attenuation-corrected images before and after manual re-registration in the anterior, septal, inferior and anteropapial segments. The finding of this study, that over two-thirds of all patients showed a maximal misalignment of more than one SPECT pixel, suggests that careful realignment of SPECT and CT data is essential to prevent interpretation errors.

Another recent article also evaluated the direction and magnitude of misregistration between myocardial perfusion SPECT and low resolution, non-diagnostic CT in 248 consecutive stress-rest MPI studies in 124 patients. SPECT and CT misregistration of more than one pixel was found in 73 percent while 23 percent had misregistration of more than two pixels. Changes in the summed stress score due to misregistration were assessed. A three-pixel ventral shift caused an average decrease of 15.4 percent in polar map scoring in the lateral wall and a 7.5 percent decrease in the inferior wall. The most significant misregistration-related defects occurred in the lateral and anterior walls when the myocardium on SPECT overlapped lung tissue on CT, as seen in 16 percent of the patients.

The studies mentioned above, using non-diagnostic CT with SPECT, show that slow CT-related averaging of the cardiac motion does not reduce misregistration errors. In fact, the high prevalence of z-direction misalignments and the cranio-caudal re-registration may be complicated by the poor-quality, thick-slice, slow, non-diagnostic CT. This is a powerful argument in favor of integrated, multislice CT combined with SPECT for improved CT attenuation correction in myocardial perfusion scintigraphy.

The Symbia® TruePoint SPECT•CT with an integrated, 2-3,6- or 16-slice CT is able to perform diagnostic, spiral CT in a very short time (5-20 sec) with three to five mm overlapping slice reconstructions in order to obtain high-quality, coronal and sagittal reconstructions. This makes it possible to obtain a CT study covering the entire thorax in a single breath-hold, even with a dual-slice CT. Due to the fast rotation (0.5-0.8 sec) of the CT tube, every slice shows minimal respiratory motion, even if the acquisition is performed as a free-breathing study. With both free-breathing and breath-hold acquisitions, the coronal and sagittal reconstructions can be obtained with sharp diaphragmatic margins without major motion artifacts due to the fast CT, which aids in the accurate fusion of the SPECT and CT. Manual corrections, based on easy manipulations of the SPECT and CT data in three orthogonal planes, are easier since the high-quality CT ensures clear delineation of cardiac and diaphragmatic margins. Breath-hold CT acquired as an end-tidal expiratory breath-hold study (the patient holds his/her breath in a normal breathing position without deep inspiration or expiration) has been shown to be optimal for accurate fusion of SPECT and CT. Even in a free-breathing CT, all related motions, which contribute to misregistrations, are minimized due to the CT being performed in one or two respiratory cycles with a maximum of 20-second acquisition time. This ensures a reasonable coregistration of the SPECT and CT in the majority of acquisitions, with minor manual adjustments, if required. Z-direction misregistration, if any, can be easily corrected because of the high-quality, coronal and sagittal CT reconstructions and the thin-slice, overlapping, spiral CT acquisition. Fast, diagnostic CT ensures high-quality images, even at low doses, so that the radiation burden to the patient is not increased compared to non-diagnostic CT.

Diagnostic CT, integrated with SPECT, may be able to eliminate problems of claustrophobia due to the fast table movement without rotation of the SPECT detectors around the patient during the CT acquisition. The 70-centimeter CT gantry and the patient table, capable of holding up to 500-pound patients, also ensure accurate CT studies in very obese patients, since it is unusual for the CT field of view in a diagnostic CT to be smaller than the girth of the patient. Another major advantage is the ability of diagnostic CT to identify and characterize incidental findings on chest CT, even if it is a low-dose CT for attenuation correction. Previous studies have shown that in up to 10 percent of cases of myocardial perfusion SPECT/CT, incidental findings are visualized even with low-dose, low-resolution, non-diagnostic CT. This may include solitary pulmonary nodules, pneumonia, pleural effusion and, in some situations, proper characterization of these lesions using diagnostic CT helps the diagnosis and further management of these patients.

Recent abstracts on the accuracy of myocardial perfusion imaging with CT attenuation correction performed on SPECT/CT using integrated, multislice, diagnostic CT have demonstrated the value of diagnostic, CT-based CT AC. An abstract at the ASNC 20082-7, highlighted the diagnostic accuracy of hybrid, cardiac SPECT/CT for attenuation correction of stress myocardial perfusion imaging in obese patients compared to normal-weight patients with angiography correlation. They evaluated 234 patients with a recent coronary angiography, which included 101 patients with BMIs <30 (normal weight group) and 133 patients with BMIs >30 (obese group). This study was performed on Symbia T6, incorporating a 6-slice CT with SPECT. Breath-hold CT acquisitions were acquired at end tidal expiration with five to seven second acquisition time, both at stress and at rest. SPECT images were reconstructed for attenuation correction, including scatter correction and resolution recovery. Perfusion defects were assessed by scoring their severity and extent of defect in each coronary artery distribution. With CT AC, sensitivity increased from 86 percent to 94 percent in normal-weight patients and from 76 percent to 94 percent in obese patients. Specificity increased from 81 percent to 94 percent in normal-weight patients and from 48 percent to 83 percent in obese patients. The sensitivity and specificity for coronary artery disease was based on coronary angiography correlation of significant stenosis. This study clearly shows that diagnostic, CT-based attenuation correction significantly improves diagnostic accuracy of myocardial perfusion SPECT, both in normal, and in obese patients.
Another abstract\textsuperscript{2,8} by the same group compared the diagnostic accuracy of SPECT/CT for CT-based attenuation correction of myocardial perfusion imaging between men and women. Two hundred thirty-seven patients with a recent coronary angiography, including 143 consecutive males and 94 consecutive females, were evaluated with SPECT•CT using integrated, diagnostic CT on a Symbia T6. The mean weight for the male group was 98.9 kg and 86.8 kg for the female group. Breath-hold CT acquisitions were acquired at end tidal expiration with five to seven second acquisition time for attenuation correction. With attenuation correction, sensitivity increased from 78 percent to 93 percent in female patients and from 82 percent to 94 percent in male patients. Specificity increased from 57 percent to 82 percent in female patients and from 61 percent to 91 percent in male patients. Sensitivity, specificity and accuracy all increased significantly with CT AC as compared to non-AC SPECT. The increase in specificity in male patients was slightly higher than in the female patients. This study also proves the enhanced diagnostic accuracy of myocardial perfusion SPECT due to diagnostic, CT-based attenuation correction.

A few case examples performed on Symbia TruePoint SPECT•CT illustrate the impact of diagnostic CT for attenuation correction. The first example (Figure 2-1) is of a 68-year-old male patient with a low likelihood of coronary artery disease. The stress study revealed an inferior wall perfusion defect, which was corrected by CT AC. This study was performed on a Symbia T6 with integrated 6-slice, diagnostic CT.

Figure 2-1  Data courtesy of University of Michigan Health System, Ann Arbor, MI, USA
The second case (Figure 2-2) is another example where CT AC with diagnostic CT is able to confirm normality in a patient. This was a 38-year-old female patient with a low likelihood of coronary artery disease, where a stress study showed a large defect in the anterior and anteroseptal wall. CT AC corrected the defect and demonstrated normal perfusion in the LAD territory, suggesting that the defect was related to breast attenuation.
Another example (Figure 2-3) illustrates the value of CT AC in ascertaining normality in an otherwise at-risk patient. This was a 71-year-old female with several risk factors for coronary artery disease. A stress study showed apical and inferior wall perfusion defects with evidence of reversibility at rest. However, CT AC showed a near normalization of the apical and inferior wall in the stress study, confirming the absence of functionally significant coronary artery disease in this patient.
A fourth example (Figure 2-4) illustrates the value of CT AC in proper characterization of the degree of ischemia in patients with established coronary artery disease (CAD). This was a 55-year-old male with CAD and chest pain. A non-attenuation corrected study showed reversible ischemia in the anterior wall and septum. CT AC showed severe ischemia in the anterior wall and septum, but also demonstrated ischemia in the posterolateral segment suggestive of involvement of the left circumflex artery. A rest study with CT AC showed reversibility in the circumflex territory as well. This is an example of CT AC defining the true extent of coronary artery disease.

Another example (Figure 2-5) illustrates a similar situation of CT AC defining the true extent of ischemia. This was a 75-year-old man with a history of myocardial infarction and bypass surgery who presented with chest pain. A non-attenuation corrected study showed a fixed, inferior wall defect suggestive of infarction. CT AC showed a smaller size of the fixed defect with a significant amount of reversible peri-infarct ischemia, which may have been related to graft failure.
Figure 2-5  Data courtesy of University of Michigan Health System, Ann Arbor, MI, USA
The next example (Figure 2-6) illustrates the accuracy of fusion obtained using diagnostic, spiral CT. This was an 82-year-old male patient who presented with chest pain and abnormal EKG at rest. There was greater than a one to two millimeter ST depression during exercise stress, but no chest pain. CT AC images showed an apical and anterior defect that was mostly reversible and an inferior and inferior-septal defect that showed significantly higher reversibility than what was illustrated in the uncorrected images. CT AC showed reversibility of the inferior-septal defect while non–attenuation corrected images suggested a fixed defect.

The next example (Figure 2-7) also illustrates the ability of CT AC in delineating the true extent of ischemia. This was a 66-year-old, overweight male weighing 94 kg (207 lbs) who presented with typical angina with multiple coronary risk factors. The uncorrected stress study showed severe perfusion defects in the septal, apical and inferior walls, suggesting two-vessel disease. CT AC, however, showed a significantly reduced defect. Coronary angiography revealed total proximal RCA and total mid LAD occlusions, both with extensive collaterals from normal LCx, which explains the limited ischemic defect size in the inferolateral wall seen on the CT AC images.
The next images (Figure 2-8) illustrate the importance of identification and characterization of incidental findings using diagnostic CT as part of the CT AC procedure. This was a 58-year-old female undergoing myocardial perfusion SPECT for a pre-operative evaluation. The diagnostic CT identified a breast tumor. The next example showed a solitary lung nodule identified on the low-dose, diagnostic CT using the lung window.
This example (Figure 2-9) shows attenuation artifacts due to misalignment of the SPECT and CT and the effect of manual re-registration in three orthogonal axes, eliminating the artifact. This was a 59-year-old female with a low likelihood of CAD, where the attenuation corrected stress study showed normal perfusion throughout the left ventricle. However, the attenuation corrected rest study showed a large defect in the inferolateral wall and apex. The coregistration images for the rest study demonstrating the alignment of the CT and SPECT in three orthogonal planes showed a major lateral shift of the SPECT from the CT with more than a 2-pixel misalignment, which created the attenuation artifact in the rest study. Manual re-registration was performed easily in three orthogonal planes with accurate fusion of CT and SPECT. Note the sharp margin of the diaphragm and inferior wall of the heart as well as the sharp, lateral, cardiac margin, which helps accurate registration. Repeat CT AC following re-registration showed normal perfusion, both in stress and rest studies, which confirmed normality in this patient.
The next case (Figure 2-10) illustrates the effect of a small misregistration of CT and SPECT, which may cause a significant attenuation-related artifact. This was a male patient with a low likelihood for CAD, in whom the stress study with attenuation correction showed a significant defect in the anterior wall and anterolateral wall. Review of the registration of SPECT and CT showed a minor misregistration of the lateral wall of the left ventricle, which was probably one pixel or less. Manual re-registration to ensure accurate fusion of SPECT and CT was performed in all three orthogonal planes, helped by the sharp, diaphragmatic contour provided by diagnostic CT. Following manual realignment, there was normalization of the uptake in the anterior wall and anterolateral walls, confirming the absence of CAD in this patient.
A lot of interest has been generated in technological innovations that attempt to reduce acquisition time. Several vendors have different strategies for fast cardiac acquisition – from reconstruction algorithm-based acquisition time reduction, to the use of novel collimation and acquisition orbit in standard SPECT/CT systems to new crystal technology for dedicated cardiac systems – all of which are being evaluated. The IQ•SPECT technology introduced by Siemens is aimed to be compatible with existing SPECT/CT systems and can provide fast cardiac solutions to an otherwise multi-purpose hybrid SPECT/CT system. A converging collimator, which increases the sensitivity along with a cardio-centric orbit of the camera heads that ensures the heart always remains at the center of rotation during the acquisition as well as 3D iterative reconstruction enable SPECT acquisitions in typically 5 minutes without compromise in image quality and diagnostic confidence. Apart from the faster cardiac acquisition capability, IQ•SPECT technology also opens up the possibility of reducing injected dose without compromising image quality due to its ability to obtain higher count rates for the same injected dose compared to standard collimators. The diagnostic CT integrated within the Symbia SPECT•CT systems provides CT-based attenuation correction and fast IQ•SPECT-based cardiac acquisition.

The accuracy of this approach of fast cardiac imaging with IQ•SPECT has been demonstrated in recent abstracts and congress submissions. In an oral presentation at EANM 2009, a team from the University of Erlangen demonstrated the diagnostic equivalence of approximately 5-minute IQ•SPECT myocardial perfusion imaging compared to 23 minute standard acquisition protocol using an LEHR (low energy, high resolution)
collimator on a Symbia T6 SPECT•CT system. The injected dose was 200-300 MBq at stress and 800-900 MBq at rest. Out of 12 patients studied, 10 showed a minimal difference in overall scan findings and summed stress scores between the LEHR and IQ•SPECT studies. The mean deviation of LV ejection fraction between the two acquisition protocols was approximately 4%. This study, although performed in a small patient population, showed the image quality and diagnostic equivalence obtained using an ultrafast IQ•SPECT study.

Another abstract submitted for publication at the Society of Nuclear Medicine 2010 from the University of Michigan\textsuperscript{2,10} demonstrates the clinical validation of attenuation corrected cardiac imaging with IQ•SPECT with integrated CT. Fifty four patients referred for myocardial perfusion imaging underwent standard exercise SPECT•CT on Symbia T6 using LEHR collimators followed by a 4-minute IQ•SPECT exam. Both studies were corrected for attenuation using the initially-acquired free breathing CT. Images were scored from 0 (unacceptable) to 4 (excellent). Image quality after attenuation correction was similar between the two methods with an average score of 3.11 for standard and 3.21 for IQ•SPECT acquisition. The percentage of studies rated as excellent by both methods was similar. Normalcy rates were also similar for both methods (91% for LEHR and 97% for IQ•SPECT). Angiographic correlation was performed which showed similar correlation between both methods, especially in patients without significant coronary stenosis. This study also highlights the comparable image quality and normalcy rate obtained with IQ•SPECT with CT attenuation correction relative to standard SPECT/CT myocardial perfusion acquisition which was almost four times longer.

Typical IQ•SPECT myocardial perfusion studies with integrated CT attenuation correction from Symbia SPECT•CT systems are shown here to demonstrate the similarity in image quality, the defect size and overall diagnostic information when compared with standard LEHR collimator studies acquired over a much longer time.
The first case (Figure 2-11) is of a patient with normal myocardial perfusion and shows the similar image quality of four-minute IQ•SPECT reconstructed images compared to standard LEHR collimator images with much longer acquisition time.

The second study (Figure 2-12) shows reversible ischemia in the anteroseptal walls both in the standard as well as the IQ•SPECT images, which were acquired in just four minutes. The comparison shows the remarkable similarity of the defect size and the degree of reversibility between the two acquisitions.

CT attenuation correction using integrated diagnostic CT is instrumental for generating high-quality, attenuation-corrected SPECT images acquired with such a low scan time.
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Combining CT Calcium Scoring and Myocardial Perfusion SPECT

Stress myocardial perfusion SPECT imaging is an established modality for clinical management and decision making in patients with coronary artery disease. It is especially useful to differentiate patients likely to benefit from coronary revascularization, as well as to assess the risk of adverse events and prognosis. CT coronary calcium scoring has also been widely evaluated for the diagnosis of early subclinical atherosclerosis and for risk stratification in asymptomatic individuals. Higher calcium scores are associated with increased plaque burden and increased cardiovascular risk. There is, however, a large discrepancy between the anatomic extent of atherosclerosis and the presence of ischemia. High calcium deposition may occur in the wall of the vessel without a reduction in luminal diameter due to remodeling of the luminal wall. Luminal stenosis and consequent stress-induced ischemia occur only after substantial atherosclerotic deposition. There is a large population of patients with significant coronary calcium burden, but with no evidence of stress-induced ischemia on myocardial perfusion studies. This has prompted some authors to suggest that a combination of calcium scoring and myocardial perfusion scintigraphy may be useful for identifying patients with extensive atherosclerosis, but without stress-induced ischemia, who may benefit from more aggressive risk factor modification and medical treatment. Further, calcium scoring may help in guiding decision making for patients with equivocal myocardial perfusion results. At least 50 percent of the time, the first indication of atherosclerosis is sudden cardiac death, acute myocardial infarction or an episode of unstable angina. In asymptomatic individuals, the calcium-containing, noncritical, atherosclerotic plaques are at risk for rupture, causing acute coronary syndrome and sudden cardiac death. It has been suggested that 70 percent to 90 percent of acute cardiac events can be prevented by appropriate risk factor modification and aggressive drug therapy. A combined approach of calcium scoring and myocardial perfusion imaging may be able to unearth a large number of patients who may potentially benefit from aggressive medical management and may help avoid acute cardiac episodes.

The Symbia® TruePoint SPECT•CT makes it possible to perform CT calcium scoring as an integrated procedure with myocardial perfusion. SPECT is ideally suited to a combined imaging strategy. Accurate risk stratification and proper management decision-making can be enhanced in a large population with intermediate to high risk for CAD (coronary artery disease). However, understanding the relationship between coronary calcium scoring and the likelihood of stress-induced myocardial ischemia is necessary to define guidelines for a combined imaging strategy.

One of the early studies, using calcium scoring with electron beam computed tomography (EBCT) and myocardial perfusion SPECT\textsuperscript{3,1}, identified 3895 asymptomatic patients with coronary artery calcium, of which 411 underwent myocardial perfusion SPECT. All individuals with a calcium score <10 had normal perfusion SPECT. As coronary artery calcium increased, there was an increase in patients with SPECT perfusion defects. Patients with a calcium score of 101 to 399 (11%) and with a calcium score >400 (47%) had myocardial perfusion defects, while only 2.6 percent of the patients with a calcium score of 11 to 100 had perfusion defects. Even within the 47 percent of patients in the group with calcium score >400 who had abnormal SPECT, only a small percentage had a high-risk imaging study that might have benefited from coronary angiography. This study clearly demonstrated the close correlation of high coronary calcification with the presence of stress-induced ischemia. However, it is to be noted that a substantial portion of asymptomatic individuals with high coronary calcium had no ischemia.

This was further studied in a large group of 1195 patients who underwent stress myocardial perfusion SPECT and calcium scoring by EBCT\textsuperscript{3,2}. Of 1195 patients, 76 had greater than five percent ischemia on SPECT. Compared to patients with normal myocardial perfusion, patients with an ischemic study had a higher number of coronary risk factors and a more abnormal risk profile. The ischemic patient group had significantly higher mean calcium scores compared to that of the normal perfusion group. In patients with calcium scores <100, the frequency of an ischemic study was very low (<2% overall). However, for patients with calcium scores >1000, 20 percent had ischemic myocardial perfusion SPECT. Overall, 8.6 percent of all patients with a calcium score >1000 showed moderate to severe ischemia on SPECT. Of patients with ischemia on SPECT, 88 percent had calcium scores >100. However, 56 percent of the patients with normal perfusion also had calcium scores >100. The comparison of the presence of ischemia with calcium scoring percentile groupings showed that, for patients below the 50th percentile of calcium score abnormality, the frequency of ischemic myocardial perfusion SPECT was very low (<2%). However, the frequency was substantially increased for patients above the 50th percentile, but did not vary substantially between the higher percentile groups.

There was, however, a stepwise increase in the presence of ischemic SPECT defects as the absolute calcium score value increased. It is important to note that patients with a high percentile ranking, but low absolute calcium score (because of a relatively young age), did not show ischemia on SPECT. Correlating calcium scoring and perfusion defects, with the presence of symptoms, led to the finding that for similar calcium scores, patients with symptoms had a significantly higher frequency of ischemic defects than patients without symptoms. When a calcium score was >400, there was a significantly higher frequency of ischemia in the symptomatic group (18.5%) compared to the asymptomatic group (10.4%). The same was
evident in the group with low calcium scores, in which patients with ischemia almost always had symptoms.

This study shows that a threshold phenomenon exists in the relationship between the extent of calcified plaque and the presence of myocardial ischemia. Among patients with calcium scores <100, ischemia was rare (<2%). Even in this group, ischemia, if present, was predominantly in patients with symptoms. As the calcium score increased, the frequency of ischemia on SPECT increased progressively. Among patients with calcium scores >1000, 20 percent had an ischemic perfusion defect on SPECT. This suggests that a large percentage of patients with very high coronary calcification do not have any inducible ischemia. These patients may be at a low short-term risk, but a high long-term risk for adverse cardiac events. Consequently, they should be managed by aggressive risk-factor modification and drug therapy in order to potentially reduce future adverse events. Another finding of this study is the relatively close correlation of an absolute calcium score, rather than percentile scores, with a presence of myocardial ischemia.

The previous study used a patient population with and without symptoms. Another study1,3 performed calcium scoring with multidetector CT on 794 consecutive asymptomatic patients with risk factors for CAD. Four hundred twenty-two out of 794 patients (53%) showed detectable coronary calcium with 14 percent showing moderate (101-400) and 9 percent showing severe (>400) calcium scores. Of the 422 patients with coronary calcium, 102 (24%) underwent stress perfusion SPECT imaging with 51 having moderate and 32 having severe calcium scores. Ischemia was detected in only 5 percent of patients with calcium scores <100, 24 percent of patients with a score of 101 to 400 and 53 percent of patients with a score >400. Severe ischemia was seen in 8 percent and 22 percent of patients with moderate and severe calcium scores respectively. In the group of patients with calcium scores below 100, there were no abnormal SPECT studies considering both perfusion and ejection fraction and wall motion analysis. The presence of significant ischemia in over 50 percent of the patients with calcium scores >400 suggests this to be an optimum threshold for initiation of myocardial perfusion scintigraphy. However, 24 percent of the patients with calcium scores between 101 and 400 showed ischemia as well. This supports the concept that a combination of calcium scoring and myocardial perfusion SPECT would be the most optimum method of early identification for at-risk patients.

Both calcium scoring and SPECT have been used to monitor the progress of CAD with or without medical management. One study1,4 showed that calcium score values progressed 20 percent to 33 percent per year for untreated patients, with the Agatston score doubling every 2.5 to 4 years. Another study3,5 showed the value of sequential calcium scores for documentation of the efficacy of statins in reducing or halting the progression of atherosclerosis. This makes a combination of serial calcium scoring and SPECT studies an effective tool for monitoring aggressive risk factor modification and drug therapy in order to determine further management and the most effective time for invasive investigations, if necessary.

A recent study3,6 evaluated 77 prospective patients who were scheduled for coronary angiography because of suspected CAD. The patients underwent stress myocardial perfusion SPECT and calcium scoring prior to coronary angiography. Forty-two of 77 patients (55%) had significant CAD on angiography, with 38 patients having >75 percent luminal stenosis. Gated SPECT showed perfusion defects in 35 out of 77 patients (45%). Calcium scores were minimal or mild (0-100) in 29 percent of the patients, moderate (101-400) in 26 percent and severe (>400) in 45 percent of patients. No patients with calcium scores <10 had perfusion defects, while 10 of 20 patients with severe, and 13 of 15 patients with extensive (>1000) calcium scores had perfusion defects. Comparing gated SPECT to coronary angiography, there were 10 patients with normal SPECT, but significant coronary stenosis. Of these, two patients had two-vessel disease, and two patients had three-vessel disease. However, SPECT combined with calcium scoring (cutoff of 709) had a sensitivity of 86 percent and specificity of 86 percent. This study is also illustrative of the advantage of combining calcium scoring and myocardial perfusion to determine the true extent of disease, especially when the optimal threshold of coronary calcium is used to improve interpretation of equivocal SPECT abnormalities.

Another recent study3,7 evaluated the value of integrating the calcium score and SPECT myocardial perfusion results to predict the short- and long-term risk of cardiac events. Eleven-hundred twenty-six asymptomatic subjects without previous cardiovascular disease, who had a calcium scoring and stress SPECT scan, were followed-up for a median period of 6.9 years. Total cardiac events and deaths due to myocardial infarction as a percentage of total deaths were analyzed. There was an increase in the incidence of abnormal SPECT results with increasing calcium scores from <1 percent (calcium scores <10) to 29 percent (calcium scores >400). Total cardiac events and the percentage of total death due to myocardial infarction also increased with increasing calcium scores and abnormal SPECT results. In subjects with a normal SPECT result, the calcium score added incremental prognostic information, with a 3.55-fold relative increase for any cardiac event and 2.75-fold increase for death due to myocardial infarction when the calcium score was severe (>400) versus minimal (<10). The study concluded that calcium scoring and SPECT findings are independent and complementary predictors of short- and long-term cardiac events. Despite a normal SPECT result, a severe calcium score identifies subjects at high long-term cardiac risk. This study thus supports the approach of performing a calcium scoring ACS in patients who are at intermediate or high clinical risk for coronary artery disease, to better define those who will have a high long-term risk for adverse cardiac events even if they have normal SPECT myocardial perfusion results.
A pattern emerges from all these studies, which clearly emphasizes the fact that perfusion abnormalities have a significant correlation to the absolute value of the coronary calcium score. Patients with low calcium scores have a very low likelihood of ischemia unless they are symptomatic. Similarly, on the other end of the spectrum, ischemia can be present in 20 percent to 50 percent of patients with calcium scores above 1000. The patient group with calcium scores between 101 and 400 is a grey zone with varying levels of ischemia and a corresponding correlation of the presence of symptoms. Thus, a combination of calcium scoring and myocardial perfusion SPECT can help improve the characterization of such patient groups and the identification of patients with higher long term risk with appropriate management modification. This combined approach can also serve as an effective tool for treatment monitoring and decision-making in further invasive investigations.

A few clinical examples from Symbia TruePoint SPECT•CT help illustrate the points made above.

The first clinical example (Figure 3-1) is an asymptomatic patient with several risk factors for coronary artery disease. Calcium scoring and stress myocardial perfusion SPECT performed on a Symbia T6 showed heavily calcified coronary arteries in the presence of normal myocardial perfusion. A high calcium score of 2332, in the presence of normal perfusion, suggests that the patient was at a low short-term, but high long-term risk for adverse cardiac events, requiring aggressive risk-factor modification and drug therapy.
The next case (Figure 3-2) also shows a similar example where the calcium score was very high (>3000) with severe calcification in the LAD and RCA, but with normal stress myocardial perfusion. Calcium scoring data was also used for attenuation correction, and an inferior wall attenuation defect as seen in the non-corrected images showed normal uptake following attenuation correction. This patient also falls in the category of high long-term risk, but low short-term risk for CAD and requires aggressive medical management.

The recent introduction of fast cardiac scanning techniques (IQ•SPECT) on the Symbia TruePoint SPECT•CT system makes it possible to acquire a CT calcium scoring study followed by a fast myocardial perfusion SPECT in approximately five minutes. The CT calcium score data is also used for CT attenuation correction of the fast cardiac SPECT. The technology enabling such fast SPECT acquisition is comprised of a converging collimator with four times higher sensitivity than the standard low-energy, high-resolution (LEHR) collimator, as well as a cardio-centric orbit, which ensures the heart is always at the center of rotation by controlled movement of the detector heads. Such a combination of integrated, diagnostic CT and fast cardiac SPECT enables calcium scoring and high quality stress or rest SPECT studies to be completed in five minutes or less, thereby improving patient throughput and patient compliance. This approach has the potential of becoming a major tool for fast, effective evaluation and risk stratification of patients at risk of coronary artery disease.
This clinical example (Figure 3-3) is of an IQ•SPECT fast cardiac SPECT and calcium scoring performed on a Symbia SPECT•CT system with integrated 16-slice CT, in a 68-year-old male patient with hypercholesterolemia and occasional chest pain, to evaluate for inducible ischemia. A standard LEHR SPECT study, followed by IQ•SPECT, was performed following treadmill stress. Integrated CT calcium scoring was performed, including attenuation correction. Both the LEHR and IQ•SPECT studies demonstrated normal perfusion throughout the left ventricular myocardium at peak stress. CT calcium scoring showed high levels of calcification in all coronary arteries. The patient was put on aggressive medical therapy. It is important to note that the image quality of the four-minute IQ•SPECT reconstructions was comparable to that of the LEHR study with an acquisition time that was more than four times longer.
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Evaluation of Bone Lesions

Bone scintigraphy has played a major role in the staging of many cancers, as well as in orthopedics. SPECT/CT has added value in improved localization of skeletal lesions. A major advantage of SPECT/CT has been improved characterization of indeterminate bone lesions and differentiation of benign from malignant lesions due to additional CT information.

One study\textsuperscript{4.1} performed SPECT/CT with low resolution, non-diagnostic CT in 47 patients with tumors who had a total of 104 focal lesions found on planar bone scintigraphy. SPECT/CT was able to correctly classify 88 of 104 (85\%) lesions compared with 37 of 104 (36\%) on SPECT. SPECT/CT increased the specificity of bone lesions for identification of malignancy very significantly. The highest diagnostic gain was in the spine, thoracic cage, skull, and pelvis. Small osteolytic lesions were missed because of the limited resolution of transmission images.

Another team\textsuperscript{4.2} studied non-oncological patients referred for bone scintigraphy using SPECT/CT with non-diagnostic CT. Planar scintigraphy identified 85 indeterminate lesions in 76 patients. SPECT/CT was able to adequately characterize the lesion in 59 percent of the cases. The lesions diagnosed by SPECT/CT using low-resolution, non-diagnostic CT included fractures; osteochondral lesions; nonossifying fibroma; enchondroma; and fibrous dysplasia. SPECT/CT also diagnosed spurs; posterior osteophytes; bursitis; osteoarthrosis; exostosis; spondylolysis; hemilumbarization; and vertebral collapse. SPECT/CT was of no additional value in eight (11\%) patients. In five patients, CT detected no clear morphological abnormality, and in three patients the quality of CT data was not sufficient for proper diagnosis. All these patients underwent high-quality, diagnostic CT following inconclusive SPECT/CT. In five of these patients, diagnostic CT reached the proper diagnosis.

This study demonstrates the fact that diagnostic CT combined with SPECT offers far superior lesion characterization compared to poor-quality, non-diagnostic CT. Moreover, identification of conditions like fibrous dysplasia, exostosis, and spondylolysis, may have a major impact on patient management and may be often the source of symptoms in non-oncological patients. High-quality, diagnostic CT, for proper evaluation of these lesions, combined with SPECT, appears to be the best strategy for comprehensive diagnosis.

Several authors have explored this approach of fusing SPECT with diagnostic CT. A group in Switzerland\textsuperscript{4.3} prospectively studied 37 patients with 42 focal lesions using SPECT fused with a separately-performed, diagnostic CT. Of 42 lesions, 11 were metastatic, 27 degenerative, two post-traumatic and two benign. Sensitivity and specificity for differentiating benign from malignant bone lesions were 82 percent and 94 percent respectively for planar, 91 percent and 94 percent respectively for SPECT and 100 percent and 100 percent respectively for SPECT fused with diagnostic CT. Diagnostic confidence dramatically increased when SPECT was fused with diagnostic CT. The author puts forward a strong argument for the use of diagnostic CT fused or integrated with SPECT.

“Often patients with malignant tumors have unclear pain in the skeleton. In these situations, it does not suffice to rule out metastasis. The cause of benign focal uptake should be evaluated carefully because many underlying diseases can influence treatment. Osteoid osteoma can be managed by resection or radiofrequency ablation. In the case of osteoporotic vertebral body, sacral, and rib fractures, bisphosphonate treatment and vertebroplasty can be considered. Degenerative lesions, if concordant with the symptoms, can be managed with percutaneous injections of anesthetics or corticosteroids. It has been found that findings on bone scintigraphy are predictive of the short-term outcome of facet-joint injections in patients with lower back pain. It may be possible to use SPECT and, even better, SPECT/CT to differentiate costovertebral joint osteoarthritis and facet joint osteoarthritis and to guide therapeutic intervention.”

Another study\textsuperscript{4.4} used a specially designed system where a gantry-free SPECT scanner and an 8-detector row CT were juxtaposed in such a way that the CT table could move from the CT to the SPECT. The SPECT and CT images were then retrospectively fused. In 45 patients, 82 foci of uptake were analyzed. Of these patients, 42 were metastatic and 40 benign on final analysis with SPECT and CT fusion and radiological follow-up. Diagnostic confidence was significantly higher for proper characterization of 17 indeterminate lesions (15 characterized as benign and two as malignant) due to the fusion of SPECT and diagnostic CT. Benign lesions consisted of arthritis, compression fractures of osteoporotic vertebral bodies, old rib fractures, etc. Malignant lesions showed osteolysis or sclerotic changes on CT. A few hot foci could not be properly characterized on CT, and these were either located very close to articulations or had no corresponding CT changes.

The studies discussed above clearly point out that integrated, high-quality, diagnostic CT with SPECT can improve the characterization of indeterminate bone lesions, and the additional CT information on individual lesions influences management.
A study performed to determine the value of SPECT/CT with integrated, multislice, diagnostic CT in the characterization of indeterminate bone lesions was performed by the University of Erlangen. An approach of "SPECT-guided CT" was used by which lesions difficult to characterize on SPECT were then subjected to limited, diagnostic CT so as to minimize radiation exposure and to obtain the maximum information. In 44 patients, 52 lesions were labeled on planar and SPECT as indeterminate and were subjected to SPECT/CT with diagnostic CT and, as 35 of 52 (63%) lesions were clearly characterized as benign by diagnostic CT. Most of these lesions were osteochondrosis, spondylitics, and spondyloarthrosis of the spine; 15 of 52 (29%) lesions were clearly determined as malignant due to osteolysis or bony sclerosis visible on CT. Four lesions (8%) remained indeterminate even after CT. Of these, two were in the scapula and two in the ribs. There were no characteristic CT changes associated with these lesions, and additional investigations and follow-up were deemed necessary. However, the percentage of lesions, which remained indeterminate after SPECT in combination with diagnostic CT, was very low.

Other studies have demonstrated similar accuracy. SPECT/CT with integrated spiral CT was used to study 141 bone lesions of 125 cancer patients with nonspecific bone findings on MDP bone scintigraphy. The final diagnosis was based on biopsy results and radiologic follow-up over one year. SPECT/CT showed sensitivity and specificity of 98.4 percent and 93.6 percent compared to 82.5 percent and 66.7 percent with that of SPECT. These values, using SPECT evaluation with side-by-side CT reading, were 93.7 percent and 80.8 percent. This clearly demonstrates the additional value of integrated, diagnostic CT with SPECT, particularly because of the accuracy of fusion due to integrated hybrid imaging. Among 37 equivocal lesions seen with SPECT, the diagnosis was clarified with SPECT/CT in 32. Of the five lesions, which could not be clearly defined by SPECT/CT, only one proved to be malignant in a follow-up period of one year.

A new study determined the added value of multislice SPECT/CT in evaluation of equivocal bony lesions in patients with prostate carcinoma. Using SPECT/CT with integrated 16-slice diagnostic CT, 40 consecutive patients with prostate cancer were studied using 99mTc-MDP. Of 50 focal lesions of abnormal tracer uptake, 61 percent (30/50) were termed equivocal on planar and SPECT imaging. However, after SPECT/CT evaluation only 8 percent were still termed equivocal. Thus, the use of SPECT/CT with integrated diagnostic CT was able to clarify the diagnosis in 84 percent of equivocal lesions. In the majority of cases, SPECT/CT was able to clearly pinpoint benign (24%) or malignant (68%) lesions due to the morphological clarity provided by CT. Six vertebral lesions in five patients were reclassified based on CT findings like sclerotic vertebral lesions on CT, suggesting malignancy or compression fracture in the vertebrae indicative of the benign nature of the uptake. Certain SPECT/CT uptake patterns were rated as benign uptake at the edge of vertebral bodies adjacent to the disc space or uptake in the facet joints but sparing the pedicles. However, uptake within vertebral bodies including pedicles was suggestive of metastases.

Several studies and case reports demonstrate the value of SPECT/CT in evaluation of bone lesions unrelated to cancer. SPECT/CT has positively influenced clinical decision-making in orthopedics, particularly in stress fractures, osteomyelitis, arthritis and other joint conditions.

A recent study used SPECT/CT to evaluate post-operative knee pain. SPECT/CT was helpful in establishing the cause of pain in patients treated with surgery for knee osteoarthritis like high tibial osteotomy or medial unicompartmental arthroplasty.

Another study used SPECT/CT for precise localization of osteoarthritic changes in 20 patients with pain of uncertain origin in the foot and ankle. Intraobserver reliability for SPECT/CT for lesion localization was significantly higher than CT and SPECT evaluated separately. Reliability of lesion localization was particularly significant with SPECT/CT when evaluating the naviculocuneiform and tarsometatarsal joints. This study clearly demonstrated the usefulness of SPECT/CT in localizing active arthritis in the ankle where the number of joints and anatomical complexity creates difficulty in exact localization of arthritic foci.

The same study also used SPECT/CT for the assessment of coronal plane hindfoot deformities in 27 patients with varus or valgus malalignment in the ankle. The amount of deformity, stage of osteoarthritis, and level of activation on SPECT/CT was correlated with radiography. The stage of osteoarthritis seen on plain radiographs correlated significantly with the level of activity detected on SPECT/CT. The varus malaligned ankles showed higher radioisotope uptake in the medial areas, while the valgus malaligned ankles showed increased uptake in the lateral areas on SPECT/CT. SPECT/CT was of value for the assessment of the degree and staging of osteoarthritis secondary to hindfoot deformity. Diagnostic CT integrated with SPECT thus shows a major advantage in characterization of skeletal lesions and improves therapeutic decision making by providing comprehensive morphological and functional information in a single study.
A few examples using Symbia® TruePoint SPECT•CT from the University of Erlangen, the same group which published the paper on the role of SPECT/CT in the clarification of indeterminate bone lesions, illustrate the major advantage of its use. The first case (Figure 4-1), of an 84-year-old male with malignant melanoma, shows SPECT•CT images of vertebral bodies, which had small focal hypodensity/osteolysis in the C5 vertebrae. SPECT showed multiple foci of increased uptake in the mid-cervical spine, which, after coregistration with diagnostic CT, were confirmed as massive degenerative changes. The small lytic area in vertebral body showed an absence of tracer uptake, thereby confirming its benign nature (Schmorl’s node). The study was performed on a Symbia T2 with integrated, dual-slice, diagnostic CT.
The second case (Figure 4-2) illustrates the value of accurate localization of a SPECT lesion by CT and the relevance of CT findings for diagnosis. This was a patient with a focal area of increased uptake in the right acetabulum in a planar bone scan who had associated joint pain. A SPECT-CT performed with integrated, dual-slice, diagnostic CT with sharp kernel reconstruction showed the focal hot area on SPECT to be localized in a small area of sclerosis in the acetabular margin, while a larger lytic area adjacent to the focal SPECT lesion showed an absence of tracer uptake. This accurate localization of the SPECT lesion and associated CT findings of minor sclerosis defined the lesion to be related to severe arthritic changes, while the lytic area on CT was determined to be a subchondral cyst also related to the arthritic process.
More case examples from Symbia TruePoint SPECT•CT were provided by users. A $^{99m}$Tc-MDP bone SPECT study on a 40-year-old patient, with a suspected bone tumor in the right humeral head, showed focal hypermetabolism in the humeral head, which was indeterminate (Figure 4-3). Diagnostic CT, performed as an integrated procedure, demonstrated focal lytic areas with surrounding sclerosis typical of a benign bone tumor likely to be an osteochondroma.
Another example (Figure 4-4) involved a patient who presented with pain in the left foot. Bone SPECT showed a small focal area of increased uptake in the tarsal bone. SPECT•CT performed with integrated 6-slice CT localized the lesion to the lytic area surrounded by the zone of sclerosis within the middle cuneiform bone. Localization of this small Brodie’s abscess in a tarsal bone of 1.5 cm size was assisted by integrated, thin-slice, spiral CT with SPECT.

This example (Figure 4-5) is of a patient with a backache where ⁹⁹ᵐTc-MDP bone SPECT showed a focal area of increased uptake in the L3 vertebral body. SPECT was coregistered with diagnostic CT performed as part of an integrated SPECT•CT procedure, and reconstructed with thin slices and sharp kernel. The image showed that the focal uptake corresponded to a small well-defined lytic area in the vertebral body, adjacent to the lower end plate with surrounding mild sclerosis. The lytic area seen on CT was typical of a Schmorl’s node, which is a benign lesion. Thus, CT findings were instrumental in clarifying the abnormality seen on SPECT.
This example (Figure 4-6) is of a patient who was treated for prostate cancer and presented with a mild increase in PSA. $^{99m}$Tc-MDP SPECT showed an indeterminate, focal vertebral lesion. Diagnostic CT performed as an integrated SPECT•CT procedure showed an area of lysis one centimeter in diameter with a sclerotic rim in the body of the T3 vertebrae just adjacent to the costovertebral junction. The central part of the vertebral body appeared normal. The lesion was identified as a solitary, atypical metastasis by SPECT•CT due to the characterization of the lytic lesion by diagnostic CT.
This is similar example (Figure 4-7) of a 66-year-old patient with prostate cancer who presented with back pain. A planar bone scan showed a solitary focal area of increased uptake in the right lateral part of the T11 vertebrae, possibly in the pedicle. SPECT•CT, performed on a Symbia T system with dual-slice diagnostic CT, demonstrated the focal uptake exactly at the costovertebral junction and not in the vertebral body. CT also demonstrated the sclerosis in the vertebral facets and not in the adjacent body, which clearly defined the uptake to be related to facet arthropathy and not a metastatic bony lesion.
This example (Figure 4-8) is of a patient with treated breast carcinoma who presented with lower back pain. SPECT showed focal uptake in the L5 vertebrae. To confirm metastases, a SPECT-CT study was performed with integrated, thin-slice CT, which showed degenerative facet arthropathy in the L5 vertebrae with associated sclerosis. This confirmed the benign nature of the lesion.
Another example (Figure 4-9) shows a patient who had pain in the knee joint. A focal hot area in one condyle was seen on SPECT. Coregistration with diagnostic CT showed the focal hot area to correspond to a small, lytic area in the condylar surface, which was confirmed as a subchondral cyst related to arthritic changes. Proper diagnostic confidence was achieved due to the combination of diagnostic CT findings with SPECT.
This example (Figure 4-10) involves a young man with minor ankle trauma who was treated conservatively, but continued to have persistent pain and restriction of movement. SPECT showed two focal areas of increased uptake in the ankle, suggestive of stress fractures. SPECT•CT with integrated, dual-slice, diagnostic CT demonstrated small subchondral fracture fragments involving the posterior calcaneal articular surface of the talus and anterior articular surface of the calcaneus. Focal increase in bone metabolism at the fracture fragment sites is related to shearing stress and the repair process. Accurate visualization of bone fragments by diagnostic CT helped to identify the fracture fragments as a cause for recurrent pain, and surgical removal was required.
This is an example (Figure 4-11) of SPECT•CT-based delineation of a fracture of a small carpal bone. The patient presented with a history of a fall and persistent pain in the wrist. An X-ray of the wrist was normal. A ⁹⁹ᵐTc-MDP SPECT•CT study showed a focal area of increased uptake in the wrist, which was localized to the trapezoid bone. Thin-slice CT showed minor sclerosis without a well-defined fracture line. The patient’s diagnosis was a traumatic fracture of the trapezoid. Examples like these highlight the added value of diagnostic CT integrated with SPECT for improved characterization of skeletal lesions, both in oncology and orthopedics. High-quality CT information along with SPECT helps differentiate malignant from bony lesions with high accuracy, and CT information adds to diagnostic confidence as well as influences management decisions.
This example (Figure 4-12) demonstrates the value of SPECT•CT in evaluation of avascular necrosis. This was a 58-year-old male patient who presented with severe pain in the right hip joint following minor injury. The planar whole-body bone scan did not show focal accumulation of MDP. The CT exam showed diffuse osteoporosis in the right femoral head and neck. Reflex sympathetic dystrophy was suspected. A $^{99m}$Tc-MDP SPECT•CT bone study showed a focal area of increased uptake in a small part of the femoral head. CT showed minor sclerosis along with a small lytic focus in the same area superimposed on the generalized osteoporosis of the femoral head and neck. In view of the localized skeletal hypermetabolism, along with minor sclerosis, this focal femoral head lesion was diagnosed to be a focal avascular necrosis.

Another example (Figure 4-13) demonstrates the relevance of bone changes seen with diagnostic CT in the diagnosis of complex regional pain syndrome. A patient with a history of traumatic lower fibular fracture, treated conservatively, presented with persistent ankle joint pain. A $^{99m}$Tc-MDP bone SPECT•CT study shows increased uptake of the tracer in the lower end of the fibula including the fracture site and adjacent joint space extending into the tibial articular surface with associated osteoporotic changes seen on CT. An increased uptake in the talocalcaneal joint is visualized along with severe talar osteoporotic changes. SPECT•CT findings of skeletal hypermetabolism and corresponding osteoporosis support the diagnosis of complex regional pain syndrome.
This case example (Figure 4-14) is of a 23-year-old male with intermittent bilateral knee pain who underwent a $^{99m}$Tc-MDP bone SPECT•CT. The study shows focal areas of increased uptake of the tracer in the tibial tuberosity on both sides at the insertion of the patellar ligament. Focal increased uptake is also visualized at the femoral end of the capsular ligament as well as at the insertion of the tibial collateral ligament. The pattern of skeletal hypermetabolism at the tibial tuberosity is typical of Osgood-Schlatter's disease, which involves avulsion stress at the tibial tuberosity with associated inflammation of quadriceps tendon. Thin-slice CT helps delineate the exact site of skeletal hypermetabolism, aiding the diagnosis.
SPECT/CT has positively impacted the diagnosis of vertebral infections, compression fractures and other benign lesions. This example (Figure 4-15) shows a case of tuberculous osteomyelitis. A 65-year-old male patient with a history of prostate cancer presented with sudden back pain after lifting a heavy load. The bone scan revealed increased uptake in the T6 vertebrae, suspicious for metastases. A SPECT•CT study demonstrated increased uptake of $^{99m}$Tc-MDP in the bodies of adjacent vertebrae (T5 and T6) and corresponding destruction of the adjacent vertebral bodies and soft tissue mass in the paravertebral space in the CT study. Involvement of adjacent vertebral bodies with bone destruction, hypermetabolism and paravertebral soft tissue mass strongly suggested vertebral osteomyelitis, possibly tubercular. An MRI of the spine also showed vertebral body destruction with disc involvement. High-quality, diagnostic CT combined with SPECT aided in comprehensive diagnosis without the need for further investigation.

This example (Figure 4-16) shows a patient with carcinoma of the nasal sinus, treated with surgery and reconstruction of the nasal septum, who presented with necrotizing external otitis. A SPECT•CT of the bone was performed to evaluate for osteomyelitis. The study shows a focal increase in uptake within the left mastoid air cells. Integrated thin-slice CT shows a loss of mastoid air cells. The SPECT•CT appearance is suggestive of osteomyelitis confined to the mastoid air cells within the temporal bone without extension to the brain or adjacent soft tissue. There is also a focal area of increased uptake in the base of the skull extending to the sphenoid bone which is suspicious of a recurrent tumor. Thin-slice CT helps define mastoid air cells and the absence of soft tissue extension.
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Neuroendocrine Tumors

Neuroendocrine tumors are a heterogeneous group of tumors, 70 percent of which are characterized by their ability to overexpress somatostatin receptors. Typical clinical symptoms are related to hormone secretion from the tumors. The non-secreting tumors are often diagnosed late or even incidentally. Aggressive surgery and treatment with radiolabeled somatostatin analogs have improved survival. Scintigraphy, using a radiolabeled somatostatin analog like 111In-octreotide and 123I-labeled MIBG (for adrenal tumors and somatostatin negative neuroendocrine tumors), is the mainstay of initial diagnosis, as well as evaluation for recurrence.

SPECT/CT has been shown to improve the specificity for the detection of neuroendocrine tumors. An early study using SPECT/CT with low-dose CT5.1 showed that in 41 percent of patients with abnormal SPECT findings, SPECT/CT improved image interpretation by providing a better anatomic localization of SPECT-detected lesions. Another article 5.2 showed that SPECT/CT improved localization of SPECT-detected lesions in all positive studies and brought about a change in management in 25 percent of cases. The limitation of early studies was that low-dose CT was only capable of mere localization of SPECT positive lesions. Their focus was not on the relevance of CT findings as an independent diagnostic factor, and there was no direct comparison or correlation with high-quality diagnostic CT.

Several studies, however, have elaborated on the limitations of low-dose, non-diagnostic CT as a part of a SPECT/CT procedure in the evaluation of neuroendocrine tumors. In a study involving 54 patients with neuroendocrine tumors5.3, SPECT/CT was performed with low-dose CT using 111In-octreotide and 123I-labeled MIBG in relevant patients, and the results were compared with contrast-enhanced, diagnostic CT. There were a total of 114 lesions detected by scintigraphy and/or CT. SPECT/CT and diagnostic CT results were concordant in 49 percent (56/114). In 51 percent of the lesions, interpretation of SPECT/CT-fused images along with side-by-side correlation of contrast-enhanced, diagnostic CT altered the initial diagnosis. Image interpretation was altered in 39 CT and 19 SPECT studies: 31 lesions initially interpreted as benign or equivocal were reclassified as malignant; 12 of these lesions were characterized by diagnostic CT and 8 of these lesions were small liver metastases that were not well visualized on SPECT/CT. Low-dose CT was inadequate for any soft tissue characterization. Seven false-positive findings in SPECT/CT were clearly characterized by diagnostic CT, including focal uptakes in the colon without a clear tumor on CT. Twelve false-negative SPECT findings were reported in patients with small liver metastases, because of a small intestinal carcinoid obscured by physiological uptake in the gut and a lesion by the bladder, which were clearly defined by diagnostic CT. Sensitivity and specificity of SPECT/CT were 91 percent and 75 percent respectively. However, when SPECT/CT was combined with the visual correlation of high-end CT, the sensitivity and specificity increased to 100 percent and 96 percent respectively. According to Pfannenberg et al., “Adding visual correlation of SPECT/CT to high-end CT led to a significant improvement in accuracy in comparison with SPECT/CT alone.” The authors clearly state, “The problem of false-negative SPECT results cannot be solved by SPECT/CT because of inherent low resolution and lack of oral and intravenous contrast of the low-dose CT component. SPECT/CT is better than SPECT or CT alone but cannot replace high-end CT. Therefore a higher end CT component should be implemented in the SPECT/CT device to allow for combined acquisition of high-quality contrast-enhanced CT in addition to SPECT.”

The above study clearly supports the rationale of using Symbia® TruePoint SPECT•CT, which combines diagnostic, multislice CT and dual head SPECT for the more accurate diagnosis of neuroendocrine tumors. Symbia is aimed to ensure the highest level of diagnostic confidence, sensitivity and specificity by combining high-resolution SPECT and diagnostic CT findings in one integrated procedure.

Another group of authors has used separate SPECT and diagnostic CT studies in neuroendocrine tumor patients with fiducial markers and immobilization devices, and has performed software fusion5.4. SPECT was performed with a dual-head gamma camera using 99mTc-octreotide. The patient was immobilized using a vacuum mattress along with multimodality fiducial markers and a separate diagnostic CT with contrast was performed with the patient in the same immobilized position. The accuracy of software fusion was confirmed using the fiducial markers. SPECT without image fusion was true-positive (TP) in 18 patients (34%), true-negative (TN) in 16 patients (30.2%), false-negative (FN) in 10 patients (18.9%) and false-positive (FP) in nine patients (17%). However, when diagnostic CT was fused with SPECT and the fused images were interpreted, the TP results increased to 27 (50.9%) and the TN to 25 (47.2%). There were no false-positives. Only one FN case had very small liver metastases from the intestinal carcinoid, which was missed by both CT and SPECT and later confirmed on MR. Of 103 abnormal findings identified on SPECT, nine lesions were false-positives and 12 lesions were missed by SPECT but identified by diagnostic CT. These included liver metastases, small lung metastases and a small pancreatic head insulinoma. There were discrepancies between the interpretation of the SPECT and the fused SPECT/diagnostic CT in 18 patients (nine FP, nine FN on SPECT), all but one of which were clarified by diagnostic CT. Image fusion provided further clinically relevant information in 21 patients (40%), and seven patients were upstaged. False-positive SPECT lesions consisted of tracer uptake in the gall bladder and nonspecific uptake in the small bowel and the colon. Diagnostic CT with contrast was required to characterize these lesions.

This study clearly demonstrates the additional value of diagnostic CT for characterizing indeterminate or false-positive
lesions on SPECT, as well as for delineating lesions not well defined on SPECT, either because of the small size, low tracer uptake or problems in delineation on SPECT due to interference from physiological uptake. The author states, “Integrated diagnostic CT also yielded additional information in a further nine patients in whom the initial SPECT evaluation was negative and provided valuable supplementary information about the true nature of the SPECT findings in some other patients. It is important to characterize certain morphological features indicative of malignancy on diagnostic CT, e.g. contrast medium enhancement, even in the absence of corresponding tracer uptake. This especially applies to tumor entities with a lower density of somatostatin receptor expression, e.g. thyroid carcinomas”.

A recent study used a Symbia SPECT•CT with integrated 6-slice diagnostic CT to assess the incremental diagnostic value of $^{111}$In-octreotide SPECT/CT imaging compared with planar and SPECT imaging. Forty-nine patients with neuroendocrine tumors (carcinoid tumors, medullary thyroid cancer, paragangliomas and multiple endocrine neoplasia type 2) were evaluated. $^{111}$In-octreotide SPECT/CT improved lesion localization compared to planar and SPECT in 62 percent of the lesions (55/89). In 31 of 89 lesions, SPECT/CT localized the lesion in a different organ compared to the impression from planar and SPECT. SPECT/CT improved lesion characterization in the classification of 28 percent (25/89). Eighteen additional sites of disease were identified using SPECT/CT compared to planar imaging. Seven lesions deemed metastatic on SPECT were characterized as physiologic on SPECT/CT. CT findings that characterized focal tracer uptake as physiologic included fusion of activity to a normal gallbladder, liver, spleen, kidneys, thyroid and bowel, including demonstration of splenules in two cases, which may otherwise have been characterized as metastatic abdominal nodes. SPECT/CT demonstrated incremental diagnostic value in 20 of 49 patients (40.8%) and changed management in 12 of these 20 patients.

Clinical data found in these previous examples point clearly to the major role that can be played by integrated, diagnostic, multislice CT as an integral part of the SPECT evaluation of neuroendocrine tumors. To illustrate the efficacy of the Symbia TruePoint SPECT•CT system in this disease segment, let us look at a few case examples.

The first (Figure 5-1) is a case of a patient with an intestinal carcinoid, which was treated by surgery, who presented with recurrent symptoms of carcinoid syndrome. An $^{111}$In-octreotide SPECT•CT with integrated contrast CT comprising a three-phase liver study was performed on a Symbia T6. SPECT identified two focal lesions, one clearly within the liver. The other was in the liver margin, but it was not clear from the SPECT if it was within...
Another case (Figure 5-2) involves a patient who presented with symptoms of a carcinoid tumor. An $^{111}$In-octreotide SPECT•CT was performed with an integrated three-phase contrast CT. The SPECT showed focal uptake in the abdomen, which was localized to the pancreatic head by the SPECT•CT fusion. Contrast CT during the arterial and venous phases showed enhancement in a well circumscribed area in the anterior aspect of the pancreatic head, which coregistered exactly to the focal area of uptake of $^{111}$In-octreotide. This suggested that the region of contrast enhancement was the tumor surrounded by normal pancreatic parenchyma. Localization of the tumor and clear separation from normal tissue in the head of the pancreas gave the surgeon the ability to resect the tumor while sparing as much normal pancreatic tissue as possible. Only integrated, diagnostic CT with contrast results in such differentiation, which impacts the surgical plan and enables normal tissue to be spared.
Another similar case (Figure 5-3) illustrates the value of high-resolution breath-hold contrast CT in tumor localization, particularly if the tumors are small. This case shows a small carcinoid tumor in the uncinate process of the pancreatic head, which was clearly localized due to the high-quality breath-hold contrast CT that defined the relationship of the lesion to the major vessels. In view of the absence of organ motion due to breath-hold CT, it was easier to localize the lesion, thereby aiding the surgeon and preventing extended surgical exploration. Case examples like these illustrate the value of diagnostic CT with an integrated SPECT/CT in the evaluation of neuroendocrine tumors. Improved diagnostic confidence, due to such technological advancements, should put SPECT/CT with $^{111}$In-octreotide on par in accuracy with $^{68}$Ga DOTATOC PET/CT. At present, the available literature only compares PET/CT with $^{111}$In-octreotide SPECT. One study\textsuperscript{5,6} showed a clear advantage of PET/CT over SPECT. SPECT had a high number of false-negatives. SPECT/CT with diagnostic CT and contrast should significantly improve its accuracy, and further studies comparing this approach to PET/CT are warranted.
This case example (Figure 5-4) is of a 67-year-old male patient who presented with upper abdominal pain. A USG-guided biopsy of a liver lesion showed a carcinoid tumor. $^{111}$In-octreotide SPECT•CT shows multiple liver metastases with avid tracer uptake, which are hypodense on noncontrast CT, and showed CT contrast enhancement. A mass in the splenic flexure shows avid tracer uptake and mild contrast enhancement on CT and appears to be a primary intestinal carcinoid. A paraaortic nodal metastasis was also demonstrated with avid tracer uptake. Contrast enhancement on CT often helps characterize small focal metastatic sites.
This example (Figure 5-5) is of a 51-year-old female with hemangiopericytoma in the frontal lobe referred for an $^{111}$In-octreotide SPECT•CT study to evaluate for somatostatin receptor-positive metastases. The study shows tracer-avid metastases in the liver. Integrated contrast-enhanced CT shows corresponding areas of focal decreased enhancement in the liver. Small focal uptake in the thorax localized to the right eighth rib was also confirmed as metastatic.
Another example (Figure 5-6) is of a 68-year-old male patient who presented with medullary carcinoma of the thyroid and suspected metastases. $^{111}$In-octreotide SPECT•CT shows tracer-avid functioning lymph node metastases, involving the superior mesenteric nodal group, at the level of upper margin of the body of the pancreas, adjacent to the superior mesenteric vein. Integrated diagnostic CT helps to accurately localize lymph nodes and helps to differentiate functioning metastases from physiologic uptake in the bowel.
This example (Figure 5-7) demonstrates the value of SPECT•CT for delineation of a primary carcinoid tumor in a patient presenting with multiple metastases. This is a 37-year-old male patient presenting with carcinoid syndrome with liver and paraaortic metastases visualized on CT. $^{111}$In-octreotide SPECT•CT showed multiple $^{111}$In-octreotide-avid functioning metastases in the right lobe of the liver with corresponding CT hypodensities. Several large paraaortic lymph node metastases were visualized at the level of the renal arteries. A small focus of increased uptake localized to the tail of the pancreas (green arrow) was defined as the primary carcinoid tumor. Integrated diagnostic CT helped accurately localize the small focal uptake of $^{111}$In-octreotide to the pancreatic tail thereby delineating the primary tumor from several adjacent paraaortic lymph node metastases.
This example (Figure 5-8) shows SPECT•CT localization of gastrinoma. A patient with abdominal pain and persistent high-serum gastrin levels underwent an $^{111}$In-octreotide SPECT•CT study for localization of a suspected neuroendocrine tumor. Breath-hold diagnostic CT was performed as an integrated procedure. The study shows an increased uptake of the tracer in the soft tissue mass located between the gastric antrum and the head of the pancreas suggestive of a gastrinoma without evidence of functioning peri-pancreatic, paraaortic or liver metastases. Clear localization of the lesion behind the pancreatic head due to integrated breath-hold diagnostic CT was of help for surgical planning.
The last example (Figure 5-9) is of a 77-year-old woman with ileocecal resection secondary to a carcinoid tumor. She presented with symptoms of carcinoid syndrome, including flushing and diarrhea, along with elevation of tumor marker chromogranine A. Planar $^{111}$In-octreotide images showed increased uptake in the posterior aspect of the thorax as well as in the diaphragmatic region. SPECT-CT demonstrated octreotide-avid metastases in the third rib on the right, as well in the anterior mediastinum, attached to the pericardium and infiltrating into the ventricular wall.

References:


Pheochromocytoma and Neuroblastoma

Pheochromocytoma is a neuroendocrine tumor in the medulla of the adrenal glands (originating in the chromaffin cells) or extra adrenal chromaffin tissue, which secretes excessive amounts of catecholamines. Extra adrenal paragangliomas are closely related to tumors that originate in the ganglia of the sympathetic nervous system: 90 percent occur in adults and 10 percent of the tumors are extra-adrenal.

Neuroblastoma is a neuroendocrine tumor arising from any neural crest element of the sympathetic nervous system and is seen in children, with 50 percent of the cases occurring in children less than two years old. Neuroblastoma presents as solid tumors, which take the form of a lump or mass, and commonly begin in one of the adrenal glands, although they can also develop in nerve tissue in the neck, chest, abdomen or pelvis.

Both pheochromocytoma and neuroblastoma can be imaged by scintigraphy using $^{123}$I or $^{131}$I MIBG scintigraphy; in certain cases $^{131}$I MIBG therapy has been used for treatment. SPECT/CT has been used to improve scintigraphic imaging of these tumors due to the improved localization of lesions and attenuation correction.

Using SPECT and low-dose non-diagnostic CT, one group$^{6,1}$ studied 31 patients with suspected pheochromocytoma. In 74 percent of the cases, SPECT/CT fusion images demonstrated the benign or physiological nature of the uptake seen on SPECT. In six percent of the cases, the primary adrenal tumor was correctly localized by CT. Bone metastases were correctly identified in six percent of the cases, and liver metastases were identified in six percent of the cases. Due to poor-quality CT, the study did not comment on CT findings independent of SPECT, nor was there follow-up documenting false-negative SPECT studies.

Another more recent study$^{6,2}$ using SPECT with low-dose, non-diagnostic CT imaged 11 patients (3 pheochromocytoma and 8 neuroblastoma) with $^{131}$I MIBG SPECT/CT and compared the results with diagnostic CT. Of the 15 imaging studies there were nine cases of discordance between diagnostic CT and SPECT/CT (within integrated, low-dose CT). SPECT findings helped clarify abnormalities in diagnostic CT, especially in one case of pheochromocytoma where anatomy was distorted due to surgery, and the adrenal gland had shifted from its normal position. Correlation of SPECT and diagnostic CT was essential to correctly localize and define the tumor. In another case, also with distorted anatomy, a soft tissue mass was characterized by diagnostic CT based on SPECT findings. In four patients with neuroblastoma, a residual mass was identified where $^{131}$I MIBG was negative. This study illustrates the additional value of diagnostic CT over that of integrated, low-quality CT for the localization of SPECT masses in areas of distorted anatomy, as well as in the characterization of residual masses without MIBG uptake, and the clarification of false-negative scintigraphy situations.

The shortcomings of SPECT/CT with low quality CT are further explored in another paper$^{6,3}$, which compared $^{11}$C hydroxyephedrine PET/CT with $^{123}$I MIBG SPECT/CT in 19 patients. PET/CT identified 80 out of 81 total detected lesions while MIBG SPECT/CT identified 75 out of 81 lesions. PET/CT had 99 percent sensitivity compared to 93 percent with SPECT/CT. Of 61 soft tissue lesions identified by PET/CT, only 56 were identified by SPECT/CT. Six soft tissue lesions were false-negative by $^{123}$I MIBG SPECT/CT. Thus, false-negatives of MIBG SPECT are a concern and define the major role of CT in combination with SPECT for complete evaluation.

Studies comparing the fusion of separately performed SPECT and diagnostic CT in pheochromocytoma patients have also been conducted. One study$^{6,4}$ evaluated 76 patients (60 adrenal and 33 extra-adrenal tumors) with both preoperative $^{123}$I MIBG, CT and MR for primary pheochromocytoma. The overall sensitivity of $^{123}$I MIBG was 75 percent. Tumor detection was lower for extra-adrenal (58 percent) versus adrenal (85 percent) pheochromocytomas. $^{123}$I MIBG missed four carotid body tumors, four retroperitoneal, and one pelvic pheochromocytoma. MRI and CT demonstrated 68 of 68 and 72 of 74 primary pheochromocytomas, respectively. Two large $^{123}$I MIBG negative adrenal tumors contained large areas of necrosis or hemorrhage. CT and MR identified all false-negative $^{123}$I MIBG lesions.

Another study$^{6,5}$ evaluated 64 patients with suspected pheochromocytoma using $^{123}$I MIBG scintigraphy and CT. Twenty-five patients were finally diagnosed and operated for primary pheochromocytoma. The remaining 39 patients had no proof of pheochromocytoma. Sensitivity for MIBG scintigraphy was 88 percent (22/25) and for CT was 100 percent (25/25). The specificity for MIBG scintigraphy was 89 percent (35/39), but only 50 percent for CT (18/36). Two of six extra-adrenal tumors were among the false-negative MIBG scintigrams, which were identified with CT.

These studies illustrate the value of $^{123}$I MIBG scintigraphy combined with diagnostic CT. Diagnostic confidence is enhanced by the addition of diagnostic CT, which not only helps to accurately localize SPECT-positive lesions, but also helps identify lesions in patients with false-negative SPECT studies.

The combination of SPECT and diagnostic CT also helps in the planning of $^{131}$I MIBG therapy in such patients. A study$^{6,6}$ using a combination of diagnostic CT with SPECT demonstrated that anatomic information from coregistered CT images can improve the measurement of $^{131}$I MIBG uptake in tumors, which can influence determination of therapy doses.

Another study$^{6,7}$ was conducted using $^{123}$I MIBG SPECT/CT with integrated diagnostic CT to assess improvement in diagnostic
confidence for localization of pheochromocytoma, particularly in patients at high risk of multifocal or recurrent disease. Twenty-two patients had $^{123}$I MIBG SPECT/CT imaging for a suspected pheochromocytoma. Fourteen patients had positive lesions on SPECT/CT all of which correlated with CT and MR findings. SPECT/CT provided additional information altering the original diagnosis in six patients. In five patients with a pheochromocytoma-associated germline mutation, SPECT/CT ruled out multifocal disease. $^{123}$I MIBG SPECT/CT demonstrated a significant advantage in detection of local recurrence, small extra-adrenal pheochromocytomas and multifocal tumors as well as accurate detection and localization of metastases.

Symbia® TruePoint SPECT•CT is ideally suited for the comprehensive evaluation of pheochromocytoma and neuroblastoma with $^{123}$I MIBG SPECT in combination with diagnostic CT, with or without contrast. A few clinical case examples performed on Symbia TruePoint SPECT•CT amply illustrate the clinical value of integrated diagnostic CT for localization and characterization of lesions as well as for providing additional information relevant for a comprehensive diagnosis.

Figure 6-1 Data courtesy of the University of Minnesota Medical Center – Fairview, Minneapolis, MN, USA

The first case (Figure 6-1) shows the follow-up $^{123}$I MIBG SPECT•CT of a 20-year-old female patient with a long history of neuroblastoma who was treated with surgery and radionuclide therapy. The study shows tracer-avid functioning metastases in the body of the sacrum and in the L4 and L5 vertebral bodies as well as in the left ilium and in the trochanter of the left femur. CT demonstrated mild sclerosis in the affected vertebrae and in the sacrum. No abnormal soft tissue uptake was visualized. The patient was referred for further $^{131}$I MIBG therapy. The accurate coregistration of SPECT uptake with diagnostic, spiral CT is effective in the determination of accurate tumor burden and in the planning of $^{131}$I MIBG therapy.
The second example (Figure 6-2) is of a 14-year-old male patient with neuroblastoma that was treated with surgery followed by $^{131}$I MIBG therapy. The follow-up $^{123}$I MIBG SPECT•CT study shown here was performed six months later. The study demonstrated tracer-avid paraaortic lymph node metastases at the level of the renal arteries and also, in the pelvis at the level of the iliac bifurcation. Integrated diagnostic CT clearly defined the lesion and its relation to surrounding structures, including the aorta and renal vessels. Significant reduction in metastatic burden was visualized when compared to the SPECT study that was performed nine months before MIBG therapy.

This case (Figure 6-3) illustrates the value of integrated contrast CT as a part of a $^{123}$I MIBG SPECT•CT study of an 83-year-old female with MEN 2A syndrome. The patient underwent a thyroidectomy for medullary thyroid cancer. There was persistent hypertension with elevated serum metanephrine. The $^{123}$I MIBG SPECT•CT study showed increased activity in the left adrenal and the right supraclavicular region. A sequentially performed contrast CT study demonstrated a non-enhancing mass in the left adrenal with an enhancing rim of normal adrenal cortical tissue. Fusion images showed SPECT focal uptake corresponding exactly to the adrenal mass. Abdominal surgery was performed and the adrenal mass removed. Histopathology showed pheochromocytoma. The patient also had right supraclavicular metastases, which showed significant enhancement with contrast, suggesting that metastatic lesions had a different character as compared to the primary tumor in this case.
Figure 6-3  Data courtesy of Maaslandziekenhuis, Sittard, The Netherlands
Another case example (Figure 6-4) shows $^{123}$I MIBG SPECT•CT performed on a Symbia T6 in a 6-year-old male patient with neuroblastoma. An $^{123}$I MIBG study showed a large tracer-avid paraaortic mass. Integrated contrast CT demonstrated a larger tumor mass with multiple focal calcified areas, which did not show MIBG uptake. Diagnostic CT performed as an integrated procedure demonstrated a larger tumor with calcified areas deemed nonfunctioning by MIBG SPECT. The extent of required surgical resection was better defined by integrated, diagnostic CT compared to SPECT alone. The patient was spared additional investigations due to the information provided by the SPECT•CT study.
This example (Figure 6-5) is of an $^{123}$I MIBG SPECT•CT study in a patient with primary adrenal pheochromocytoma which shows a focal area of increased uptake in the left adrenal gland with adjacent uptake in the paraaortic area suggestive of extension of the primary tumor. Diagnostic CT is helpful in defining the true extent of the tumor and its relationship to surrounding structures.
The next example (Figure 6-6) shows an $^{123}$I MIBG SPECT•CT study for restaging in a patient with neuroblastoma who was treated with surgery. The image shows increased uptake of the tracer in the left acetabulum with corresponding lytic area interspersed with zones of sclerosis seen on CT. Smaller tracer-avid focal areas are also visualized in the right iliac crest just above the acetabulum.
In some situations, diagnostic CT identifies lesions not visible on SPECT, which may add value to patient management. In this example (Figure 6-7) a seven-year-old male patient with metastatic neuroblastoma presented with a large pelvic mass with calcification. An $^{123}$I MIBG SPECT•CT study showed high uptake in the primary tumor site in the pelvis. However, contrast CT performed as an integrated procedure showed a small retroperitoneal paraaortic mass at the level of and posterior to the renal arteries, which did not show MIBG uptake but appeared to be a metastasis. Due to integrated diagnostic CT the additional lesion was delineated, which radically altered the management, as well as the prognosis, of this patient.

References:


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Lymphoscintigraphy

Lymphoscintigraphy for detection of sentinel lymph nodes in breast carcinoma and melanoma has become an integral part of management. SPECT/CT has improved the sensitivity of lymphoscintigraphy, leading to the detection of more nodes compared to planar lymphoscintigraphy, and the localization of nodes has resulted in improved surgical planning for sentinel node biopsy.

One study evaluated 157 patients with breast carcinoma using SPECT/CT. Planar lymphoscintigraphy identified 329 hot nodes in 134 (85%) women. Four percent of these hot lesions were identified by SPECT/CT as false-positive, non-nodal sites of uptake. SPECT/CT identified 361 hot nodes in 142 (90%) patients. Five percent of the patients had sentinel nodes detected only on SPECT/CT. Nine percent of the patients had non-visualized nodes both on planar and SPECT/CT. Three percent of the nodes identified on SPECT/CT were located in less common drainage sites, including interpectoral and internal mammary lymph nodes. SPECT/CT detected far more nodes compared to planar when the primary breast lesion was non-palpable. In 14 out of 15 patients with non-detected nodes on SPECT/CT, sentinel nodes were identified using an intraoperative gamma probe. All these nodes had very low counts on the intra-operative probe. SPECT/CT was positive in 13 patients with negative planar imaging. Several nodes identified only by SPECT/CT were not visualized on planar because they were obscured by scattered radiation from the primary injection site, or because separate, but adjacent, nodes were interpreted as a single node on planar imaging. This study highlights the value of SPECT/CT in identification of additional nodes, as well as more accurate localization of sentinel nodes. The identification of internal mammary or interpectoral nodes only by SPECT/CT is of clinical importance since these nodes are often not considered for surgical sampling and may be involved with disease in up to 9.8 percent of operable breast cancers. Non-visualization of sentinel nodes with SPECT/CT may be related to tumor infiltration in these nodes or problems with the injection technique.

Sentinel node identification by SPECT/CT lymphoscintigraphy using low-dose, non-diagnostic CT in melanoma of the head and neck region has been studied by Mar et al. In patients with melanoma in the head and neck, it is difficult to predict lymphatic drainage due to the extensive lymphatic network in the cervical region. This study recommended the use of dynamic, planar imaging combined with delayed SPECT/CT to identify the sentinel nodes. The problem of masking small sentinel nodes by the scatter from the tracer injection in the primary lesion is also of major concern in these patients.

Diagnoses of head and neck malignancies do benefit significantly from SPECT/CT lymphoscintigraphy. In a study from Austria, using SPECT/CT with low resolution CT, 30 patients with squamous cell carcinoma of the head and neck were evaluated. Planar and SPECT/CT were compared. Seven of 30 patients demonstrated lymphatic flow in the contralateral side of the neck. Forty-nine sentinel nodes were identified by SPECT/CT, whereas only 38 were identified on planar imaging. In 11 of 30 cases, an unpredictable pattern of lymphatic drainage was observed.

Problems of identification of small sentinel nodes in head and neck cancer, often with unpredictable distribution, highlight the value of integrated, diagnostic CT combined with SPECT for improved lymphoscintigraphic accuracy. Diagnostic CT was used to define deep-seated oropharyngeal tumors and for CT-guided, intratumoral injections for lymphoscintigraphy on a stand-alone gamma camera in another study. Thirteen patients with squamous cell carcinoma in the larynx and hypopharynx, who could not be injected by visual inspection, were injected using a diagnostic, CT-guided procedure prior to lymphoscintigraphy. Sentinel nodes were identified in 9 out of 13 patients. This study demonstrates the potential of integrated, diagnostic CT for lymphoscintigraphy of head and neck tumors where accurate visualization of the tumor prior to injection followed by SPECT/CT with thin-slice, high-quality CT should identify sentinel nodes in otherwise remote, deep-seated tumors. Accurate surgical planning for sentinel node biopsy in deep oropharyngeal tumors definitely has a major impact on management and may spare extensive blind lymph node dissection in a subgroup of patients.

One study using SPECT/CT with low-resolution, non-diagnostic CT in overweight patients with breast carcinoma found sentinel nodes in 59 percent of patients in whom planar lymphoscintigraphy failed to identify sentinel nodes. In a cohort of 220 overweight patients, planar imaging identified 337 hot nodes. Of these, 317 sites were identified as sentinel nodes in 171 patients (78%), while the other 20 were termed as false-positive, non-nodal uptake (skin folds, propagation from the injection site, leakage from the wire tract, sternoclavicular joint uptake and mediastinal uptake in blood vessels) by SPECT/CT. In 200 patients (91%), 402 hot nodes were identified while in nine percent of the patients, SPECT/CT also failed to visualize sentinel nodes. Fifty-nine percent of the patients (29/49), with non-visualization of lymph nodes on planar studies, had visualization with SPECT/CT. Eighty-five hot nodes included nodes obscured by activity in the injection site, separated adjacent nodes and nodes revealed by improved spatial resolution of SPECT, as well as improved attenuation correction by SPECT/CT. Rates of sentinel node detection by planar and SPECT/CT were 78 percent and 91 percent respectively. However, SPECT/CT was unable to
identify sentinel nodes, visualized only by SPECT/CT, in 20 of the patients, most of whom were grossly overweight (BMI >29.5). In 12 of these 20 patients, an intraoperative gamma probe and blue dye technique failed to identify sentinel nodes. In five of these patients, sentinel nodes were full of tumors, which may have contributed to non-visualization. Even with non-diagnostic CT, the advantage of SPECT/CT lymphoscintigraphy in overweight patients was very clear from this study. In view of the difficulty in localizing small structures in obese patients, high-quality, diagnostic CT integrated with SPECT is ideally suited to improve visualization and localization of sentinel nodes, and also for the visualization of enlarged or borderline enlarged nodes, which may be tumor infiltrated and not visualized on SPECT. Improved attenuation correction and SPECT resolution also contribute to better results in such overweight patients.

Lymphoscintigraphy with SPECT/CT using integrated, multislice diagnostic CT has been studied in breast carcinoma and melanoma patients by another group that studied 31 breast cancer and nine melanoma patients who had inconclusive planar studies. SPECT/CT identified sentinel lymph nodes in all patients and helped surgeons plan the biopsy procedure. In breast cancer patients, SPECT/CT localized the exact position of the internal mammary and interpectoral lymph nodes to the exact intercostal space or intermuscular fascial plane for accurate surgical retrieval. Planar imaging identified 96 sentinel nodes in 37 of 40 patients. SPECT/CT identified six additional nodes in four patients, apart from the ones identified on planar. In three patients with non-visualized nodes on the planar study, SPECT/CT was able to localize sentinel nodes. Two of the six nodes visualized only on SPECT/CT were tumor-positive. These two nodes were the only tumor-positive nodes in these two involved patients, and demonstration of these nodes by SPECT/CT had a major impact on management. In seven patients (18%), 15 additional nodes were identified intraoperatively by a gamma probe or blue dye, which were not visualized on SPECT/CT. These were mostly sentinel nodes clustered together and appearing as a single node on SPECT/CT. Two of these nodes were tumor positive. This study highlights the value of integrated, diagnostic CT in localization of the internal mammary chain of nodes since management modifications in 29 percent of patients are due to the presence of these nodes. In melanoma, SPECT/CT was especially helpful in localizing sentinel nodes draining from primary tumors high on the trunk and in the head and neck region. In four melanoma patients, six additional sentinel nodes were identified by SPECT/CT, of which two were tumor-positive. Accurate localization of small nodes in the head and neck region, due to integrated, diagnostic CT, contributed substantially to improved surgical planning and subsequent management.

Non-visualization of sentinel nodes on planar lymphoscintigraphy has been studied using SPECT/CT with diagnostic, multislice CT in another study. Fifteen breast carcinoma patients with non-visualization and 13 patients with extra-axillary sentinel node visualization on planar lymphoscintigraphy were studied using SPECT•CT (Symbia® T). SPECT•CT demonstrated sentinel nodes in eight of 15 (53%) patients with non-visualization on planar, including axillary and internal mammary nodes. Three of these nodes only visualized on SPECT•CT were tumor-positive. Of the seven patients with non-visualization on SPECT•CT, a blue dye method delineated five nodes, two of which were involved with the tumor. In 13 women with extra-axillary sentinel nodes on planar, SPECT•CT identified axillary sentinel nodes in only two patients, but clearly localized the extra-axillary nodes in all patients. Relatively low axillary sentinel node visualization with SPECT•CT in this group of patients with extra-axillary nodal visualization suggests that tumors in some areas of the breast may have a predominantly extra-axillary distribution. Visualization of only extra-axillary nodes was associated with previous therapy of the same breast in two patients.

All these studies in breast carcinoma patients highlight a common finding that extra-axillary localization of sentinel nodes, especially in internal mammary and interpectoral nodes, has a major impact on management. With its improved delineation of soft tissue, muscle and facial planes as well as costal cartilage and intercostal spaces, SPECT/CT with integrated, diagnostic, multislice CT is uniquely suited to provide additional value in lymphoscintigraphy. The issue of non-visualized sentinel lymph nodes is complicated by the presence of tumor cell deposits, which may hinder uptake of radiolabeled colloid and cause non-visualization even with SPECT/CT. In such situations, high-quality, diagnostic CT, preferably with thin slices, may be able to delineate borderline nodal enlargement, which may alert the surgeon to the possibility of tumor deposits in the main sentinel node.

It is well known that sentinel node biopsy is not 100 percent accurate for the prediction of subsequent lymph node metastases, and that nodal metastases have been reported in patients with negative sentinel node biopsy results. There is a strong belief that in several tumors the principal sentinel node may often be non-visualized due to tumor infiltration, and the lymph may be diverted to secondary nodes, which are then identified as sentinel nodes but which may be free of tumor cells and, therefore, may mislead the management. It is, thus, of utmost importance that tumor-positive, sentinel nodes are not overlooked, and high-quality, morphological imaging, like diagnostic CT combined with SPECT, may aid in this goal. This
assumption was tested in a study of 17 patients with penile cancer with unilaterally enlarged and palpable inguinal lymph node metastases, who were evaluated with SPECT/CT lymphoscintigraphy using integrated, diagnostic CT. SPECT/CT revealed an uptake of radioactivity in only four of 17 palpable nodal metastases, thus demonstrating the extent of sentinel node non-visualization due to tumor involvement. Rerouting of lymph to a neo-sentinel node was visualized in 10 of 17 (59%) patients. Nine of these neo-sentinel nodes were located in the ipsilateral groin, and one was located in the contralateral inguinal region. In three patients, there was a complete absence of any lymphatic drainage to other nodes.

The authors note, “The phenomenon of tumor blockage and rerouting of lymphatic drainage was demonstrated for lymph nodes with clinically palpable metastases. It seems plausible that this observation can be extrapolated, at least in part, to lymph nodes with nonpalpable metastases. Such nodes cannot be detected by physical examination either because of their small size or because the patient is obese.”

Thus, this study clearly defines the need of integrated, high-quality, diagnostic CT in SPECT/CT lymphoscintigraphy for identification of minimally enlarged nodes, which, although not palpable, may harbor tumor infiltration and may not be detectable on SPECT lymphoscintigraphy. Identification of such nodes non-visualized on SPECT, but identifiable as enlarged and suspicious on diagnostic CT, opens up the possibility of reducing errors in sentinel node biopsy procedures by identifying all nodes requiring sampling. This may significantly reduce the incidence of false-negative sentinel node biopsy procedures.

Use of SPECT/CT with diagnostic CT has expanded to a larger spectrum of cancers, where it has proved its clinical value. This is especially relevant for tumors in deep locations like gastrointestinal, gynecological and urological malignancies. For malignant tumors of the pelvis (prostate, bladder, cervix, endometrium and rectum), drainage is expected to the lymph node groups around the iliac vessels and obturator fossa. Sentinel nodes may also be found in the paraaortic nodes. Malignancies of the kidneys and testes principally drain to the area around the aorta and inferior vena cava. A group from the Netherlands Cancer Institute has established a novel approach using a small portable gamma camera in the operating room along with an \(^{125}\text{I}\) seed on the gamma probe to coregister the exact position of the \(^{99m}\text{Tc}\) signal from the sentinel node with the \(^{125}\text{I}\) signal to ensure accurate identification of the sentinel node. The fused images of the SPECT•CT with diagnostic CT (Symbia T) are displayed on the monitor during surgery in order to correlate with the image from the portable gamma camera and to improve accuracy of sentinel node biopsy for deep-seated tumors like cervical, endometrial, prostate and bladder carcinomas.

The author states that, “SPECT/CT and real-time intraoperative imaging will become essential tools for malignancies in the pelvis, abdomen and mediastinum and to a lesser degree in the neck”.

Use of diagnostic CT with SPECT provides the ideal localization accuracy for sentinel nodes in such deep tumors, which promises to expand the procedure of SPECT/CT lymphoscintigraphy to a larger spectrum of malignancies with resultant improvement in management decision making.

This approach was clinically tested in a study of 20 patients (16 prostate cancers, two renal cell cancers; two testicular cancers) which combined SPECT/CT with diagnostic CT and a portable gamma camera in the operating room to localize accurately and remove pelvic sentinel lymph nodes. Pelvic sentinel nodes were delineated in all prostate cancer patients. In seven patients, sentinel nodes were in unusual locations. Seven of these patients had tumor-positive sentinel nodes. In renal cell carcinoma and testicular carcinoma, paraaortic sentinel nodes were localized and removed in all patients, and all nodes were tumor free. In this study, intratumoral injection was performed by transrectal ultrasound (prostate) and ultrasound (renal cell cancer and testicular cancer). However, the possibility of using diagnostic, CT-guided, intratumoral, radiocolloid injection prior to dynamic scintigraphy and subsequent SPECT/CT is a very elegant clinical proposition.

Another paper from the same group used a Symbia SPECT•CT with diagnostic CT for detection and localization of sentinel nodes in 46 patients with prostate cancer of intermediate prognosis, prior to sentinel node lymphadenectomy. Lymphadenectomy for sentinel nodes in prostate cancer routinely involves dissection of the obturator fossa and the region around the external iliac vein. However, extended pelvic lymphadenectomy, involving areas between the external iliac arteries, the pelvic wall and the area around the common iliac and internal iliac arteries, can be performed in situations where sentinel nodes are demonstrated in these areas or in cases where no sentinel nodes are visualized on imaging. Highly sensitive detection and accurate localization of pelvic sentinel nodes in relation to the large vessels are therefore of critical importance for correct surgical planning, localization and identification of the sentinel
nodes during surgery. SPECT/CT may spare some patients from extended pelvic lymphadenectomy by improved delineation of pelvic sentinel nodes, which may be explored using the standard procedure. In cases requiring extended lymphadenectomy, SPECT/CT helps the surgeon by accurately localizing the node in relation to the vessels.

All 46 patients underwent peri- or intratumoral injection of 99mTc-nanocolloid guided by transrectal ultrasonography. Planar imaging at 15 minutes and two hours was followed by SPECT/CT. SPECT/CT visualized sentinel nodes in 98 percent (45/46) of the patients compared to 91 percent on planar (42/46). In 29 of 46 patients (63%), SPECT/CT revealed additional sentinel nodes not seen on planar, which led to excision of more nodes and therefore more accurate staging. Sentinel lymph nodes (SLN) near the injection site and in presacral region were better visualized with SPECT/CT. Thirty-five percent of patients (16/46) had SLN outside the region of extended pelvic lymphadenectomy. The locations included inguinal, aorto-iliac junction and presacral regions, as well as in the anterior abdominal wall near the umbilical ligament. SPECT/CT accurately localized every single one of these nodes. In nine patients, these nodes were visualized only on SPECT/CT.

Of the patients who were node positive on histopathology, 47 percent had metastases in the nodes detected only on SPECT/CT. In four of these patients (27% of all node positive patients and 9% of total), the metastatic node detected only on SPECT/CT was the only node positive for metastases, thereby leading to upstaging and modification of the treatment approach. SPECT/CT thus was critical for accurate staging of these patients. On overall assessment, SPECT/CT was advantageous in 89 percent of the cases. In nearly half of all tumor positive patients, a SLN missed on planar, but detected only on SPECT/CT, was tumor positive. All SLN-negative patients received 78 Gy external beam radiation to the prostate and six months of hormonal therapy. For SLN-positive patients, the radiation therapy regime was expanded (70 Gy to prostate and 50 Gy to the pelvic area), along with three years of hormonal therapy. Identification of additional tumor-positive SLN by SPECT/CT was definitely of major therapeutic significance. SPECT/CT localization of SLN guided surgeons to successfully identify and excise all detected sentinel nodes.

Expanding further into the role of SPECT/CT, the same group studied sentinel node detection in renal cell carcinoma (RCC). The main route of tumor spread in RCC is hematogenous and 58 percent to 95 percent of patients with lymph node involvement have associated hematogenous metastases. However, detection of early nodal metastases has major prognostic relevance. Patients with no nodal metastases have a five-year survival, of 75 percent while survival in node-positive patients was only 20 percent. There is evidence that patients with early lymph node involvement without hematogenous metastases may potentially be cured by lymph node dissection. In this study, eight patients with RCC, with no metastases detected on imaging, underwent lymphoscintigraphy, using SPECT/CT with diagnostic CT on a Symbia SPECT•CT system. 99mTc-nanocolloid was injected into tumors percutaneously using ultrasound or CT guidance. Planar images localized SLN in four patients, while SPECT•CT localized SLN in six of eight patients. SPECT•CT was particularly helpful in proper localization of retrocaval and interaorto-caval SLN. Drainage to an extraperitoneal node in the internal mammary chain was demonstrated in one patient. Accurate localization with SPECT/CT was helpful for guiding surgeons, who were able to locate and excise all identified sentinel nodes correctly. In two patients, neither SPECT•CT nor surgical exploration using a gamma probe demonstrated sentinel nodes.

Vermeeren et al assessed the value of preoperative SPECT/CT lymphoscintigraphy for mapping of paraaortic sentinel lymph nodes in a series of 18 patients with abdominal or pelvic tumors (eight prostate cancer, six renal cell cancer and four testicular cancer patients). In 16 patients, in whom abdominal SLN was visualized on planar scintigraphy, SPECT/CT accurately depicted the relationship of the nodes to the abdominal vessels. In two patients, abdominal SLNs were seen only on SPECT/CT. In testicular cancer and renal cell carcinoma, the sentinel nodes were located along the abdominal aorta and vena cava. In prostate cancer, most patients showed drainage to a pelvic node, but 13 percent of patients demonstrated direct drainage to a paraaortic sentinel node. SPECT/CT localization assisted the surgeons to locate and excise all demonstrated SLN by laparoscopy or open surgery (in renal cell carcinoma patients with associated nephrectomy). Information on the location of paraaortic SLN anterior to or behind the aorta and vena cava was of major importance for successful laparoscopic excision of the nodes. Intraoperative localization of SLN was assisted by the use of a portable gamma camera.
Clinical examples depicted here illustrate the value of integrated, diagnostic, multislice CT as part of SPECT/CT lymphoscintigraphy.

The first example (Figure 7-1), from the Netherlands Cancer Center, shows a patient with breast carcinoma where a planar study showed no sentinel nodes. However, SPECT•CT defined axillary as well as internal mammary nodes. Accurate localization of both nodes was due to the high quality CT coregistration.

Another example (Figure 7-2) from the same institution, shows planar lymphoscintigraphy revealing only one extra-axillary sentinel node while SPECT•CT showed an additional axillary node.
A third example (Figure 7-3) of SPECT-CT lymphoscintigraphy, on a patient with left scapular melanoma, showed left, supraclavicular and axillary sentinel nodes. SPECT-CT with diagnostic CT showed a left scapular node but also two sentinel nodes in the right scapular region.
A fourth example (Figure 7-4) of SPECT•CT lymphoscintigraphy, in a patient with penile cancer, shows lymphatic drainage bypassing the enlarged metastatic left inguinal node with tracer uptake in the secondary nodes on the right side.
Another example (Figure 7-5) from the same institution, with planar images in early and delayed phases, shows lymph vessels draining to the right, inguinal region with an enlarged metastatic node, which did not show tracer uptake. Delayed images also showed crossing over of lymphatics from the right side to the left with visualization of a neo-sentinel node on the left side. SPECT•CT with diagnostic CT clearly defined the enlarged right inguinal, metastatic node without tracer uptake as well as multiple, small, left inguinal sentinel nodes.
A few more examples from Symbia TruePoint SPECT•CT users further demonstrate the accuracy of the localization of sentinel nodes. This example (Figure 7-6) is of a 50-year-old female with primary breast carcinoma. SPECT•CT lymphoscintigraphy showed small axillary sentinel nodes with low tracer uptake, which were clearly delineated due to the fusion and correlation of thin-slice, diagnostic CT.
This example (Figure 7-7), also of lymphoscintigraphy performed on a Symbia T6 in a patient with primary breast carcinoma, further demonstrates the accuracy of the localization of sentinel nodes. SPECT•CT lymphoscintigraphy demonstrated two sentinel lymph nodes in the axilla, adjacent to the trapezius and pectoralis major muscles. Volume rendering of fused datasets of thin-slice, spiral CT and SPECT clearly helped to determine the exact positions of the sentinel nodes in relation to the major axillary muscles, and the depth perception from the reconstructed images helped the surgeon plan the node removal with precision.
Another example (Figure 7-8) is of a 27-year-old female patient with melanoma of the back. SPECT•CT lymphoscintigraphy identified three right axillary nodes. The size of the smallest node detected was four mm. Integrated, thin-slice, diagnostic CT helped to clearly define the nodes in spite of the low tracer uptake and small size.
Another example (Figure 7-9) demonstrates a melanoma in the scalp on the left side. SPECT•CT lymphoscintigraphy showed lymph nodes in the superficial cervical, superior and inferior deep cervical as well as the supraclavicular lymph node groups. Clear localization of the small inferior deep cervical and supraclavicular sentinel nodes are primarily due to integrated, thin-slice, diagnostic CT.
In another example, (Figure 7-10) $^{99m}$Tc-sulfur colloid SPECT•CT lymphoscintigraphy demonstrated tiny sentinel lymph nodes in a patient with melanoma of the right cheek.
This case example (Figure 7-11) demonstrates the accuracy of SPECT lymphoscintigraphy with integrated, multislice, diagnostic CT in delineating deep-seated sentinel nodes, as in a case of vulvar melanoma with sentinel nodes identified in the pelvis. The study showed clearly delineated sentinel lymph nodes demonstrating focal uptake of the tracer in the internal iliac and deep subinguinal nodes. Diagnostic CT clearly delineated the exact location of the sentinel nodes showing faint tracer uptake and helped define the surgical approach for excision biopsy.
This example (Figure 7-12) is of a 61-year-old male patient with melanoma in the right cheek. SPECT•CT lymphoscintigraphy demonstrates sentinel nodes in the superficial and superior deep cervical region. Thin-slice diagnostic CT was instrumental in the clear definition and localization of small sentinel lymph nodes, and helped in planning the excisional biopsy.

Another example (Figure 7-13) is of SPECT•CT lymphoscintigraphy for melanoma performed in a 51-year-old female patient with melanoma in the left heel. Sentinel nodes are localized with help from diagnostic CT in the left inguinal, external iliac and common iliac regions.
This example (Figure 7-14) shows the use of SPECT•CT lymphoscintigraphy in identification of SLN in a patient with cervical carcinoma. This is a 66-year-old female patient with carcinoma of the uterine cervix. SPECT•CT lymphoscintigraphy performed with intratumoral injection of $^{99m}$Tc-sulfur colloid demonstrated sentinel nodes in the left inguinal and external iliac regions. Accurate localization of a small pelvic SLN, using diagnostic CT, improved surgical planning for excisional biopsy.
This example (Figure 7-15) is of a patient with primary carcinoma in the base of the tongue, who underwent SPECT•CT lymphoscintigraphy performed following an intratumoral injection of radiolabeled colloid. Sentinel nodes are visualized in the right and left supraclavicular region, as well as in three well-defined upper cervical (level II) lymph nodes adjacent to the internal jugular vein, just medial to the upper part of the sternocleidomastoid muscle. Note the clear visualization of small sentinel nodes with SPECT•CT and the accurate localization due to fusion with thin-slice, diagnostic CT.

This example (Figure 7-16) demonstrates the use of SPECT•CT lymphoscintigraphy in evaluation of pelvic sentinel nodes in prostate cancer. Rectal ultrasound-guided intratumoral injection of radiolabeled colloid was followed by a SPECT•CT examination, which demonstrated sentinel nodes in the bilateral internal iliac, right external iliac and common iliac lymph nodal groups.
This example (Figure 7-17) also demonstrates SPECT•CT lymphoscintigraphy performed in a patient with prostate carcinoma without clinically detectable metastases. Sentinel nodes are visualized in the right inguinal, external iliac and common iliac nodes at the aortic bifurcation, as well as in the left inguinal lymph nodal group. Integrated, diagnostic CT helps to accurately localize small pelvic and abdominal sentinel lymph nodes, thereby helping to improve surgical planning for excisional biopsy.

This example (Figure 7-18) shows a 45-year-old patient with penile cancer, without clinically palpable lymph nodes in the groin. Preoperative, ultrasound-guided FNAC was negative in both inguinal regions. The patient underwent ⁹⁹ᵐTc-nanocolloid SPECT•CT lymphoscintigraphy, which showed drainage to both groins. Integrated CT demonstrated slightly enlarged lymph nodes (green arrows) corresponding to the sentinel nodes seen on fused SPECT•CT images. It is important to note the small size of the sentinel nodes identified on SPECT•CT. The right inguinal node was eight mm in the transverse axis. Histopathology showed metastases in the left sentinel node.
This example (Figure 7-19) shows a 47-year-old patient with testis carcinoma. Lymphoscintigraphy was performed on a Symbia T following administration of the tracer by intratesticular injection. Early planar images show drainage to retroperitoneal lymph nodes. After two hours, another lymph node placed more laterally on the right was also visualized. SPECT•CT demonstrated a cluster of sentinel nodes between the aorta and inferior vena cava just above the bifurcation. A sentinel node just anterior and adjacent to the right psoas muscle was also well delineated. Integrated CT showed the corresponding nodes to be of very small size. Histopathology demonstrated the paraaortic sentinel nodes to be without metastases. However the psoas sentinel node demonstrated micrometastases. Accurate localization of the sentinel nodes, especially that of the psoas muscle, by integrated diagnostic CT was critical for accurate localization and surgical excision of the sentinel nodes.

The last example (Figure 7-20) shows a 55-year-old female patient with chylothorax and chylous ascites without any obvious precipitating etiology. Planar lymphoscintigraphy was performed after injection of radiolabeled sulfur colloid in the webspaces of both feet. Planar images were acquired at 20 min and one hour after injection. Sequential SPECT•CT was performed two hours and four hours after injection. Planar images at one hour show bilateral ascent of activity to both the inguinal and iliac lymph nodes as well as activity in the paraaortic region. SPECT•CT at two hours shows pooling of activity in the right paraspinai retroperitoneal region at the level of the diaphragm suggestive of lymphatic ectasia. Mild pooling of activity was seen in the left pleural effusion. There was non-visualization of the hepatic parenchyma suggesting that there was a block in the thoracic duct. In the subsequent SPECT•CT study, performed four hours after injection, there was a progressive increase in activity in the left paraspinal region, which extended further up the thorax, as well as significant increase in tracer accumulation in the left pleural effusion. However, the amount of activity in the ectatic right paraspinal lymphatics was reduced. This was suggestive of a chylous communication between the right retroperitoneal lymphatic ectasia with the left hemithorax contributing to the chylothorax. No significant tracer activity was visualized in the right pleural cavity in spite of the presence of large effusion. There was also an area of increasing activity in the region of the right kidney, which was confirmed by MRI to be a lymphangioma. Sequential SPECT•CT was helpful in delineating the progressive thoracic collection of the tracer as well as the extent of effusion and associated mediastinal and lung parenchymal changes.
Figure 7-20  Data courtesy of University of Minnesota, Minneapolis, MN, USA
References:


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Thyroid Carcinoma

Thyroid carcinoma is usually treated with a total thyroidectomy followed by radioiodine ablation. Whole-body, planar scintigraphy with $^{131}$I following radioiodine therapy and as follow-up is the mainstay for detection of metastases, combined with measurements of serum thyroglobulin levels. An $^{131}$I whole-body scan may show uptake owing to a variety of causes other than residual thyroid tissue or metastases, such as ectopic foci of normal nonthyroidal tissue; physiological uptake in the oral cavity; uptake due to contamination; ectopic gastric mucosa; and gastrointestinal or urinary tract abnormalities. It may also be due to inflammation and infection; breast abnormalities; nonthyroid neoplasms; and serious cavities and cysts. The differentiation between iodine-avid lymph node metastases in the neck versus thyroid remnants and between lung versus bone or mediastinal metastases is often difficult. SPECT/CT has been shown to be of value in accurate localization of lesions visualized on planar whole-body scans and SPECT, as well as for characterization of indeterminate lesions.

SPECT/CT with low-resolution, non-diagnostic CT has been used by one study in a series of 71 patients who had undergone a thyroidectomy for thyroid carcinoma. SPECT/CT had an incremental diagnostic value in 57 percent of the patients (41/71). For lesions in the neck, SPECT/CT had an incremental value in 27 percent of the patients (19/71), which included a major change in lesion localization in five patients. SPECT/CT correctly characterized lesions in 14 out of 17 patients with equivocal neck findings on planar imaging. Included in this group were residual thyroid tissue, regional lymph node metastases and physiological uptake of iodine. For lesions outside the neck, SPECT/CT had incremental value in 36 percent of the patients (26/71), which included proper localization of lesions in the skull, chest, abdomen and pelvis. SPECT/CT also helped in the characterization of equivocal foci in 13 percent of the patients, including physiological uptake in the parotid gland and colon. Seventeen percent of the patients had bone metastases, and six percent had lung or mediastinal nodal metastases. The SPECT/CT finding changed the therapeutic approach in 41 percent of the patients.

Another study evaluated 25 patients with SPECT/CT who had inconclusive findings on planar scans. Using low-resolution CT, 41 lesions were identified in these 25 patients, and 95 percent of these lesions were correctly identified by SPECT/CT. In 44 percent of the cases, SPECT/CT improved anatomical localization compared to what was determined by a planar scan or SPECT alone.

A third report studied 117 consecutive patients with SPECT/CT using low-resolution CT. SPECT/CT showed substantially more foci compared to planar imaging in the neck as well as in rest of the body. Five of 50 foci initially identified as residual thyroid were confirmed to be metastatic lymph nodes by SPECT/CT. All had elevated thyroglobulin and were identified at surgery. SPECT/CT also characterized 17 foci, which were considered indeterminate on planar and SPECT, as thyroid bed residue (8), locoregional metastases (2), bone metastases (2) and nonspecific physiological uptake (5). It is important to note that all patients with nonspecific physiological uptake had borderline thyroglobulin values.

In the thorax, SPECT/CT changed characterization of four lesions from pulmonary metastases to mediastinal lymph node metastases (2) and to chest wall metastases (2). Several foci were identified as physiological uptake by SPECT/CT, which were indeterminate on planar and SPECT imaging, and all these patients had low thyroglobulin values. This is particularly well illustrated in a patient with bilateral iodine uptake in bilateral bronchi localized on SPECT/CT. It was initially suspected, despite low thyroglobulin values, that the patient had lung metastases based on the SPECT findings, but SPECT/CT characterized the findings as bronchial mucus secretion. This pattern of suspicious lesions with low thyroglobulin values, characterized as physiological uptake by SPECT/CT, underlines the importance of the correlation of hybrid imaging with serum tumor markers. It is easy to comprehend the additional value of diagnostic CT in such situations where morphological information by high-quality CT combined with thyroglobulin levels are critical for decision making about an iodine-avid lesion.

Another large series published from China studied 66 patients with planar imaging soon after a large dose of $^{131}$I therapy. SPECT/CT with low-resolution CT was performed whenever planar imaging was inconclusive. SPECT/CT was performed in 23 out of 66 patients. In these 23 patients, there were 81 equivocal foci — 36 in the neck and 45 outside the neck. SPECT/CT accurately localized 69 of 81 (85%) of the foci, thereby characterizing 24 physiologic or benign foci and 43 malignant lesions. Of 23 patients equivocal on the planar study: 17 patients had their diagnoses modified because of SPECT/CT, 16 patients were classified as having malignancies, and one was classified as exhibiting physiological uptake. Treatment strategy was altered in eight out of 17 (47%) patients, including changes to surgery in six, external beam radiotherapy in one and interventional therapy in
one. SPECT/CT was, however, equivocal in three out of 23 (13%) patients. On a site-based analysis, five out of 81 (6.2%) lesions remained inconclusive even after SPECT/CT. Based on clinical follow-up and other imaging techniques, including diagnostic CT, the final diagnoses in these patients were sphenoid bone metastases (1 patient), maxillary sinusitis (1 patient), and inflammatory lung disease (1 patient). Uncommon metastatic sites were found in nine of 66 patients with SPECT/CT, which included lesions in subcutaneous soft tissue, the parapharyngeal space, muscles, and salivary glands. In addition, nine of 81 foci detected by a whole-body planar study could not be visualized on SPECT/CT.

This study highlights the additional value that diagnostic CT integrated with SPECT brings to the evaluation of $^{131}$I SPECT/CT studies in thyroid carcinoma. The three patient diagnoses, which could not be made correctly even with SPECT/CT, were probably due to the low-resolution, non-diagnostic CT, which would make proper tissue characterization impossible. Since CT findings of subtle bone erosion for sphenoidal metastases require thin-slice, high-quality CT with sharp kernel, proper characterization of such a lesion requires integrated, diagnostic CT with SPECT rather than the low-quality, non-diagnostic CT, which was used in the study. The authors conclude that the inability to characterize equivocal lesions and non-visualizations of iodine-avid foci with SPECT/CT is related to the low amount of radioiodine accumulation by the lesion and the low resolution of the CT scan. Further, in view of the atypical locations of thyroid carcinoma metastases, like the parapharyngeal space, parotid gland and erector spinae muscle, it appears logical that integrated, diagnostic CT, as part of SPECT/CT, should further improve lesion localization and characterization of such lesions by virtue of the high-quality, morphological evaluation.

Initial studies using SPECT/CT with integrated spiral CT show promise. One group studied 55 consecutive patients who underwent SPECT/CT following post-ablation $^{131}$I therapy. SPECT/CT showed higher lesion detection than a planar, whole-body scan. In 16 patients, who were indeterminate on the planar study, SPECT/CT ruled out the suspicion of disease in nine patients and confirmed the presence of malignant lesions in four patients. Sixteen percent of the patients presented with treatment failure. Positive SPECT/CT predicted treatment failure better than a positive planar, whole-body scan.

The University of Erlangen has studied 54 patients using SPECT•CT with integrated, diagnostic, multislice CT (Symbia® T2), after the initial ablation with $^{131}$I therapy. Neck foci (143) were identified on planar as well as SPECT•CT. In 28 (19%) of these foci, SPECT•CT led to a revision of the original diagnosis.

Six of 11 lesions, initially considered as lymph node metastases, and 11 of 15 lesions, considered indeterminate, were reclassified as benign due to the information provided by high-quality, diagnostic CT. SPECT•CT also allowed identification of 11 lymph node metastases initially misinterpreted as indeterminate. SPECT•CT was responsible for down-staging disease in 12 patients and up-staging in eight patients. SPECT•CT improved the information on the nodal stage in 35 percent of the patients and altered risk stratification in 25 percent, leading to a change in the follow-up approach in these patients. This study clearly demonstrated the superiority of SPECT•CT over planar imaging for identifying cervical lymph node metastases and differentiating them from thyroid tissue remnants following surgery.

A follow-up study from the same group used $^{131}$I SPECT•CT to evaluate the same patient group to detect the occurrence or persistence of cervical radioiodine-positive lymph node metastases five months after the first radioablation. Later, 81 thyroid carcinoma patients underwent an $^{131}$I whole-body scan with TSH stimulation along with SPECT/CT with integrated multislice diagnostic CT of the neck and areas with abnormal uptake five months following radioablation. All patients had a previous SPECT/CT study performed immediately after thyroidectomy and the first radioablation. Sequential SPECT/CT studies were compared to assess response of thyroid remnants and iodine-avid cervical lymph node metastases to radioablation. Of 61 patients without a SPECT/CT diagnosis of $^{131}$I-positive lymph node metastases at the first study immediately after radioablation, 60 had no $^{131}$I positive nodal metastases at follow-up. New radioiodine-positive nodal metastases were detected in only one patient. In 17 of 20 patients with $^{131}$I positive cervical lymph node metastases detected on the initial SPECT/CT at first radioablation, no $^{131}$I positive nodes were detected on the follow-up study. Three patients demonstrated persistent radioiodine positive nodes. This observation, regarding the excellent response of the majority of iodine-avid cervical lymph node metastases within five months of radioablation, highlights the efficacy of radioiodine for ablation of neck node metastases over and above residual thyroid tissue. It also explains why postthyroidectomy radioiodine ablation reduces the rate of thyroid carcinoma recurrence. This finding suggests that diagnosis of lymph node metastases at radioablation by $^{131}$I SPECT/CT does not always warrant early surgical reintervention since the majority of radioiodine-positive metastatic nodes disappear within five months of radioablation. In this study, 94 percent of lymph node metastases smaller than 0.9 ml in volume were eliminated by radioiodine, whereas only one of four nodes with a volume larger than 0.9 ml responded to radioiodine. This suggests that the volume
Another recent study used 131I planar whole-body studies and SPECT/CT with integrated 6-slice CT in 53 patients with thyroid carcinoma. Planar scans depicted 130 neck foci and 17 distant lesions. SPECT/CT identified 98 of 130 neck foci as residual thyroid tissue and thyroglossal duct remnants and 26 as cervical nodal metastases. Due to outstanding lesion localization and additional morphological information derived from diagnostic CT, SPECT/CT demonstrated significant diagnostic value over planar imaging in 70 of 147 lesions (47.6%), including 53 of 130 neck lesions (40.8%) and all 17 distant lesions. SPECT/CT findings led to correct downstaging of 26 of the 53 neck foci from cervical lymph node metastases to thyroid remnants. Eleven of the 53 foci were correctly upstaged from thyroid remnants to cervical lymph node metastases. SPECT/CT also identified physiological dental or salivary activity as well as differentiated thyroglossal duct remnants from residual thyroid tissue in several patients, due to additional anatomical information from integrated diagnostic CT.

Another study using SPECT/CT with integrated diagnostic CT performed a total of 53 131I SPECT/CT studies in 41 patients with thyroid cancer after high-dose 131I therapy. All patients had diagnostic uncertainty on planar whole-body scanning. In the neck, SPECT/CT identified a larger number of lesions (5.6%) compared to planar. Of 11 equivocal lesions in the neck, nine were diagnosed as benign by SPECT/CT. SPECT/CT changed diagnosis in nine lesions from lymph node metastases to thyroid remnants (on whole-body SPECT) to residual thyroid tissue and vice-versa in six lesions. Of 90 neck lesions, SPECT/CT had a significant impact in diagnosis of 26 lesions (28.9%). Three lymph node metastases and two local recurrences were detected by SPECT/CT but were missed on planar imaging. SPECT/CT information led to upstaging in N status in five patients who subsequently underwent radiiodine ablation. It also led to downstaging in three patients by identifying residual tissues, which were wrongly perceived as metastases on planar imaging. SPECT/CT also identified additional iodine-negative metastases in the neck in four patients. All these patients underwent neck dissection, and histopathological confirmation was obtained. SPECT/CT changed nodal status in 36.4% of the patients. SPECT/CT characterization of neck lymph node metastases and local recurrence had a direct impact on management in eight of 33 patients (24.2%) in whom complete neck dissection was performed.

SPECT/CT was even more successful in detection of distant lesions (19 patients) since it identified 31 percent more lesions than a planar scan. Most lesions were lung metastases with few mediastinal bone and lymph node lesions. SPECT/CT correctly diagnosed three lesions as bone metastases and two as mediastinal metastases instead of lung lesions as suggested by planar. SPECT/CT had a diagnostic impact in nine of 71 distant lesions (12.7%). It led to upstaging of M status in four patients due to demonstration of additional bone and pleural metastases as well as additional iodine-negative lung metastases. SPECT/CT directly impacted therapy in two patients whom external beam radiation was delivered for stabilization of bone metastases. According to the authors, such impact of SPECT/CT “can be predominantly explained due to the accurately focused localization provided by SPECT especially in the field of lung metastases and by the possibility of localizing a faint iodine uptake with the morphological pathology visible on CT”.

More studies, using integrated diagnostic CT as part of SPECT/CT, are required to comprehensively define the added value for the characterization of metastases from thyroid carcinoma. However, it is obvious, from the analysis of available literature, that accurate coregistration with high-quality, diagnostic CT improves localization and characterization of residual thyroid tissue, lymph node metastases, and local recurrence, as well as detection of distant lesions like lung, mediastinal lymph node, and bone metastases. High quality, morphological information of the entire body, currently obtained using whole-body SPECT/CT with diagnostic CT, can clearly define lytic or sclerotic areas in the bone for improved characterization of iodine-avid lesions suspected of being skeletal metastases. Differentiation of nodular from diffuse lung lesions, as well as evidence of bronchiectasis and pneumonitis, helps improve the characterization of lung uptake of iodine since iodine uptake may be seen in bronchial secretions, bronchiectasis and other benign lung conditions. The prevalence of physiological uptake of iodine by lesions suspected of being metastatic, even in the presence of normal thyroglobulin levels, indirectly supports the assumption that diagnostic CT would be a major advantage in the characterization of such indeterminate lesions and would lead to more effective staging of such patients. CT information about surrounding structures helps further characterize the metastatic lesion, especially in the neck and lungs, since compression or erosion of vessels, bone and bronchi is critical information that has an impact on patient management. Since thyroid carcinoma typically has a better prognosis than many other cancers if detected early, such technological advancement is needed for effective management.
An example (Figure 8-1) from the University of Erlangen, performed on a Symbia T2 illustrates this point. A 74-year-old male, with differentiated thyroid carcinoma, was treated with thyroidectomy, without clinical evidence of a neck node or distant metastases. SPECT•CT identified a thyroid remnant (b) and several lymph node metastases in the cervical (a) and in the mediastinal (c and d) nodal groups. Integrated, diagnostic CT, acquired with thin, overlapping slices, ensured accurate localization of small cervical lymph node metastases. Note the absence of swallowing or breathing artifacts, which can complicate interpretation if poor-quality, slow CT is used in such situations.
Another example (Figure 8-2), from a Symbia TruePoint SPECT•CT user, showed a patient with a focal, thoracic lesion on a planar $^{131}$I study performed as a follow-up. SPECT•CT identified three lesions — one in retropharyngeal space at the root of the neck, and another in the paraaortic lymph node, just behind the heart. High-quality CT clearly defined the relationship of the lesions to the trachea and aorta, and consideration needs to be given to possible compression of the trachea and aorta by these lesions following a second dose of radioiodine therapy.
Another case (Figure 8.3) illustrates the value of high-end CT for clear localization and characterization of an iodine-avid lesion. A patient underwent a follow-up $^{131}$I SPECT•CT with diagnostic CT for follow-up due to the increased serum thyroglobulin. The SPECT showed a markedly increased focal uptake in the lungs. Exact coregistration with diagnostic CT not only localized the lesion to the rib, but subtle, sclerotic changes within the rib seen on CT confirmed that the lesion was indeed a rib lesion and not a lesion in the pleura adjacent to the rib. This characterization due to the findings on diagnostic CT is the major advantage of Symbia TruePoint SPECT•CT.
This example (Figure 8-4) demonstrates the value of diagnostic CT for clarification of doubtful and atypical lesions in a case of thyroid carcinoma in a patient who underwent an ¹²³I whole-body scan, followed by SPECT•CT, following a near total thyroidectomy. The study shows a small amount of residual thyroid tissue in the neck. A focal area of uptake was visualized in the left abdominal flank, which was localized to the margin of the descending colon. Diagnostic CT correlation showed that the uptake was within a colonic diverticula and hence unlikely to be of metastatic origin.

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Scintigraphy using $^{99m}$Tc MIBI has become the mainstay for localization of hyperfunctioning parathyroid adenomas in patients with hyperparathyroidism. SPECT/CT has further improved localization of such adenomas, especially when they are located ectopically.

One study\textsuperscript{9.1} was performed preoperatively with SPECT/CT and lose-dose non-diagnostic CT in 16 patients with severe hyperparathyroidism. The results were compared with findings during parathyroidectomy. SPECT/CT confirmed all 23 probable parathyroid lesions, offering more precise localization and an evident improvement in diagnostic accuracy. Surgical detection of the 23 sestamibi-positive lesions was correctly matched with 100 percent of the SPECT/CT images and 61 percent of the SPECT data alone. Hybrid imaging, thus, provided additional data in 39 percent of lesions, and in three patients with retrotracheal glands, it modified the surgical approach.

Another study\textsuperscript{9.2}, which included 36 patients with primary hyperparathyroidism, used SPECT/CT with non-diagnostic CT when planar $^{99m}$Tc MIBI scintigraphy was negative or when an ill-defined focus in the neck or an ectopic site on the planar views was visualized. Imaging data were compared with intraoperative findings. Of 33 patients with a positive MIBI study, parathyroid adenoma was confined to the neck in 23 patients and to the lower neck/mediastinum in 10. SPECT/CT facilitated the surgical exploration of all 10 ectopic parathyroid adenomas and four of the 23 cervical parathyroid adenomas. SPECT/CT contributed to the localization of parathyroid adenomas and to surgical planning in 14 of 36 (39%) patients, predominantly those with ectopic parathyroid adenomas or those who had distorted neck anatomy.

An article from M.D. Anderson Cancer Center\textsuperscript{9.3} studied 32 patients with hyperparathyroidism and showed marginally improved results between SPECT and SPECT/CT performed using non-diagnostic CT. SPECT identified 89 percent of surgically confirmed parathyroid adenomas, with or without CT correlation. SPECT/CT changed the diagnosis from positive to negative in only one patient and better located the glands in only four patients. However, SPECT/CT was particularly helpful in locating two ectopic parathyroid adenomas in the series. The authors conclude that SPECT/CT did not add clinical value except for the localization of ectopic adenomas.

The value of SPECT/CT, with non-diagnostic CT for ectopic parathyroid adenoma, has been determined by several authors. A study\textsuperscript{9.4} performed in four patients with ectopic parathyroid adenoma was able to correctly localize them in all patients as confirmed by surgical exploration.

In this context, the value of SPECT/CT with integrated diagnostic CT, becomes even more valuable for accurate localization and surgical planning since diagnostic CT, with contrast, is able to better delineate parathyroid adenomas and to determine its relationship with surrounding structures. Most centers with Symbia\textsuperscript{9} TruePoint SPECT•CT perform parathyroid scintigraphy almost entirely on the Symbia due to the superior localization and the anatomical detail provided by diagnostic CT.

A recent study\textsuperscript{9.5} used $^{99m}$Tc MIBI/$^{123}$I subtraction SPECT/CT with diagnostic CT on a Symbia T6 to scan 57 patients. Sensitivity for SPECT and SPECT/CT was similar. However, the specificity of SPECT/CT was far superior to SPECT. SPECT identified 97 sites; 70 of those sites were identified by SPECT/CT to be parathyroid lesions and were later confirmed by surgery. The findings were that 48 patients had single parathyroid adenomas; six patients had double adenomas; and two patients had three hyperplastic parathyroid glands. In the remaining 27 sites identified by SPECT, correlation with diagnostic CT established their association with normal anatomical structures (nine normal thyroids, three longus colli muscles and three adipose tissues). The other 12 sites were confirmed to be non-parathyroid pathologies on histopathology (five thyroid adenomas, three multinodular goiters, two associated with Hashimoto’s thyroiditis and two with thyroid cancer metastases). Diagnostic CT profoundly influenced the accuracy of results, properly characterizing the false-positive SPECT findings and thereby, increasing specificity of SPECT/CT.

Previous results have not elaborated on such specificity improvements with CT correlation. The study by Neuman et al. clearly defines the major role played by integrated, diagnostic CT for accurate localization of parathyroid adenomas, including ectopic adenomas, which in turn aids surgical planning. It also highlights the value of diagnostic CT in the characterization of false-positive lesions seen on SPECT due to correlation of high-quality CT findings with the lesion identified on SPECT.

Parathyroid Adenoma
A few examples from Symbia TruePoint SPECT•CT users illustrate this point. A fused SPECT•CT in a 71-year-old woman localized a small parathyroid adenoma located posterior to the right thyroid lobe, which was confirmed at surgery. (Figure 9-1)
Another example (Figure 9-2) demonstrates the value of lesion characterization by diagnostic CT. A SPECT•CT study, in a 64-year-old woman with primary hyperparathyroidism, defined a small focus of uptake in the neck located posterior to the right thyroid lobe, which was localized to a small nodule identified during surgery as a 150 mg parathyroid adenoma. However, the large intense area of uptake on the left side of the neck was localized on CT to a three centimeter thyroid adenoma, which was also confirmed by surgery.
Some other examples from Symbia illustrate the value of diagnostic CT for improved localization and surgical planning of ectopic parathyroid adenomas.

This example of fusion with non-contrast CT (Figure 9-3) shows accurate localization of a small parathyroid adenoma in the superior mediastinum. The focal uptake is exactly localized to the nodule, and diagnostic CT clearly defines the relationship of the adenoma to the surrounding vessels, especially the carotid and the jugular vein.
Another example (Figure 9-4) of a mediastinal, ectopic adenoma SPECT defines a focal area of uptake in the mediastinum. Breath-hold contrast CT showed a small focal area of enhancement just below the aortic arch and above the pulmonary arteries, which coregistered exactly with the focal uptake in SPECT. Such accurate localization, with the help of contrast enhancement in diagnostic CT, helped the surgeon to minimize exploration time in the mediastinum.
The last example (Figure 9-5) is of a parathyroid adenoma in the neck, located in the retropharyngeal space, which is also well delineated by contrast CT and shows contrast enhancement of the adenoma. Diagnostic CT clearly defined the relationship of the adenoma with the esophagus and trachea, as well as the vertebral and carotid arteries. Due to the speed and quality of diagnostic CT, there was clear delineation of the lesion, without motion artifacts that can be caused by swallowing, and the accuracy of detection and characterization was enhanced.

These examples amply illustrate the value and potential of integrated diagnostic CT with SPECT for the localization and characterization of parathyroid adenomas, not only for ectopic lesions, but also to clarify false-positives, as well as to aid the surgeon in planning minimally invasive surgery.

References:


Infection Imaging

$^{67}$Ga scintigraphy, $^{111}$In and $^{99mTc}$ HMPAO-labeled white blood cell scintigraphy, have been widely used in the assessment of suspected infection. However, lack of adequate anatomical localization has hampered SPECT imaging with each radiopharmaceutical. High $^{67}$Ga uptake in the liver, colon or kidneys hampers interpretation of infection imaging in abdominal-pelvic sites of infection. Labeled leukocytes are highly specific to areas of infection, but require correlation with anatomical landmarks for proper interpretation. Physiological uptake in vessels and marrow may also hamper interpretation. All these drawbacks point to the relevance of SPECT/CT as the modality of choice for scintigraphic imaging of infections.

Studies using SPECT/CT with low-resolution, non-diagnostic CT have shown promise in infection imaging. One study$^{10.1}$ used $^{99mTc}$ antigranulocyte antibodies for SPECT/CT with non-diagnostic CT in 27 patients with a history of trauma, secondary bone infection, and a suspicion of reactivation of chronic post-traumatic osteomyelitis. Twenty-nine sites were identified by SPECT/CT. In four patients, SPECT/CT identified active bone infection requiring surgery with intramedullary curettage. Four patients were identified to have soft tissue infection without bone involvement. Another four patients had soft tissue infection with cortical reaction in the adjacent bone, but without erosion. Five patients had joint empyema. Nine suspected sites were delineated as free of infection by SPECT/CT.

One major advantage of SPECT/CT over SPECT was its correct delineation of soft tissue infection from osteomyelitis, so that bone surgery could be avoided. It was also advantageous in excluding osteomyelitis in cases with uptake related to inflammatory reaction following surgery and in a case of rheumatoid arthritis with antibody accumulation involving the metatarsophalangeal joint. CT correlation was particularly helpful in the differentiation of soft tissue infection with “reactive cortical” uptake without bone erosion from actual bony involvement, since management of soft tissue and bone infection are quite different. The specificity of infection imaging was increased using SPECT/CT (89%) compared with SPECT (78%). The authors conclude that, “CT is particularly helpful in detecting small areas of cortical destruction, foci of gas, foreign bodies, sequestration, involucra or cloacae. In addition, CT can detect surrounding soft tissue abscesses, the replacement of the normal bone marrow by pus, and joint empyema.” In view of the importance of CT findings in the diagnosis and characterization of infectious foci, especially when delineation of sequestration and cortical erosion may enhance surgical decision making, it is logical to conclude that diagnostic CT integrated with SPECT would be a major advantage in infection imaging. The authors also conclude that fused images may guide the surgeon to the most suitable place to operate and to decide on the extent of debridement of the inner bone surface. Integrated, diagnostic CT, coregistered with SPECT, is ideally suited for improved surgical decision-making in similar clinical situations.

Another study$^{10.2}$ evaluated $^{99mTc}$ HMPAO-labeled leukocyte SPECT/CT with low-resolution, non-diagnostic CT in 28 patients with suspected bone and joint infection. Patients were divided into two groups: suspected acute osteomyelitis and suspected infection of prosthetic joints (hip and knee). Scintigraphy was true positive for infection in 18 of 28 patients and true negative in 10 patients. In the first group (osteomyelitis), SPECT/CT provided correct anatomical localization for infectious foci. In three patients with lower limb osteomyelitis, SPECT/CT was able to clearly define the exact uptake site and to differentiate bone involvement from soft tissue. In two patients with bone infection, SPECT/CT localized additional soft tissue infection sites, thereby significantly impacting the management. In the second group (prosthetic joint infection), SPECT/CT provided accurate anatomical localization of foci of prosthetic joint infection in all patients positive on SPECT, but did not help in the evaluation of patients with negative SPECT findings. In five patients, SPECT/CT was able to discriminate between prosthesis and soft tissue uptake. In two patients with knee implants, SPECT/CT correctly localized uptake in the synovium, thereby excluding prosthetic joint involvement. SPECT/CT excluded osteomyelitis in seven patients and delineated the extent of infection more adequately in three patients, which significantly impacted management. In this study, the authors observed that metal artifacts due to prosthetic implants can complicate the assessment of abnormal foci of labeled-leukocyte uptake in the immediate vicinity of the prosthesis. The authors also comment on the limitations of the fusion of SPECT with low-resolution CT and state that, “fusion imaging cannot be a substitute for conventional high-resolution CT, which maintains its diagnostic role in most clinical situations.”

Studies have evaluated the impact of SPECT/CT in the diagnosis and management of the diabetic foot, especially in the differentiation between cellulitis and osteomyelitis and accurate localization and assessment of the extent of the osteomyelitis. Filippi et al$^{10.3}$ used $^{99mTc}$ HMPAO-labeled leukocytes and SPECT/CT with low-resolution, non-diagnostic CT to evaluate 18 diabetic patients with clinical signs of infection. All patients were followed up clinically and radiologically. SPECT/CT was true positive in 14 of 17 patients and true negative in three patients. Eight of 16 sites of labeled leukocyte uptake were osteomyelitis. SPECT/CT demonstrated infection in the bone combined with neighboring soft tissue involvement in three sites. In one patient, SPECT/CT localized the focus of osteomyelitis to the lateral malleolus. Eight of 16 sites had soft tissue infection (cellulitis) without bone involvement, as evident from follow-up. SPECT/CT was instrumental in excluding osteomyelitis in six of these
eight sites, thereby sparing the patients an amputation. In all these patients, SPECT imaging was highly suggestive of infection in the bone. SPECT/CT substantially changed diagnosis in 52.6% percent of the cases by excluding osteomyelitis, localizing bone infection in an atypical site and better defining the extent of osteomyelitis and cellulitis. SPECT/CT thus had major treatment implications due to avoidance of amputation in some patients, as well as improved treatment plans due to accurate assessment of the depth of infection, since duration of antibiotic therapy would depend on the extent of tissue involvement as well as the presence of infective foci in the bone. Although this study used non-diagnostic CT, the impact of such findings on treatment decisions demonstrates the clinical advantage of using diagnostic CT as part of a SPECT/CT procedure to further improve localization of infective foci and to delineate additional bone, soft tissue and joint changes.

New SPECT radiotracers have been used along with SPECT/CT for infection imaging. Lazzeri et al[10.4] used 111In-labeled biotin for early identification and localization of vertebral infections in 72 patients. SPECT/CT showed similar sensitivity and specificity to SPECT (~ 93%), but correctly localized infection sites in bones, or soft tissue, or in bones with soft tissue extension, in 16 patients. Recognition of the essential role of diagnostic CT in bone and joint infection lends credibility to integrated SPECT with diagnostic, multislice CT in infection imaging. Improved localization and characterization of small, infectious foci would be possible with thin-slice CT, and accurate characterization of bone and soft tissue using diagnostic CT would help differentiate osteomyelitis and joint effusion or empyema from soft tissue infections. Fast CT also limits patient motion between CT and SPECT, which can hamper coregistration.

SPECT/CT infection imaging with 67Ga or labeled-WBC has been studied in a large spectrum of infectious foci by a team in Israel[10.5] who studied 82 patients with SPECT/CT using low-resolution, non-diagnostic CT. Patients included those with fever of unknown origin (FUO), suspected osteomyelitis and visceral or soft tissue infection. SPECT/CT identified infectious foci in 58 of 82 (71%) patients. Thirty patients had soft tissue abscesses in the pelvis, lung, spleen, liver, paravertebral and subdiaphragmatic regions, which were localized by SPECT/CT. Twelve patients had osteomyelitis and 10 had vascular graft infection. Twenty-four patients (29%) had no evidence of infection on SPECT/CT. In 20, the uptake on SPECT was identified as related to a non-infectious condition, including malignancy, degenerative spine disease, drugs, fever or other inflammatory conditions (compressed vertebral fracture, avascular necrosis, rupture of shoulder ligaments, chronic lung disease and vascular graft pseudoaneurysm). SPECT/CT and SPECT were concordant in 21 of 82 patients. Twenty-four studies were positive for infection, and 17 were negative. Results were discordant in 41 patients (50%). Infection was diagnosed in 34. In five of the 41 patients, SPECT/CT was instrumental in excluding infection while SPECT was suggestive of infection. Two patients were included with FUO, which turned out to be drug-induced fevers. All of the 41 patients had foci of uptake within the bowel loops, which were localized and characterized by SPECT/CT. One focus of suspected osteomyelitis turned out to be multiple myeloma. SPECT/CT was misleading in one patient with a fever and bilateral ovarian cystic lesions who had a left pelvic focus, which was shown to be within bowel loops on 67Ga SPECT/CT and was considered physiological uptake. A left ovarian abscess was diagnosed at laparotomy. SPECT/CT was also misleading for the location of infection in one study with labeled-WBC. The patient presented with a left inguinal, surgical wound infection following thombectomy within a vascular graft. SPECT/CT localized the focus of increased uptake to include both the vascular graft and adjacent infected soft tissue. Antibiotic therapy led to rapid response and indicated the absence of any graft infection, thereby confirming the presence of only soft tissue infection. This example illustrates the potential advantage of integrated, multislice, diagnostic CT as part of the SPECT/CT procedure, which can provide high-quality CT with thin slices, high resolution, and improved lesion localization, as well as proper characterization based on CT findings. Contrast CT, as an integrated procedure fused with SPECT, should be able to delineate soft tissue foci from vascular uptake, thereby providing comprehensive clinical information for management decision-making. This study also highlights the varying spectrum of infectious foci, which is routinely encountered in infection imaging. This includes intra-abdominal, peritoneal, and subdiaphragmatic sites, which would benefit from integrated, diagnostic CT, preferably with breath-hold and contrast, if necessary, for better characterization. Even in suspected bone infection, delineation of soft tissue involvement, cortical erosion, spread of focus into the marrow, clear delineation of periosteal elevation and evidence of a sequestrum are of critical importance for management decision-making, which makes integrated, diagnostic CT desirable for SPECT/CT imaging of such conditions.

A few examples of infection imaging from Symbia® TruePoint SPECT•CT users will illustrate the impact of integrated, diagnostic CT on diagnosis and management.
The first case (Figure 10-1) is of a 62-year-old female with recent, left tibial nail removal, who presented with an infected left tibia and an abscess. Incision and drainage of the left tibial canal and placement of antibiotic beads were performed. After surgery, there was persistent serosanguineous discharge from the drainage site. $^{111}$In WBC SPECT•CT was performed to define infection foci. The focal area of accumulation of labeled-WBC in the left tibial cortex showed periosteal elevation with bony erosion, thus defining the exact area of bone infection. The site was subsequently incised and drained. SPECT•CT provided the exact location of the infectious focus due to accurate fusion and correlation with changes on integrated diagnostic CT.
Another case (Figure 10-2) shows $^{67}$Ga SPECT•CT infection imaging in a patient with suspected infectious foci in the first rib. Diagnostic CT showed osteolysis in the rib, correlating exactly with $^{67}$Ga uptake. However, the $^{67}$G uptake extended beyond the rib into the adjacent chest wall soft tissue, and soft tissue extension of rib osteomyelitis was confirmed.
The third case example (Figure 10-3) shows SPECT•CT imaging with $^{111}$In WBC in a case with diverticulitis and ethmoidal sinusitis. Focal uptake in the abdomen is localized to the sigmoid colonic diverticulum. Diagnostic CT helps in such cases to delineate the extent of infection, the presence of abdominal fluid and associated bowel thickening, obstruction or luminal narrowing.
Another example (Figure 10-4) shows the value of SPECT•CT in a patient with tuberculous osteomyelitis of the vertebrae. This patient presented with progressive back pain and vertebral osteolysis seen on X-ray. A $^{67}$Ga SPECT•CT study shows grossly increased tracer uptake in the lower end plate of the T9 vertebrae, the T9-T10 intervertebral disk and the upper part of the body of the T10 vertebrae. There is associated bony destruction of both vertebral end plates as well as reduction of intervertebral disk space shown on CT. There is also a soft tissue mass adjacent to involved vertebrae, which also shows increased uptake and is suggestive of psoas abscess. The SPECT•CT appearance is strongly suggestive of vertebral tuberculous osteomyelitis with destruction of adjacent vertebral bodies and soft tissue spread.

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Radioimmunoscintigraphy Imaging for Prostate Cancer

$^{111}$In-labeled capromab pendetide (ProstaScint®) is a murine monoclonal antibody that reacts with the prostate membrane specific antigen (PMSA), which is highly expressed in prostate cancer. It has been studied for use in the imaging of primary and recurrent prostate cancer. It is known that conventional imaging (CT and MRI) have limited accuracy for defining early, regional lymph node involvement. ProstaScint SPECT imaging can improve the prediction of lymph node involvement in patients at high risk for extraprostatic disease and therefore, can help in the selection of patients, who are candidates for definitive local therapy, as compared to patients with extrapelvic disease requiring systemic therapy. Radioimmunoscintigraphy with ProstaScint has been advocated in patients with newly diagnosed prostate cancer, who are at risk for advanced disease, and for patients treated with definitive local therapy (prostatectomy or radiation therapy) who present with rising PSA levels. Several studies, detailed below, suggest that an $^{111}$In ProstaScint scan can provide more accurate staging of clinically localized prostate cancer, including identification of locoregional spread and lymph node metastases compared to CT or MRI. ProstaScint has also proven to be valuable for the detection of local recurrence in patients post-surgery or following radiation, and even after salvage radiotherapy. Sensitivity and specificity of ProstaScint SPECT have been shown to be 75 percent and 86 percent respectively in a series of patients with high risk for extraprostatic prostate carcinoma metastases.$^{111,1}$ There are relatively few techniques, which have the advantage of ProstaScint in this area. PET/CT imaging with $^{11}$C choline or $^{11}$C acetate has shown promise, but its use is still relatively rare.

The interpretation of ProstaScint SPECT images is challenging because of the low spatial resolution of SPECT, particularly with medium energy collimators, the non specific antibody localizations in normal blood pool, and the lack of anatomical information for proper localization and characterization of uptake. The potential value of the fusion of SPECT and CT or MRI for improved characterization of SPECT uptake was realized early on with ProstaScint imaging. One group$^{11,1}$ studied 58 patients, who had undergone a radical prostatectomy and subsequently identified as metastases on SPECT. These included nodal disease in two patients where the activity was very close to vessels, but distinct from it, and exact coregistration with diagnostic CT or MRI was able to differentiate metastatic nodal uptake from physiological vascular uptake. In 25 of 58 patients originally thought to have regional or distant nodal disease on SPECT, fusion showed only local (prostate bed) recurrence. All these patients were treated with radiation. Seventeen of these 25 patients had post-radiation PSA available. In 12 of these 17 patients, PSA levels decreased, suggesting that a recurrent tumor was confined to the prostate bed, and SPECT imaging was accurate in its estimation of disease location. However, in five of 17 patients, PSA continued to increase even after radiation, suggesting that disease outside of the prostate bed had gone undetected, even after fusion of SPECT and CT/MRI. This study illustrates the potential benefit of the fusion of SPECT with diagnostic CT for enhanced accuracy, especially for reducing false-positive findings generated by physiologic uptake in the bowel, vessels, or marrow. However, the fusion study missed a portion of extraprostatic recurrence, which may be related to low uptake of labeled immunoglobulin in early tumor recurrence or potential misregistration, since the CT or MR were acquired separately.

Another study$^{11,2}$ evaluated the usefulness of pretreatment $^{111}$In capromab pendetide (ProstaScint) SPECT with coregistration of CT to detect occult metastatic disease and to predict biochemical failure in a group of patients with a clinical diagnosis of localized adenocarcinoma of the prostate, who were referred for primary radiotherapy. Pretreatment SPECT, with CT fusion, suggested prostate cancer metastasis (22), seminal vesicle extension (20) and organ-confined disease (197). Overall biochemical failure was 18.3 percent. Biochemical failure in patients having extraperiprostatic metastatic prostate cancer, seminal vesicle extension and organ-confined disease uptake on SPECT/CT was 43.2 percent, 33.3 percent and 15 percent, respectively. The study showed that finding of extra-periprostatic metastatic prostate on SPECT/CT significantly predicted a 4.2-fold greater risk of biochemical failure.

Positive extraprostatic uptake of $^{111}$In ProstaScint in the pelvis can lead to the decision of extensive pelvic irradiation while uptake in the abdomen, including paraaortic nodes, would lead to systemic therapy. This makes accurate delineation of lesions of paramount clinical significance. The use of SPECT, with integrated CT, using efficient CT-based attenuation correction and accurate localization due to the elimination of registra-
tion errors from separately acquired CT goes a long way in the improvement of ProstaScint imaging. Duke University\textsuperscript{11,3} studied 35 patients using SPECT/CT with low-resolution, non-diagnostic CT. Two patients were imaged for staging before therapy and 29 after treatment. Of the 29 patients imaged for initial staging, one had diffuse tracer uptake in the gland with no evidence of distant disease on ProstaScint imaging and was confirmed to have disease confined to the prostate at surgery. The second patient had high uptake in the right prostatic lobe on SPECT/CT, which was confirmed at biopsy. SPECT/CT was accurate in both cases of primary staging. Of the 29 patients evaluated after failed local therapy (prostatectomy, external beam radiation or both, hormonal therapy, cryotherapy and brachytherapy), 12 patients (41%) had no evidence of local recurrence on SPECT/CT, 11 patients (38%) had homogenous accumulation in the prostatic bed suggestive of local recurrence, six patients (21%) had heterogeneous accumulation in the prostatic bed suggestive of recurrence, and three patients (10%) had extraprostatic metastases identified by SPECT/CT in the rib, skull and retroperitoneum. CT helped delineation of physiological uptake in the marrow, bowel and vessels, especially the uptake in the rectum and symphysis pubis. This study utilized low-dose, non-diagnostic CT, as well as blood-pool SPECT for localization and characterization of \textsuperscript{111}In ProstaScint\textsuperscript{9} uptake. The use of CT eliminates the need for the blood-pool images. However, the authors note that in the case of tortuous blood vessels, correct localization of ProstaScint uptake may be problematic and may lead to false-positives.

A recent article\textsuperscript{11,4} has evaluated the value of \textsuperscript{111}In capromab pendetide SPECT/CT using non-diagnostic CT for detecting seminal vesicle invasion in patients with recurrent prostate cancer after primary therapy. The study included 59 patients with biochemical failure after primary in situ treatment including brachytherapy. The patients underwent a SPECT/CT study at the time of biochemical failure along with a prostate and seminal vesicle biopsy. SPECT/CT was compared to MRI for detection of seminal vesicle involvement compared to biopsy. In total, eight (14%) patients had a positive seminal vesicle biopsy while nine (15%) patients had positive uptake of the scan in the seminal vesicle. When comparing the \textsuperscript{111}In capromab pendetide SPECT/CT results to the seminal vesicle biopsy, the sensitivity, specificity, positive predictive value, and negative predictive value were 37.5 percent, 88.2 percent, 33.3 percent, and 90.0 percent respectively. In contrast, the ability of MRI to detect seminal vesicle invasion was 50.0 percent, 81.3 percent, 40.0 percent, and 86.7 percent, respectively. Thus, the sensitivity and positive predictive value of the SPECT/CT using non-diagnostic CT was low compared to MRI using biopsy as the gold standard, although its specificity and negative predictive value was high. The low sensitivity and positive predictive value of SPECT/CT may be attributed to the poor resolution of the non-diagnostic CT in this study, which may result in difficulty in localization of physiological uptake in the pelvis and differentiation with metastatic spread in the seminal vesicles compared to MRI with its high-resolution and superior tissue contrast compared to non-diagnostic CT. This article demonstrates the greater need for similar comparative studies utilizing the SPECT/CT techniques which use integrated diagnostic multislice CT in order to improve lesion localization.

Seo et al.\textsuperscript{11,5} used SPECT/CT with integrated diagnostic multislice CT to develop an in vivo method to quantify \textsuperscript{111}In capromab pendetide antibody uptake in primary prostatic tumors and to compare quantitative uptake values with Gleason score to evaluate the method for potential grading of prostate tumors. The group devised an advanced iterative reconstruction algorithm based on diagnostic CT-based attenuation correction, as well as corrections for photon scatter and geometric blurring using post-reconstruction, partial volume techniques. Using these techniques as well as conversion factors between image values and tracer concentrations (in Bq/ml), which were calculated from specialized phantom studies, the SPECT/CT study was able to generate quantitative values from regions of tracer uptake which were close to 90 percent of the true values (as seen in phantom measurements). The technique was then used in 10 patients with primary prostate cancer as a pre-operative procedure. Quantitative in vivo antibody uptake values generated using SPECT/CT were then compared with Gleason scores. There was a statistically significant correlation between prostatic zones with high antibody-uptake values with higher Gleason scores. This study is the first attempt at using SPECT/CT and reconstruction techniques for quantitative analysis of radiolabeled monoclonal antibody analysis and shows promise of being able to identify the tumor burden and to potentially plan and monitor therapy based on quantitative parameters. Future studies, especially comparing quantitative antibody uptake values with MR spectroscopic findings, will further enhance the confidence level with this technique. It is important to realize that integrated diagnostic CT combined with SPECT is essential for such quantitative accuracy since the CT component influences the accuracy of quantification by proper attenuation correction and improves quantitative information on radioactivity distribution.
Studies utilizing SPECT/CT with low-resolution CT, and SPECT fused with diagnostic CT, uniformly show higher sensitivity, specificity and accuracy for ProstaScint imaging. In view of the impact of a positive study on the treatment decision-making, especially in the case of a decision of local radiation compared to systemic therapy, it is logical to conclude that SPECT with integrated, diagnostic CT would be highly desirable due to its ability to further improve the accuracy of the study. The Symbia® TruePoint SPECT•CT, which combines SPECT with integrated, multislice, diagnostic CT, is ideally suited for imaging with ProstaScint. Its combined diagnostic CT and SPECT imaging ensures accuracy of morphology and functional image coregistration. In addition, high-quality CT with intravenous contrast, if necessary, as an integrated procedure provides valuable information by itself, apart from its role in characterizing SPECT lesions.

Further support for this concept of integrated, diagnostic CT and SPECT comes from radiation therapy where ProstaScint SPECT fused with diagnostic CT or SPECT/CT integrated imaging has been used to generate biological target volumes (BTV) for dose-escalation targeting or for image guided radiation therapy (IGRT). The accuracy of coregistration and high-quality CT is critical for correct contouring of radiotherapy target volumes, which enable IGRT dose escalation to discrete tumor targets defined by focal uptake on the fused radioimmunoscintigraphy image sets. SPECT/CT ProstaScint imaging also has a larger potential role in treatment selection for patients, who are at high risk for local (periprostatic) extension of disease, and who may benefit from dual therapy applications, such as seed implant plus external beam radiation using conformal therapies, such as Intensity Modulated Radiation Therapy (IMRT). These therapies present opportunities to refine dose delivery and to enable dose escalation to regions shown to be positive for focal uptake on SPECT/CT radioimmunoscintigraphy. Fused images are used to generate Gross Tumor Volume (GTV) and Clinical Target Volume (CTV) for radiation therapy planning. The use of dose escalation strategies to CTV generated from SPECT/CT fusion has been shown to benefit biochemical, disease-free survival (bDFS) and to reduce radiotherapy-related morbidity for prostate cancer.

One study\textsuperscript{11,6} evaluated 239 patients who were treated with definitive radiation therapy for clinically localized prostate cancer using brachytherapy dose escalation to BTV identified with SPECT/CT. In some cases, conformal external beam therapy was also added. Intraprostatic BTV dose targets were escalated to 150 percent of the prostate volume prescription dose. The seven-year bDFS rate for the entire group was 88 percent, which was higher than comparable studies.

Dose escalation strategies have been proven to be beneficial in reducing failure risk in localized prostate cancer. A study presented at an RSNA 2004 scientific session\textsuperscript{11,7} used IMRT to irradiate the entire prostate (75.6 Gy in 42 fractions) with a simultaneous boost (82 Gy) to regions of tumor burden found on SPECT/CT ProstaScint datasets with favorable PSA responses. The authors reported a favorable profile of dose to normal structures like the rectum and bladder with <40 percent of the rectal/bladder volume receiving >65 Gy. This would minimize treatment-related morbidity, while enhancing bDFS. SPECT/CT fusion may also guide patients, with a recurrence or rising PSA after salvage radiation therapy, to the exact region for biopsy, and in this application, fusion with diagnostic CT would play a critical role in guiding the biopsy procedure.

Another study\textsuperscript{11,8} evaluated 25 patients with ProstaScint SPECT using diagnostic CT fusion in order to modify post-prostatectomy, prostate fossa CTV definitions. The mean CTV, based on SPECT/CT fusion, was larger than the CTV generated by CT alone (35 cubic cm vs 24.4 cubic cm). Two-year biochemical, disease-free survival was 87 percent for this group. SPECT/CT fusion had a major impact on the definition of CTV and radiation planning.

Evidence in literature of the value of fusion of ProstaScint SPECT to CT, as well as the improvement in radiation therapy planning based on SPECT and CT fused datasets, clearly points to the potential of SPECT with integrated, multislice, diagnostic CT in radioimmunoscinography for prostate cancer. Identification of small nodal disease, differentiation of pathological uptake from normal uptake in the vessels, marrow and bowel, especially in post-operative or post-radiation scenarios, would logically benefit from high-quality, thin-slice CT with accurate coregistration of SPECT due to the integrated acquisition without patient movement or positional inaccuracies.
A few case examples performed on Symbia TruePoint SPECT•CT illustrate the improved image quality and diagnostic confidence obtained from this approach. The first case (Figure 11-1) is a patient with operated prostate cancer, who presented with slowly rising PSA. An $^{111}$In ProstaScint SPECT•CT study demonstrated focal areas of uptake in the abdomen, which corresponded to areas in the mesentery and were distinct from bowel loops. CT showed a normal-sized mesenteric node corresponding to the area of focal uptake. The lesion was defined as a mesenteric lymph node metastasis from prostate cancer, without pelvic or bone metastases.
The second case (Figure 11-2) is a patient with primary prostate cancer, who underwent a ProstaScint SPECT•CT for initial staging. The study showed focal uptake in the prostate bed, suggesting a primary tumor, as well as focal lesions in the left iliac and right mesenteric nodes. The clarity of high-quality CT, integrated with SPECT, helped differentiate the mesenteric nodal uptake from bowel loops.

Figure 11-2 Data courtesy of MD Anderson Cancer Center, Houston, TX, USA
The third case example (Figure 11-3) is a patient with prostate cancer treated with prostatectomy, who presented with rising PSA. An $^{111}$In ProstaScint study was performed to determine the presence of extrapelvic metastases. The SPECT•CT study localized tracer-avid metastatic lesions in the supraclavicular nodes, mediastinal nodes and peritoneum. The breath-hold, spiral CT study helped exact coregistration with small lymph node and abdominal lesions.
This example (Figure 11-4) shows a patient with primary prostate cancer who underwent \(^{111}\)In-Prostascint SPECT•CT for evaluation of abdomino-pelvic metastases. Whole-body scintigraphy followed by SPECT•CT was performed on day four and five, following intravenous injection of radiolabeled monoclonal antibody. The study shows multiple tracer-avid mesenteric nodes as well as three small, paraaortic lymph nodes suggestive of metastases. The small size of the peri-aortic lymph node metastases, well delineated by SPECT•CT, and the accurate localization of the nodal lesions due to fusion with breath-hold diagnostic CT, is clinically noteworthy.
This example (Figure 11-5) is of a 74-year-old man with prostate cancer who was treated with a prostatectomy followed by external beam radiation six years previously. He presented with a recent increase in PSA to a level of 6.6 ng/ml. SPECT•CT with integrated contrast CT was performed five days following an IV injection of $^{111}$In capromab pendetide (ProstaScint). Multi-bed SPECT of the thorax, abdomen and pelvis was performed along with contrast CT. The study shows multiple areas of focal uptake of the labeled antibody in the abdomen localized to subcentimeter lymph nodes in the mesentery (arrows) and suggests mesenteric nodal metastases. There was no abnormal pelvic uptake suggestive of local recurrence or pelvic nodal metastases. Focal tracer uptake in the prostate fossa was localized to the anterior aspect of the rectum in proximity of multiple staples related to the previous prostatectomy.
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11.5 Seo et al. (2010). In Vivo Tumor Grading of Prostate Cancer Using Quantitative 111In-Capromab Pendetide SPECT/CT. *Journal of Nuclear Medicine*, 51, 31-36.

11.6 Ellis, RJ et al. (2007). Biochemical disease-free survival rates following definitive low-dose-rate prostate brachytherapy with dose escalation to biologic target volumes identified with SPECT/CT capromab pendetide. *Brachytherapy*, 6(1), 16-25.

11.7 Schild et al. (2004). The Use of Both ProstaScint and CT Scans in Planning IMRT for Prostate Cancer.

Several applications of SPECT in the detection of cancer recurrence, and in planning and follow-up of invasive therapy, have the potential to be further enhanced by SPECT/CT, especially with integrated, diagnostic CT. The detection of recurrent brain tumors or nasopharyngeal and oropharyngeal cancer using $^{201}\text{Tl}$ SPECT has shown high sensitivity and specificity. Although PET/CT has been shown to be superior in such applications, several centers continue to use $^{201}\text{Tl}$ SPECT for such indications with good results. The integration of diagnostic CT, as part of a SPECT/CT protocol in the evaluation of tumor recurrence, has merit, especially in post-surgery and post-radiation scenarios. A combination of diagnostic CT and functional information from $^{201}\text{Tl}$ SPECT can provide comprehensive information about the extent and specific location of tumor recurrence, and soft tissue and bony changes associated with the tumor and therapy.

$^{201}\text{Tl}$ SPECT imaging, fused with diagnostic CT, has been used to evaluate recurrence in head and neck cancer. One study$^{12.1}$ evaluated 33 patients with $^{201}\text{Tl}$ SPECT suspected to have tumor recurrence, and fused the data with separately performed, diagnostic CT. Sixteen patients had histologically confirmed, recurrent disease (oropharynx, oral cavity, hypopharynx, larynx and nasopharynx). Seventeen patients had no evidence of disease on follow-up. CT demonstrated all 16 recurrent tumors but also showed 13 false-positives. SPECT showed 14 out of 16 recurrent tumors but only one false-positive. The specificity of $^{201}\text{Tl}$ SPECT was far superior to CT, while CT showed excellent sensitivity and negative predictive value.

A similar study$^{12.2}$, fusing $^{201}\text{Tl}$ SPECT with diagnostic CT, was performed in 41 cases of primary or recurrent nasopharyngeal and maxillary cancer. SPECT and CT identified all 18 primary tumors, and CT helped localize two small maxillary tumors on fused images. Out of nine patients shown to have recurrence on SPECT, seven were confirmed by fusion with diagnostic CT. Two patients showed unilateral uptake in the nasopharynx, and the findings were characterized as normal paravertebral muscle uptake by SPECT/CT fusion. In several patients, SPECT identified a recurrent tumor in the nasopharyngeal wall, which appeared unchanged on CT compared to previous studies. CT helped the localization of three small, recurrent tumors in the clivus. Fusion of diagnostic CT and SPECT helped detection and characterization of all recurrent tumors.

A similar fusing of $^{201}\text{Tl}$ SPECT with diagnostic CT and MRI was performed in a study on patients with recurrent oral cancer$^{12.3}$. Thirty-two consecutive patients, with clinically suspected recurrence of oral cancer, were evaluated with $^{201}\text{Tl}$ SPECT and CT/MRI, and the data were fused. Primary tumors were in the buccal mucosa, tongue, gingiva, floor of the oral cavity and hard palate. Most patients were treated with surgery combined with radio-chemotherapy or surgery alone. SPECT and CT/MRI correctly detected 17 out of 18 residual or recurrent tumors. However, CT/MRI yielded eight false-positive results, whereas $^{201}\text{Tl}$ SPECT accurately included all tumors with no false-positives. The specificity of $^{201}\text{Tl}$ SPECT was far superior to CT/MRI (100% vs. 43%), while both had similar sensitivity (94%).

This study further supports the use of integrated, multislice, diagnostic CT combined with SPECT for the evaluation of recurrent tumors. Thin-slice, high-quality CT is critical for proper characterization of bone and soft tissue involvement. It can identify and define viable tumors based on $^{201}\text{Tl}$ uptake and can differentiate necrotic areas as well as correctly identify the exact region for biopsy. Using integrated, diagnostic CT, a CT-guided biopsy, with sampling from the region identified by SPECT/CT as a recurrent tumor, may be able to improve the accuracy of the biopsy to yield the correct tissue sample. Moreover, diagnostic CT is useful for differentiating physiological uptake of $^{201}\text{Tl}$ in the submandibular salivary glands from nodal disease.
A case example (Figure 12-1) from Symbia® TruePoint SPECT•CT will illustrate this point. This was a 57-year-old male with a history of nasopharyngeal cancer treated with chemo-radiation. The patient presented with progressive pain. CT and MRI studies were suspicious for recurrence. SPECT•CT demonstrated increased radiotracer uptake in the right oropharyngeal region, suggesting recurrent neoplasm. CT helped define the extent and margins of the recurrent tumor, and also demonstrated the relationship of the tumor to the mandible, vertebral transverse process and parotids. 99mTc MIBI SPECT fused with diagnostic CT has also been used for the evaluation of tumor recurrence in head and neck cancers, and in recurrent gliomas, as well as to characterize lung lesions. Integrated, diagnostic CT combined with SPECT offers the same potential of improved lesion characterization in these applications.

Selective internal radiation therapy has emerged as a therapeutic modality for the management of non-resectable, hepatic malignancies, including metastases as well as primary hepatomas, using an intra-arterial instillation of Yttrium 90 microspheres. Pre-therapy CT and 99mTc MAA SPECT, following the injection of the tracer into the hepatic arterial port for assessment of the tumor volume and extrahepatic shunting, is part of the routine clinical workup. SPECT combined with diagnostic CT has been used for pre-therapy evaluation for intra-arterial chemotherapy as well as for radionuclide therapy. One study12.4 compared the perfusion patterns of hepatic arterial infusion chemotherapy on intra-arterial port-catheter CT (iapc-CT), and fused images obtained using a SPECT/CT system with an interchangeable patient table. Twenty-eight patients with primary or metastatic carcinoma of the liver, who bore an implantable hepatic arterial infusion port system, underwent abdominal SPECT imaging, using 99mTc MAA infusion as well as CT, during contrast infusion through the hepatic arterial port. The intrahepatic perfusion (IHP) and extrahepatic perfusion (EHP) patterns of hepatic arterial infusion chemotherapy on CT and fused SPECT/CT were then compared. In 23 of 28 patients (82%), intrahepatic perfusion patterns were identical. In five of the 28 patients (18%), the patterns were discordant. Fused images demonstrated extrahepatic perfusion in more patients (12/28 or 43%) compared to CT with intrahepatic arterial-port contrast infusion (8/28; or 29%). SPECT was clearly superior in this regard. This study clearly defined that fusion imaging using the SPECT combined with diagnostic CT reflects the actual distribution of the infused anticancer agent, which is valuable, not only for monitoring adequate drug distribution, but also for avoiding potential extrahepatic complications.
Using a Symbia TruePoint SPECT•CT system, it is possible to combine the evaluation of intrahepatic and extrahepatic perfusion using $^{99m}$Tc MAA infused into the hepatic arterial port, as well as a diagnostic CT with contrast infusion to obtain a CT angiography of the hepatic arterial tree, and to evaluate the CT contrast enhancement pattern of the tumor in the same sitting. This makes such a procedure convenient as well as accurate, since both hepatic vascular anatomy and perfusion patterns can be delineated at the same time without patient movement.

SPECT and diagnostic CT combinations have been used to study anatomic variations in the hepatic arteries of patients with liver tumors, since they may require hemodynamic modification to render effective hepatic arterial infusion chemotherapy delivered via implantable port systems. A further study used a combined, diagnostic SPECT/CT system to obtain fused images of the intrahepatic perfusion patterns in patients with such anatomic variations and assessed their effects on the treatment response of hepatic tumors. Fused images were obtained in 110 patients with malignant liver tumors or liver metastases from unresectable pancreatic cancer. Patients with anatomic, hepatic artery variations underwent hemodynamic modification before the placement of implantable port systems for hepatic arterial infusion chemotherapy. These patients were subsequently evaluated for their intrahepatic perfusion patterns and the initial treatment response of the liver tumors. The combination of SPECT perfusion and contrast CT definition of hepatic arterial anatomy was able to define anatomic, hepatic, artery variations in 15 of the 110 patients (13.6%). In 13 of these 15 patients (87%), occlusion with metallic coils was successful. SPECT intrahepatic perfusion patterns were predictive of the response to hepatic arterial infusion chemotherapy.

Another publication used Symbia SPECT•CT with integrated, dual-slice diagnostic CT to detect extrahepatic shunting to the lung or gastrointestinal tract prior to radioembolization with $^{90}$Y microspheres in a series of 58 patients with hepatocellular carcinoma. Each patient underwent hepatic arteriography and scintigraphy following intraarterial injection of $^{99m}$Tc MAA through a hepatic artery catheter with planar imaging, SPECT and SPECT•CT. SPECT•CT revealed gastrointestinal shunting in 16 of 68 examinations while SPECT revealed only 9. For SPECT without CT, the sensitivity and specificity for detection of extrahepatic shunting was 56 percent and 87 percent respectively, while that for SPECT•CT was 100 percent and 94 percent. SPECT•CT identified all cases of gastrointestinal extrahepatic shunting without any false negatives. In three patients, MAA deposition in the liver hilum was misinterpreted as extrahepatic on SPECT•CT. However, correlation with separately acquired contrast-enhanced CT demonstrated that these MAA deposits were tumor uptake in the portal vein tumor thrombi. The additional and vital information provided by contrast CT in these patients suggests the clinical value of integrated contrast CT as a part of the $^{99m}$Tc MAA SPECT•CT procedure. In 10 patients, extrahepatic MAA deposition was detected with SPECT•CT. This deposition was localized within the gastrointestinal tract in all patients. In six of these patients, the underlying vessel was found on subsequent angiography and was coil-embolized. In two others, the underlying vessel was detected but could not be embolized because of its small diameter. These patients were treated from a more distal catheter position. In the remaining two patients, no underlying artery was found on repeated angiography but gastrointestinal MAA uptake persisted. These patients were not treated with $^{90}$Y radioembolization. Therefore, non-target seeding was successfully avoided. No treated patient experienced gastrointestinal complications. This study clearly shows the benefits of SPECT/CT with diagnostic CT, with a significant increase in sensitivity and specificity of detection of extrahepatic shunting, and, therefore, its regular use prior to radioembolization procedures may further reduce the risk of gastrointestinal complications. Integrated, contrast CT may further enhance the diagnostic accuracy of the procedure.

Combined studies of SPECT and diagnostic CT perfusion to define hepatic arterial anatomy and tumor perfusion, as well as extrahepatic shunting, demonstrate the potential value of the combination of SPECT and diagnostic CT. A few examples from Symbia TruePoint SPECT•CT illustrate the point.
The first example (Figure 12-2) is a patient with multiple liver metastases from colorectal carcinoma, who was scheduled for intra-arterial radiation therapy using $^{90}$Y microspheres. Pre-therapy confirmation of the catheter placement and assessment of tumor perfusion for dose calculation using intra-arterial injection of $^{99m}$Tc MAA was performed 24 hours after intra-arterial administration of $^{90}$Y microspheres. SPECT•CT Bremsstrahlung imaging of $^{90}$Y-microsphere distribution was performed at the same time to confirm adequate tumor uptake.
The second example (Figure 12-3) is a patient with primary hepatoma, who was treated with intra-arterial lipiodol through a hepatic arterial port. A SPECT•CT study following $^{99m}$Tc MAA infusion, through an intra-arterial catheter, assisted in defining perfusion in the primary hepatoma after intra-arterial lipiodol therapy. SPECT•CT defines the extent of the tumor and identifies non-perfused areas of the tumor suggestive of necrosis of tumor tissue secondary to lipiodol ablation.
Another similar example (Figure 12-4) shows a SPECT•CT study in a patient with primary hepatocellular carcinoma following injection of \(^{99m}\text{Tc}\) MAA in the hepatic arterial port. This study shows uptake of labeled albumin in a large primary tumor with central necrosis, along with significant uptake in both lungs, suggesting pulmonary shunting of the tracer. Delineation of pulmonary shunting has major implications for planning and dosimetry of intra-arterial \(^{90}\text{Y}\) therapy.

The use of radiolabeled anti-CD20 monoclonal antibodies for therapy of refractory, non-Hodgkin lymphoma is an established procedure where accurate dosimetric measurements are critical to proper dose calculation and to the limitation of myelosuppression, which is the dose-limiting side effect of this therapy. Prospective, individualized bone marrow dosimetry may minimize the risk of marrow toxicity. Sequential planar imaging to ascertain the effective half-life of the radioiodinated antibody is an established procedure used to determine the total therapeutic dose, SPECT/CT has been used to enhance dosimetry calculations by providing accurate attenuation correction, as well as SPECT/CT-fused, data-based, marrow-volume estimations for accurate calculations of absorbed marrow dose. Boucek and Turner\(^{12,7}\) used SPECT/CT with low-resolution, non-diagnostic CT for the evaluation of 27 patients with non-Hodgkin lymphoma, who underwent SPECT/CT five to seven days after \(^{131}\text{I}\) anti-CD 20 Rituximab. Marrow cavities in the spine, pelvis and femur were identified on CT. In order to delineate bone marrow on SPECT, the regions of interest were drawn on CT and fused images. Regions of interest (ROIs) were transferred to SPECT slices for quantification of uptake based on the counts in the ROI. Average counts in each ROI were converted to activity and activity-concentration using calibration factors. In a subset of patients, sequential SPECT/CT studies were performed and marrow uptake quantified to measure the active-marrow, effective half-life. Bone marrow clearance rates, measured as effective half-life of \(^{131}\text{I}\) Rituximab using quantitative SPECT/CT, were similar to whole-body half-life measurements. There was a clear correlation between marrow and whole-body tracer clearance. Bone marrow uptake was also measured using SPECT/CT and whole-body effective half-life estimates, median activity concentrations for active marrow in the spine, pelvis and femur, as well as median absorbed dose. This study shows the added value of SPECT/CT for accurate delineation of marrow using CT-based ROI drawing, thereby compensating for partial volume effects. From the methodology of this dosimetry approach, it is logical to conclude that integrated, diagnostic CT with SPECT would have a favorable impact on the accuracy of marrow volume and dosimetry calculations. Due to high-quality, diagnostic CT, it would be possible to more accurately define marrow ROI in vertebrae, pelvic bones and femurs, since separation of the vertebral cortex from the spongy bone, as well as delineation of marrow from the inner cortical margin of long bones and pelvic bones, would be easier using diagnostic CT with sharp reconstruction kernels with appropriate window settings. Thus, volume accuracy for these measurements would be improved considerably using diagnostic CT integrated with SPECT. Furthermore, diagnostic CT shows the potential of improved visualization of uptake in nodal lesions adjacent to the aorta, which may show physiological uptake even five days after dose administration due to slower clearance. Similar dosimetry studies using Symbia TruePoint SPECT•CT are being performed, and future publications are expected to illustrate the additional value of diagnostic CT in such applications.
Recent studies have further expanded the use of SPECT/CT in radiolabeled monoclonal antibody therapy in lymphoma. Amro et al.\(^\text{12.8}\), from the University of Michigan, used Symbia SPECT•CT with integrated 6-slice diagnostic CT to perform sequential studies following injection of \(^{131}\)I Tositumomab in six patients with refractory non-Hodgkin lymphoma for calculation of tumor dose rate distributions. Each patient underwent three sequential SPECT•CT studies following injection of a diagnostic dose of radiolabeled antibody. Following administration of a therapeutic dose of \(^{131}\)I Tositumomab, the patients again underwent three more sequential studies to assess tumor response. A 3D imaging-based dosimetry methodology for calculation of biologically effective dose (BED) and equivalent uniform dose (EUD) was developed using an in-house MATLAB-based software package and Monte Carlo 3D dose-rate calculations. SPECT•CT scans were used to generate 3D images of cumulated activity, which were then used as inputs to Monte Carlo dose-rate calculations. Dose-rate distributions were integrated over time to obtain the 3D absorbed dose values. Diagnostic CT was instrumental in precise definition of tumor volume and consequent efficient dosimetry calculations. Cumulative dose for individual tumor masses ranged from 1.7 to 4.2 Gy. Sequential imaging following therapy demonstrated a significant correlation between fractional tumor shrinkage and initial tumor volume as well as a tendency towards greater tumor shrinkage with higher cumulative doses.

Using a SPECT/CT system with integrated 16-slice CT, Hobbs et al.\(^\text{12.9}\) determined absorbed dose to the arterial wall in non-Hodgkin lymphoma patients treated with \(^{131}\)I Tositumomab radioimmunotherapy in view of the potential concern for delayed toxicity. Four patients were administered pre-therapeutic \(^{131}\)I Tositumomab, and SPECT/CT was performed at 48, 72 and 144 hours subsequently. Regions of interest over tumor and adjacent vascular blood pools were drawn using SPECT/CT data and then fed into 3D dosimetry software for absorbed dose calculations. Diagnostic CT was helpful in accurate delineation of tumor and vascular margins. Arterial wall-absorbed doses ranged from 0.6 to 3.7 Gy, which were lower than those typical from external beam radiotherapy (1.4-10.5 Gy), thereby suggesting that potential delayed toxicity to adjacent vessels from radioimmunotherapy of lymphoma was lower.

SPECT/CT-based dosimetry has been advocated for the quantification of radiation doses delivered during \(^{131}\)I MIBG therapy using CT-based tumor volumes of interest. SPECT/CT-based, patient-specific 3D dosimetry has also been used for diffuse lung metastases in patients with thyroid carcinoma being treated with \(^{131}\)I. Song et al.\(^\text{12.10}\) performed sequential SPECT/CT using non-diagnostic CT to calculate lung residence time of radiiodine, as well as total lung metastatic volume and normal lung volume based on a predetermined thresholding algorithm used on fused images. The planned therapy dose to treat lung metastases with SPECT/CT-based dosimetry was 2.6 times higher than that calculated by the standard method. Since differentiation of metastatic deposits from a normal lung is difficult in diffuse lung metastases, thin-slice, diagnostic CT with appropriate reconstruction kernels and windowing would be highly relevant for improved dosimetry in such situations.

A few clinical examples from Symbia TruePoint SPECT•CT users illustrate the relevance of integrated, diagnostic CT with SPECT in tumor dosimetry applications.
This example (Figure 12-5) is a 63-year-old woman with recurrent follicular lymphoma shown on FDG PET/CT (a) to have right, inguinal and iliac nodal disease. She was evaluated using planar and SPECT•CT imaging after injection of 10 mCi of $^{131}$I Rituximab (Bexxar) for dosimetry. Sequential planar (b) and SPECT•CT (c, d, e) images were acquired. SPECT•CT was performed on a Symbia T6 with integrated 6-slice CT. In the SPECT•CT images, clear delineation of involved nodes from the vessels, which showed physiological uptake, was possible due to high-quality CT. Fused CT and SPECT datasets permitted accurate calculation of tumor volumes and subsequent, absorbed dose calculation. In this patient, SPECT•CT dosimetry was used to calculate the therapeutic dose of $^{131}$I Rituximab. A follow-up PET/CT (f) performed two months after $^{131}$I Bexxar therapy showed total absence of FDG uptake from the involved, right, inguinal nodes, which suggested a significant response to therapy.
Figure 12-5f Data courtesy of MD Anderson Cancer Center, Houston, TX, USA
The next example (Figure 12-6) shows the use of SPECT•CT with diagnostic CT for follow-up after therapy with $^{153}$Sm EDTMP for bone pain in a patient with skeletal metastases. Gamma emissions from $^{153}$Sm EDTMP were imaged by SPECT•CT 24 hours after dose administration to ascertain optimum uptake of the therapeutic tracer in metastatic sites. The study showed uptake in small blastic metastatic sites in the sternum and vertebral bodies. Sclerotic metastases in the T11 vertebra showed an absence of uptake, probably reflecting burnt-out disease.
References:


As SPECT/CT becomes more widely available, its use has been expanding into newer applications, which have traditionally been approached as standard gamma camera procedures. The list of such procedures is large and ever expanding. A few examples of the use of Symbia® TruePoint SPECT•CT for different indications is illustrative of the clinical value of integrated diagnostic CT with SPECT.

This example (Figure 13-1) is of a hepatobiliary scintigraphy, performed initially as a planar dynamic study, followed by SPECT•CT performed on a Symbia T6. This was a 61-year-old man who recently underwent a liver transplantation. Two weeks following transplantation, the patient developed sepsis with bilious discharge from the drain that was suspicious for biliary leakage. The exam revealed the normal flow of the tracer into the intrahepatic ducts and common bile duct and subsequently, into the small bowel. Pooling of the tracer was visualized in the superomedial aspect of the liver with extravasation into the subphrenic space. A SPECT•CT study demonstrated the exact site of the leak. Accurate fusion with integrated, thin-slice diagnostic CT confirmed that the leak site originated from the common bile duct anastomosis with the biliary duct from the transplanted liver.
Another example (Figure 13-2) of a similar study shows an integrated contrast CT with SPECT for localization of a biliary leak. This was a 56-year-old man, who underwent liver transplantation, and was referred for hepatobiliary scintigraphy for a suspected biliary leak. A dynamic, planar hepatobiliary study was performed over 60 minutes followed by a SPECT•CT with integrated contrast CT. The dynamic study showed normal clearance of the tracer from the liver with visualization of the extrahepatic bile duct 10-minute post injection with a sequential flow of the tracer into the small bowel. There was visualization of a leak of the tracer from the upper end of the extrahepatic bile duct with gradual and progressive accumulation. SPECT•CT clearly localized the site of the leak at the level of the anastomosis of the extrahepatic bile duct (recipient) and the intrahepatic ducts (donor) with collection of leaked bile in the region between the IVC and gastric antrum. The tracer was visualized passing into the drain, located in the anastomotic site.
This example (Figure 13-3) shows a patient with pancreatic carcinoma who underwent a pancreatectomy along with a cholecystectomy, choledochoduodenostomy, and gastrojejunostomy, as well as a splenectomy. $^{99m}$Tc HIDA hepatobiliary scanning was performed with initial dynamic planar images followed by SPECT•CT one hour after injection. Normal clearance of the tracer was visualized in the intestine by 10 minutes. By 50 minutes, the tracer was visualized in the stomach. SPECT•CT shows reflux of bile in the gastric antrum along with significant jejunal dilatation. There were also extensive post-surgical changes and pneumobilia in portions of the liver visualized on integrated diagnostic CT.
Detection of Meckel’s diverticulum is a common procedure performed with a gamma camera. Detection is especially enhanced by SPECT•CT due to the superior abdominal anatomical details obtained by integrated diagnostic CT. This example (Figure 13-4) shows a 22-year-old male patient with abdominal pain. The $^{99m}$Tc-pertechnetate planar study visualized focal abdominal tracer uptake suspicious of Meckel’s diverticulum. SPECT•CT localized the Meckel’s diverticulum with ectopic gastric mucosa to a part of the ileum in the left hypogastric region. Integrated diagnostic CT helps ensure accurate localization of the lesion and surgical planning.

Although several studies have used SPECT/CT for evaluation of liver perfusion prior to selective therapy of the liver tumor through the hepatic arterial port, there are only incidental reports of liver or hepatobiliary scanning using SPECT/CT. One study$^{13.1}$ used SPECT/CT with low-resolution, non-diagnostic CT for the diagnosis of hepatic hemangiomas with atypical locations (situated adjacent to the heart, the inferior cava, hepatic vessels or abdominal aorta, etc.). Fifty-two patients with suspected liver hemangiomas were studied using SPECT-labeled blood pool studies. In patients, where the location of the hemangioma was difficult to determine by SPECT alone, SPECT/CT was used. Thirty-one of 54 patients were diagnosed with hepatic hemangiomas. The localization of hemangiomas in eight patients was made possible only by use of SPECT/CT. Three of these lesions were located close to the abdominal aorta, one near the heart and four near the inferior vena cava. In addition, SPECT/CT clarified six abnormal focal uptakes as normal uptake in the inferior vena cava rather than hemangiomas.

Another series$^{13.2}$ studied 12 patients with suspected hepatic hemangiomas using SPECT/CT with non-diagnostic CT. Twenty-one of the 24 lesions were finally classified as hemangiomas. Three hemangiomas were not identified on SPECT images. Three non-hemangiomas were diagnosed as metastases. Six lesions were adjacent to blood vessels or the heart, three near hepatic or portal veins, two adjacent to the inferior vena cava and one adjacent to the heart. Four of these lesions (two hemangiomas, two metastases) were identified due to SPECT/CT correlation. This study clearly demonstrates the difficulty in identifying hemangiomas with SPECT, when they are located near vascular structures, as well as in differentiating small hemangiomas from other liver lesions like metastases. In this context, high-quality CT information, with possible contrast opacification of portal and hepatic vessels integrated with SPECT, can significantly improve diagnostic confidence and accuracy.
This example (Figure 13-5) demonstrates integrated, diagnostic CT and labeled blood-pool SPECT in a case of multiple hepatic hemangiomas. High-quality, diagnostic CT combined with SPECT is able to define very small lesions, and three-phase contrast CT helps to delineate a contrast blush in small hemangiomas in order to improve localization and characterization of these lesions. The differentiation of hemangiomas from other liver lesions like focal nodular hyperplasia is very efficient with integrated, diagnostic CT and SPECT, particularly when the lesion is small. Integrated, three-phase contrast CT would enhance the diagnostic confidence of SPECT/CT very significantly, especially for accurate characterization of small hemangiomas located very close to vessels like the portal vein and its branches, the hepatic veins, and the vena cava.
The next example (Figure 13-6) shows a case of gastrointestinal bleeding performed on a Symbia TruePoint SPECT•CT system. This was a 49-year-old male with a liver transplantation three years previously. The patient presented with hematemesis and melaena, as well as gradually decreasing serum hemoglobin. Upper and lower GI endoscopies were normal. SPECT•CT for GI bleed using $^{99m}$Tc-labeled autologous RBC was performed on a Symbia T6. The study showed small focal accumulation of the tracer within the large intestinal lumen at the level of hepatic flexure, which was identified as a site of intestinal bleeding.

Integrated diagnostic CT is of major clinical value in such situations because of the ability to define intestinal margins and blood vessels with clarity and the ability to perform breath-hold, thin-slice CT to minimize movement of abdominal contents. Fast CT almost eliminates peristaltic motion and, thereby, is able to localize small bleeding sites more effectively. Apart from the exact localization of the bleeding site, diagnostic CT can help define the potential cause of bleeding using contrast CT and CT angiography, if necessary. There are incidental reports of the use of SPECT/CT for gastrointestinal bleeding, which demonstrate the value of CT-based localization. More publications on the use of integrated, diagnostic CT with SPECT for the characterization of gastrointestinal bleeding are awaited. Attempts to compare contrast-enhanced, multi-detector CT with $^{99m}$Tc-labeled RBC SPECT for the evaluation of active lower gastrointestinal bleeding have been undertaken. Fifty-five patients were prospectively evaluated with both techniques. Eight patients were positive in both techniques and 20 patients negative on both. Two patients were positive on contrast CT, but negative on SPECT. However, 11 patients were negative on CT but positive on labeled-RBC SPECT. Sixteen of 60 (26.7%) contrast-enhanced MDCT scans were positive prospectively, with all accurately localizing the site of bleeding, and identification of the underlying lesion in eight of 16 (50%). Labeled-RBC SPECT may be more sensitive than CT since CT can demonstrate GI bleeding, only if there is active bleeding during the CT acquisition. However, the accuracy of localization using MDCT, and the identification of underlying causes of bleeding in 50 percent of the cases where CT demonstrated bleeding, makes a combination of contrast-enhanced, multi-detector CT with integrated, labeled-RBC SPECT an ideal procedure for any gastrointestinal bleeding.
This example (Figure 13-7), of a case of bilateral pulmonary embolism, illustrates the value of combined CT angiography and lung perfusion scintigraphy with SPECT performed on a Symbia TruePoint SPECT•CT system with integrated 6-slice CT. This was a patient who underwent elective surgery unrelated to the lung condition. He complained of breathlessness and was sent for a lung perfusion study. The SPECT study revealed a total absence of uptake in the left lung and multiple defects in the right lung. Immediate CT angiography was performed at the same sitting without moving the patient on the Symbia T6 system. CT angiography demonstrated large thrombi in the left main pulmonary artery and the lower branch of the right pulmonary artery. Perfusion SPECT showed the absence of perfusion in the whole of the left lung, and the middle and lower lobe of right lung, which correlated with thrombi seen on CT angiography. The upper lobe of the right lung was perfused and vasculature showed contrast opacification. Small peripheral perfusion defects in the right upper lobe suggested additional peripheral emboli.

Although 99mTc MAA lung perfusion scintigraphy with or without ventilation studies has been widely used for diagnosis of pulmonary embolism, there is a substantial percentage of false-positives. This has led to CT angiography being considered to be the imaging study of choice. However, some studies have shown lung perfusion SPECT to be superior to contrast-enhanced, multi-detector CT for small peripheral and chronic pulmonary thromboembolism. This is the rationale for combining contrast-enhanced, multi-detector diagnostic CT and lung perfusion SPECT for enhanced diagnostic accuracy in pulmonary embolism on an integrated SPECT•CT system like Symbia. A study comparing ventilation perfusion (V/Q) SPECT in 83 patients with suspected pulmonary embolism showed that SPECT was slightly superior to contrast CT on a 4-slice CT for subsegmental emboli. SPECT had higher sensitivity (97%) compared to CT (86%), but lower specificity for identification of segmental and subsegmental emboli. This study, however, is based on CT on a 4-slice system while current generation multi-
detector CT (6-, 16- and 64-slices) offer far superior visualization of peripheral pulmonary artery vasculature on CT angiography. The Symbia TruePoint SPECT•CT system has integrated 6- or 16-slice CT configurations ideally suited to CT pulmonary angiography as a combined procedure, along with lung perfusion and ventilation SPECT.

Another study comparing V/Q SPECT with multi-detector CT angiography in chronic thromboembolic pulmonary hypertension (CTPEH) concluded that V/Q SPECT was more sensitive than CT angiography in this category of patients. Since this is a curable form of pulmonary hypertension with the possibility of treatment with pulmonary endarterectomy, accurate identification of pulmonary abnormalities is critical to management. One group performed both studies in 78 patients with CTPEH. V/Q scintigraphy suggested a high-probability scan in 75 patients while CT showed abnormalities, including visualization of the thrombus, recanalization, a sudden change in vessel caliber, strictures and poststenotic dilatations, in only 40 patients.

Several studies have tried to address the issue of misregistration between breath-hold CT and non-breath-hold SPECT performed as separate studies, in order to obtain improved image fusion for the identification of small subsegmental lesions in pulmonary embolism as well as in chronic obstructive pulmonary disease (COPD). One study described a technique of deep-inspiratory breath-hold SPECT lung perfusion and fused the breath-hold SPECT images with deep-inspiratory breath-hold CT. They were able to obtain superior image fusion as well as improved delineation of small, subsegmental defects on breath-hold SPECT compared to non-breath-hold SPECT, which correlated well with CT abnormalities. The images obtained using this breath-hold technique demonstrated sharp margins of SPECT defects with accurate fusion with CT defects without the need for complex non-rigid deformation algorithms. Improved characterization of disease burden in COPD was the principle clinical advantage, as well as identification of very small focal perfusion abnormalities related to peripheral pulmonary thromboemboli.

Fusion of V/Q SPECT with separately performed CT pulmonary angiography for proper characterization of perfusion defects has been further studied in a series of 30 consecutive patients. SPECT V/Q images were correctly fused in all 30 cases with an automated registration algorithm, which was adequate in 23 cases. In 13 patients, CT pulmonary angiography was performed as the initial investigation. Nine out of 13 had positive CT angiography, and all had SPECT perfusion defects correctly coregistered to the specific segment related to the CT angiography lesion. Of the 17 patients investigated initially with V/Q SPECT, 11 had intermediate probability scans. Three of 11 were interpreted as low probability based on fusion with CT. There was only one patient with a discrepancy between SPECT and CT. There was a well-defined, subsegmental perfusion defect, but without a clear filling defect in the related pulmonary artery on CT, and the patient was treated for pulmonary emboli.

The incorporation of integrated 6- and 16-slice CT with SPECT on the Symbia TruePoint SPECT•CT enables the possibility of CT pulmonary angiography combined with lung perfusion SPECT as an integrated first-line procedure for the management of suspected pulmonary embolism. This may prove to have a higher combined sensitivity and to help with faster diagnosis and management decision making, especially in patients with associated lung abnormalities like pleural effusions, pneumonitis etc. The clinical relevance of a combined imaging approach for pulmonary conditions like emphysema, COPD, and interstitial lung disease requires further validation, although studies performed to date show promising clinical value for the accurate fusion of SPECT and CT.
References:


Future Directions

The integration of multislice CT and SPECT, as with Symbia® TruePoint SPECT•CT, opens up possibilities of further advancement in hybrid SPECT imaging, especially with new molecular imaging biomarkers. Although several new biomarkers are actively under investigation, the most promising SPECT agents in the near future are agents for the imaging of cellular apoptosis, tumor angiogenesis and metabolic activity within tumors using labeled glucosamine. In each of these areas of future development, SPECT/CT, especially with integrated, diagnostic CT, shows major promise since radiotracers targeted to visualize specific cellular processes like apoptosis require high-quality, integrated morphological imaging for accurate characterization.

Apoptosis is a regulated process of cell death, which is characterized by cell shrinkage, long-lasting plasma membrane integrity and a lack of inflammatory response. Apoptosis has been shown to be associated with myocardial damage, as well as with chemotherapy response of solid tumors. The imaging of cellular apoptosis has been widely studied using 99mTc Annexin V. Annexin V binds to phosphatidylserine, which is abnormally expressed on the cell membranes of apoptotic cells. Increased uptake of 99mTc Annexin V has been visualized in areas of acute myocardial infarction. The uptake of Annexin V has been shown in experimental models of inflamed atherosclerotic plaques, suggesting a potential role in the identification of inflamed, vulnerable plaques. One study showed an increased uptake of 99mTc Annexin V in carotid plaques with a recent history of TIA compared to the absence of uptake in carotid plaques with a remote history of Transient Ischemic Attack (TIA), suggesting an association of apoptosis in inflamed plaque with increased Annexin V uptake. An increase 99mTc Annexin V uptake has also been shown to be associated with accelerated myocyte damage in dilated cardiomyopathy as well as cardiac transplant rejection. Radiolabeled annexin V may provide an early indication of the success or failure of anticancer therapy as an in vivo marker of tumor cell killing. In another study, the absence of 99mTc Annexin V uptake in lung carcinoma and lymphoma patients immediately following chemotherapy was associated with an absence of tumor response, while increased uptake of Annexin V compared to the pre-treatment baseline correlated with a good response of the tumor to chemotherapy. This suggests increased apoptosis to be associated with chemotherapy response and that apoptosis imaging may be useful in sequential evaluation and modification of chemotherapy regimes. In view of the low tumor uptake of labeled Annexin V, SPECT/CT would be useful for accurate attenuation correction as well as the quantification of tumor uptake. Diagnostic CT as an integrated procedure may further add value by delineating necrotic areas within the tumor, as well as a change in tumor size compared to the degree of apoptosis. Although additional research is required in this arena to better define these roles and inter-relationships, it is clear that this would be a productive area of for future SPECT/CT imaging development.

The imaging of tumor angiogenesis also has a potential impact on radiation and chemotherapy decisions in several tumors. SPECT using 123I VEGF (Vascular Endothelial Growth Factor) has been studied for the imaging of tumor angiogenesis predominantly in animal models, but also in a few clinical studies with gastrointestinal and pancreatic cancers. VEGF has also been labeled with 99mTc, although studies on patients are not yet reported. Since tumor angiogenesis may be an important predictor of therapy response especially with anti-angiogenic drugs, accurate quantification of uptake and visualization of low uptake lesions using CT attenuation correction makes the use of SPECT/CT attractive for such situations. The combination of contrast CT with integrated SPECT may help delineate tumor margins more effectively and may define the true extent of angiogenesis within a tumor for improved sequential evaluation with anti-angiogenic drugs.

Another new SPECT radiopharmaceutical on the horizon is 99mTc labeled glucosamine, which may be useful in defining the extent of tumor metabolism. It is currently undergoing phase II clinical trials on lung carcinoma patients. In case this tracer achieves wider use, SPECT/CT with diagnostic CT has a major potential to expand into new territories of tumor imaging with SPECT metabolic imaging and accurate morphological imaging using diagnostic CT as an integrated procedure.

The future of SPECT/CT lies in the utilization of complete CT functionality as part of a routine SPECT/CT workup, including contrast CT, CT-based radiation therapy planning (e.g. with immunoscintigraphy as in prostate cancer) and in the utilization of new biomarkers to define expanding new clinical indications. The Symbia TruePoint SPECT•CT is the perfect step towards this goal and will be instrumental in defining the future of molecular imaging.
References:


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