SPECT/CT for tumour imaging

Jure Fettich, Marina Hodolič

SUMMARY

Hybrid imaging combining PET and CT is standard technique already for many years. Now it is becoming state of the art nuclear medicine technique also in the field of single photon emission tomography (SPECT) as SPECT/CT. Advantages of hybrid imaging are improved quality of the images using CT data for attenuation correction based on true transmission density data in the individual patient, and CT and SPECT fusion images providing accurate localisation of the tracer uptake. The former is useful in dosimetric calculation in case of tumours treated by radiopharmaceuticals emitting also gamma photons such as 177-Lu. Accurate localisation of increased tracer uptake is important especially in the diagnostic of tumours. This can improve specificity of tumour imaging, for example differentiation between abnormal uptake in the primary tumour and uptake in the metastasis in a lymph node. In this respect hybrid imaging can improve the accuracy of staging and evaluation of treatment follow-up. In several areas single photon emitting radiopharmaceuticals need to be used since there are no useful PET tracers available. This is true in case of neuroendocrine tumours, adrenal tumours, atypical haemangiomas etc., and also in case of benign parathyroid adenomas or osteoid osteomas when radioguided surgery using gamma probe is considered. Lymphoscintigraphy for radioguided sentinel node scintigraphy has become standard in various types of cancers. If exact localisation of the sentinel node can be shown on a fused image this is certainly a big help for the surgeon performing biopsy. The ability of SPECT/CT to improve diagnostic accuracy, especially specificity has great potential in further grow of nuclear medicine techniques in evaluation of tumours.

Key words: *Neoplasms; Diagnostic Imaging; Positron-Emission Tomography and Computed Tomography; Tomography, Emission-Computed, Single-Photon; Lymphoscintigraphy; Radiometry*

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INTRODUCTION

Nuclear medicine techniques provide valuable functional information but often it is difficult to localise a precise area of abnormality and with some agents it may be difficult to determine if a site of uptake is physiological or due to pathology.

An ideal combination would be to combine the accuracy of some of the single photon emission computed tomography (SPECT) techniques with the aility to localise lessions using CT. Thus the new hybrid technology of SPECT/CT could provide optimal combination for imaging such patients.

The main limitation of SPECT imaging with tumour-seeking agents is the lack of the structural delineation of the pathologic processes they detect; this drawback sometimes renders SPECT interpretation difficult and can diminish its diagnostic accuracy. Fusion with morphological studies can overcome this limitation (1) (Figure 1).

The last decade has seen the development of hybrid imaging technologies combining positron emission tomography (PET) or SPECT with x-ray computed tomography (CT). Numerous studies demonstrate the superiority of SPECT/CT over stand-alone SPECT in terms of diagnostic accuracy. SPECT/CT has revolutionized the field of conventional nuclear medicine. Available evidence indicates that this hybrid imaging technology will become the gold standard for conventional scintigraphy, including bone imaging performed for staging malignancy, and also for the so-called tumour scintigraphies that visualize neoplastic foci via tumour-specific agents labelled with 99m Tc, 111-In or 131-I (2).

SPECT in combination with CT enables a direct correlation of anatomic information and functional information, resulting in better localization and definition of scintigraphic findings.

Advantages of hybrid imaging are improved quality of the images using CT data for attenuation correction based on true transmission density data

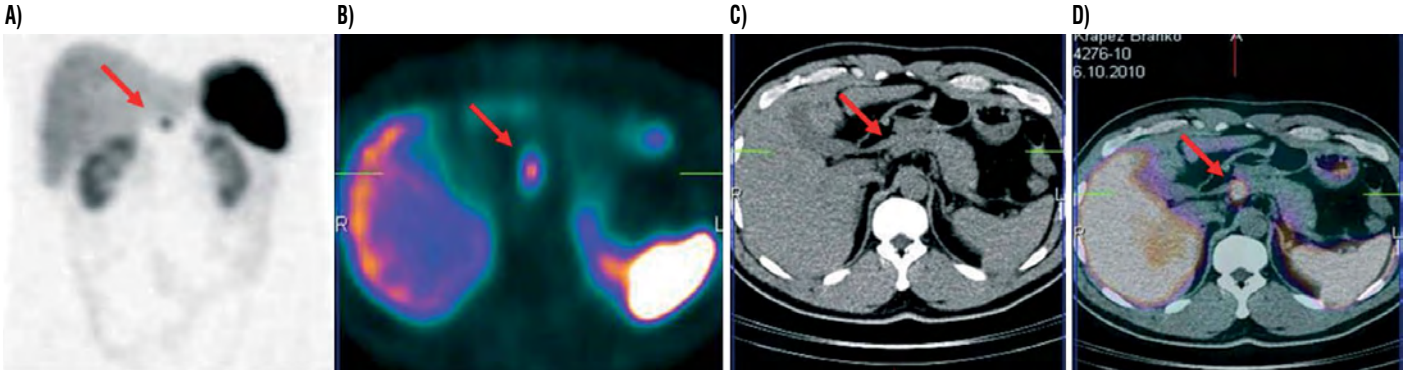

Figure 1. 99mTc labelled somatostatine analogue octreotide: Increased tracer uptake in the upper abdomen (arrow), (A) MIT (Maximal intensity image), (B) SPECT, (C) CT, (D) Fused image: lesion is located in the head of pancreas representing primary solitary neuroendocrine tumour - insulinoma

in the individual patient. Tumour to background ratio and image contrast is measurably improved after attenuation correction by SPECT-CT (3).

CT and SPECT fusion images provide accurate localisation of the tracer uptake. Although most SPECT/CT systems allow also diagnostic quality CT studies, normally only low dose "localisation" CT is acquired. Such images are good enough for attenuation correction and anatomic localisation of even small tumours (ca. 1 cm).

Accurate localisation of increased tracer uptake is important especially in the diagnostic of tumours. This can decrease number of false positive results improving specificity of tumour imaging, for example differentiation between physiological uptake and abnormal uptake in the primary tumour or uptake in the metastasis in a lymph node. In this respect hybrid imaging can improve the accuracy of staging and evaluation of treatment follow-up (Figure 1, 2).

etc. when radioguided surgery using gamma probe is considered. SPECT/CT imaging is especially suited to support the increasing applications of minimally invasive radioguided surgery (6, 7).

Lymphoscintigraphy for radioguided sentinel node scintigraphy has become standard in various types of cancers. SPECT/CT is an important indication for sentinel lymph node scintigraphy, since SPECT/CT fusion helps considerably in localizing the first lymph node draining a tumour (2). Rates of detection of sentinel nodes for biopsy can be increased with SPECT/CT (5).

PARATHYROID

Surgery is proper treatment for primary parathyroidism caused by parathyroid adenoma. Selective parathyroidectomy guided by intraoperative gamma probe or parathyroid hormone monitoring through a small

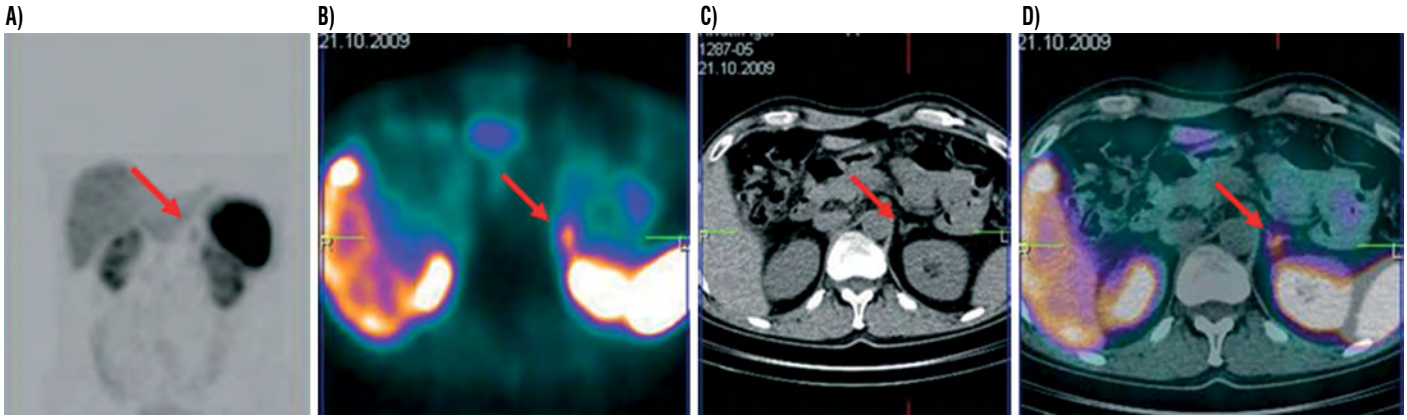

Figure 2. 99mTc labelled somatostatine analogue octreotide: Increased tracer uptake in the upper abdomen (arrow), (A) MIT, (B) SPECT, (C) CT normal left adrenal gland, (D), Fused image: uptake is located in the normal adrenal gland - physiological uptake

SPECT-CT provides improved specificity and diagnostic confidence helping to guide conventional management and assess suitability for targeted radionuclide therapy (4). Both attenuation correction and accurate localisation is useful in dosimetric calculation in case of tumours treated by radiopharmaceuticals emitting also gamma photons such as 177-Lu.

The number of clinical studies is limited, but pilot studies have indicated increased specificity of SPECT/CT imaging and a significant reduction in indeterminate findings. The superiority of SPECT/CT over planar imaging or SPECT has been demonstrated in bone scintigraphy, somatostatin receptor scintigraphy, parathyroid scintigraphy, and adrenal gland scintigraphy. (5).

In several areas single photon emitting radiopharmaceuticals needs to be used since there are no useful PET tracers available (6). This is true in case of neuroendocrine tumours, adrenal tumours, parathyroid adenomas

cervical incision has replaced traditional bilateral neck exploration as the initial approach in the surgical treatment of primary hyperparathyroidism. Preoperative 99m-Tc sestamibi scintigraphy serves as an important prerequisite for successful targeted parathyroidectomy. Single-photon emission computed tomography (SPECT) and CT fusion, provides a three-dimensional functional image with advanced contrast resolution which greatly improves preoperative localization of parathyroid tumours (5, 8). In comparison of standard planar single and dual phase 99m-Tc sestamibi imaging, SPECT and SPECT/CT the highest adenoma localising value was seen with dual phase imaging combined with SPECT/CT (9).

Tumour to background and image contrast is measurably improved after attenuation correction by SPECT-CT. Therefore there is a potential to improve the sensitivity of parathyroid SPECT (Figure 3) (3).

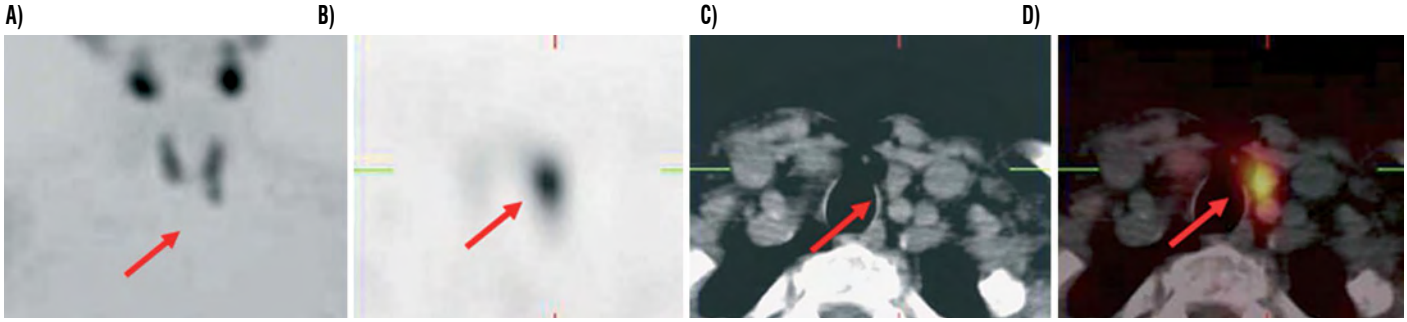

Figure 3. 99mTc sesta MIBI SPECT/CT: parathyroid adenoma behind the lower pole of the right thyroid lobe (arrow). Accurate localisation is mandatory if minimally invasive radioguided surgery is planed. (A) MIT, (B) SPECT, (C) CT, (D) Fusion image

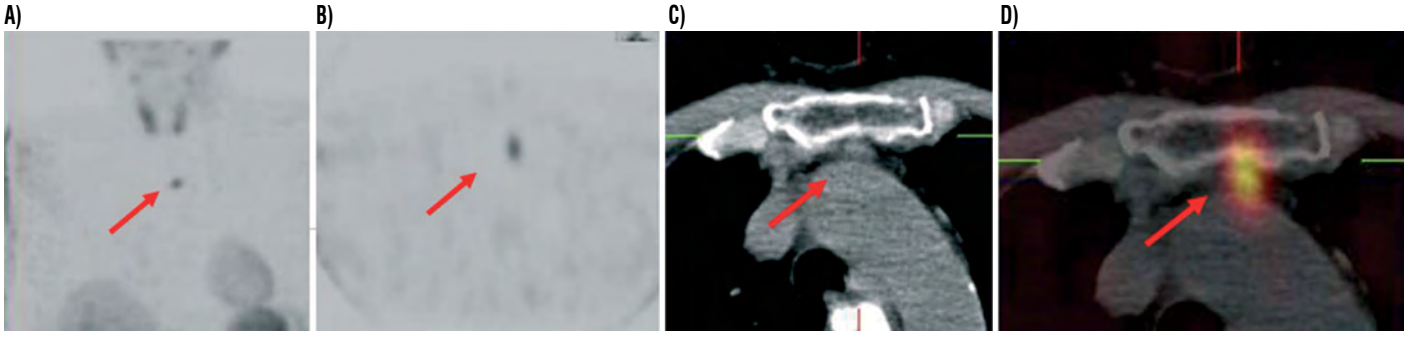

Figure 4. 99mTc sesta MIBI SPECT/CT in ectopic parathyroid adenoma retrosternally. (arrow). Accurate localisation is necessary for surgery (A) MIT, (B) SPECT, (C) CT, (D) Fusion image

99m-Tc sestamibi scintigraphy or SPECT is most useful technique to diagnose ectopic parathyroid tissue; however SPECT alone is not optimal. Since treatment of choice of ectopic parathyroid adenoma is surgery, morphologic imaging such as CT is necessary to show exact localisation of the lesion (Figure 4). The same is true for imaging of ectopic thyroid gland using 123-I SPECT/CT (10).

DIFFERENTIATED THYROID CARCINOMA

131I SPECT/CT has an incremental value in the management of patients with differentiated thyroid carcinoma (DTC). It had an incremental value over planar imaging in 67.8% of patients; it modified therapeutic management in 35, 6% of positive cases, and avoided unnecessary treatment in 20, and 3% of patients with only single benign lesions or physiologic uptake (11).

131I SPECT/CT improved planar data interpretation, showing a higher number of DTC lesions, more precisely localizing and characterizing DTC foci, and more correctly differentiating between physiologic uptake and metastases, thus permitting the most appropriate therapeutic approach to be chosen. A wider use of this method is suggested complementary to planar imaging in selected DTC patients (11).

Fusion of SPECT and CT images was of incremental value over whole body scintigraphy (WBS) in increasing diagnostic accuracy, reducing pitfalls, and modifying therapeutic strategies in 73.9% of DTC patients. As SPECT/CT techniques emerge, 131-I SPECT/CT may demonstrate higher value than WBS in the management of DTC (12).

SPECT/CT data provided information that reduced the need for additional cross-sectional imaging in 29 of 109 patients (30%) and significantly altered the initial risk of recurrence estimates in 7 of 109 patients (6.4%), thereby altering patient management recommendations with regard to frequency and intensity of follow-up studies (13). In another study it led to a treatment change in 10/41 patients (24.4%) (14).

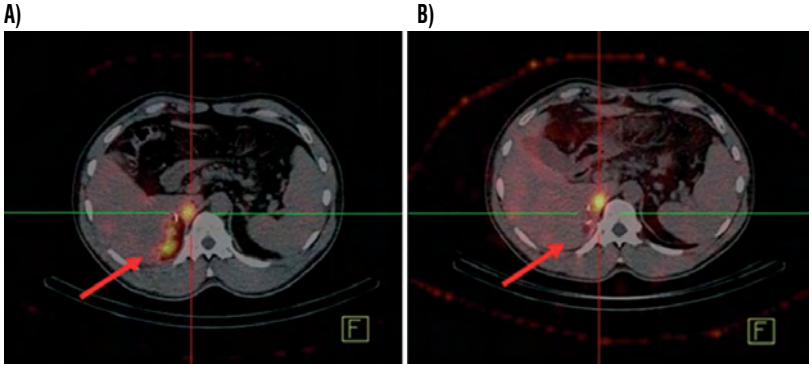

Figure 5. 123-mIBG in Pheochromocytoma. Fusion images (A) before and (B) after treatment with 131.mIBG (200 mCi)

ADRENAL GLAND: 123-I MIBG IMAGING OF TUMOURS ARISING FROM CHROMAFFIN CELLS

Benign and malignant pheochromocytoma, neuroblastoma and paraganglioma take up meta iodo benzyl guanidine (MIBG) that can be labelled with 123-I or 131-I. MIBG SPECT/CT fusion imaging is a sensitive and specific radiological imaging tool for patients suspected to have pheochromocytoma. The particular strengths of MIBG SPECT/CT are detection of local recurrence (Figure 5), small extra-adrenal pheochromocytomas, multifocal tumours, or the presence of metastatic disease (15). 123I-MIBG SPECT/CT detected 75 of 81 lesions (sensitivity, 0.93; soft tissue, 56; bone, 19). There were no false-positive lesions (16). This is important especially in patients where 131-I MIBG therapy is contemplated. SPECT/CT can show metabolically active tumour SPECT inside morphological tumour structure seen on CT (Figure 6).

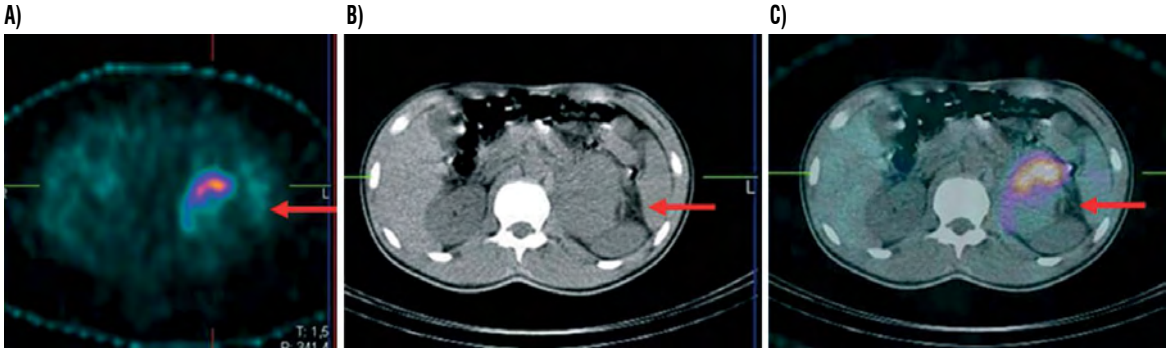

Figure 6.123-mIBG in Pheochromocytoma. (A) SPECT, (B) CT, (C) Fusion image. Not all tumour seen on CT is active on mIBG study

ADRENOCORTICAL IMAGING WITH 131-I NORHOLESTEROL

Functional scintigraphy with 131-I norcholesterol frequently represents the procedure that can identify and localise adrenocortical dysfunction, usually hyperaldosteronism, a crucial factor for planning surgery (6) (Figure 7).

A) B)

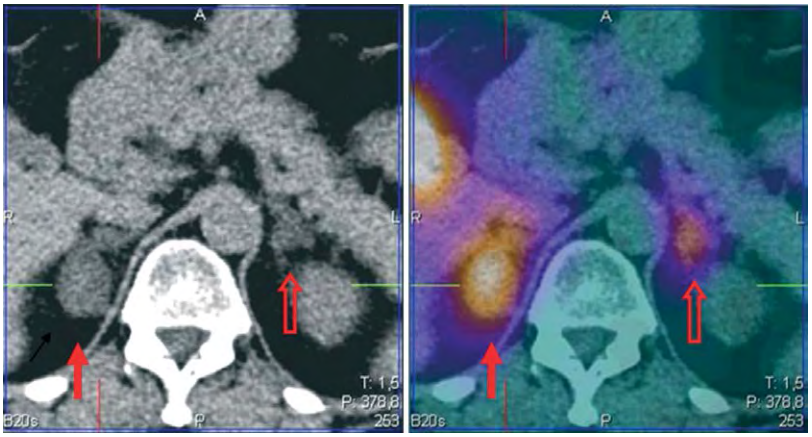

Figure 7.131-I norholesterol in adenoma (arrow) of adrenal cortex: (A) CT, (B) fusion image (normal adrenal gland: open arrow)

NEUROENDOCRINE CARCINOMAS

Nuclear medicine procedures for diagnosis (and treatment) of neuroendocrine tumours (NETs) are based on biological properties of these tumours: expression of somatostatin receptors (Figure 1). To diagnose somatostatin receptor positive tumours, comercially available somatostatine analogue 111-In pentetreotide (17). Labelling with indium-111 has several limitations: limited availability, non-optimal gamma energy for imaging, relatively high absorbed dose for patients and high price. Radioligand of choice for use in diagnostic nuclear medicine is 99m technetium. (Figure 1). In comparative studies significantly higher tumour to normal tissue ratios were obtained on 99mTc- octreotide images as compared with 111-In- pentetreotide, while no significant differences were seen in tumour to liver and tumour to spleen ratios (18).

SPECT/CT imaging led to a significantly higher proportion of patients (75/81=92.6% vs 64/81=79%) and lesions (163/169=96.4% vs 138/169=81.1%) correctly classified vs SPECT alone. SPECT/CT accurately localized 160/169 (94.7%) lesions, significantly higher than SPECT alone (77/169= 45.6%) (19).

Wong et al. found that in 55 of 89 lesions (61.8%), 111-In pentetreotide SPECT/CT imaging improved lesion localization compared to planar and SPECT imaging. In 25 of 89 lesions (28.1%), SPECT/CT imaging changed lesion classification. In 20 of 49 patients (40.8%) for reader 1 and 14 of 49 patients (28.6%) for reader 2, 111-In pentetreotide SPECT/CT imaging provided incremental diagnostic value, which was considered likely to affect patient management in twelve of 20 and seven of 14 patients, respectively. Increased reader confidence was found in 32 of 49 patients (65.3%) for both readers with uniformly high confidence after SPECT/CT interpretation. Hybrid 111-In pentetreotide SPECT/CT imaging provides incremental diagnostic value and greater reader confidence over planar and SPECT imaging (20). This is achieved though superior lesion localization, the identification of physiologic activity, and additional anatomic information derived from the nondiagnostic CT portion of the study.

PROSTATE CARCINOMA

111-In labelled MoAB against prostate specific membrane glycoprotein (111-In capromab pendetide) is available in USA. Conventional morphological imaging methods showed limited accuracy for assessment of recurrent prostate cancer; however, in recent years, functional and molecular imaging have offered the possibility of imaging molecular or cellular processes of individual tumours, often with more accuracy than morphological imaging. Hybrid imaging modalities (PET/CT and SPECT/CT) have been introduced that combine functional and morphological data and allow whole-body imaging (21).

Results strongly indicate potential for non-invasive prostate tumour grading using quantitative 111-In capromab pendetide SPECT/CT (22).

BRAIN: CEREBRAL MASSES

SPECT/CT had a significant clinical impact for functional anatomical mapping of primary brain tumours. It was useful in 13 (43.3%) out of 30 cases; in particular, SPECT/CT accurately characterized eight lesions near sites of physiological uptake (i.e., four near ventricles/choroids plexus, three near venous sinuses, one near the skull) (23).

BENIGN BONE DISEASE – OSTEOID OSTEOMA

SPECT/CT appears to overcome most of diagnostic limitations of bone scintigraphy, by enabling precise anatomical localisation of bone turnover abnormalities (24). SPECT/CT findings led to revision of the diagnostic category in the cases of 23 of 71 patients ($p < 0.01$). Compared with bone scintigraphy and SPECT, the use of SPECT/CT increases diagnostic accuracy in the evaluation of orthopaedic disorders affecting the extremities (25)

DOSIMETRY

Advanced imaging methods such as integrated SPECT/CT allow for a highly patient-specific tumour dosimetry calculation (26). 177-Lu oktreotide is used for radionuclide therapy of inoperable NETs. Cumulative radiation dose to the kidneys is the limiting factor of the therapeutic dose that the patient can receive. Accurate dosimetry is important. Since 177-Lu emmits also gamma photons this can be used for SPECT imaging. Serial attenuation corrected images and exact size of the kidney are necessary for dose calculation, especially if renal function is not symetrical. SPECT alone is not adequate for calculations. The same aproach is used to calculate the dose to the tumour (Figure 8).

Integrated systems combining functional SPECT imaging with anatomic CT imaging have the potential to greatly improve the accuracy of dose estimation in radionuclide therapy. SPECT quantification includes three-dimensional ordered-subset expectation-maximization reconstruction and CT-defined tumour outlines at each time point. SPECT/CT images from multiple time points are coupled to a Monte Carlo algorithm to calculate a mean tumour dose that incorporates measured changes in tumour volume. The therapy-delivered mean tumour-absorbed dose can be calculated in cGy.

SENTINEL NODE

Accurate lymph node staging is essential for the prognosis and treatment in patients with cancer. The sentinel lymph node is the first node to which lymphatic drainage and metastasis from the primary tumor occurs.

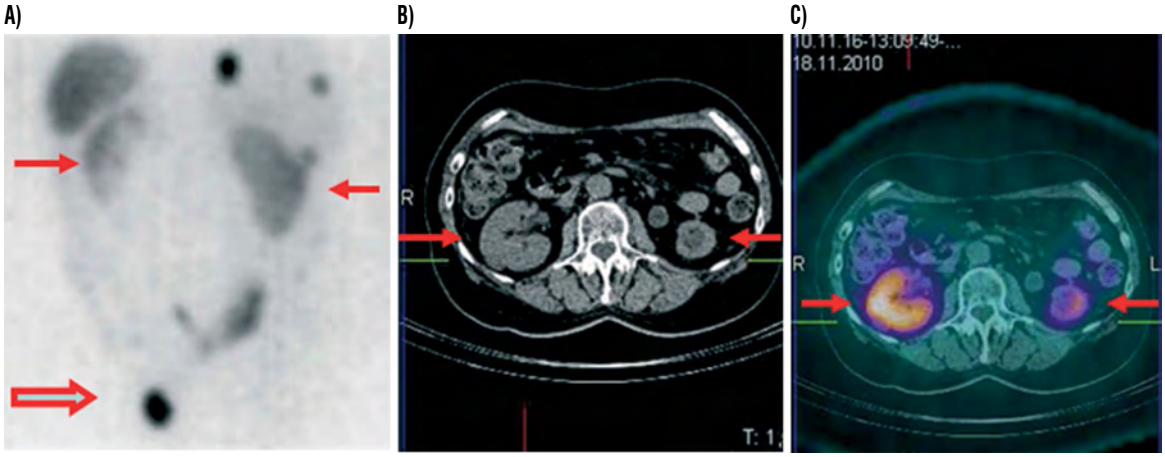

Figure 8. 177-Lu octreotide for radionuclide therapy (PRRT) of inoperable NETs.(A) MIP: kidneys – arrows, tumour- open arrow , (B) CT and (C) fused SPECT/CT images of kidneys (arrows) needed for dosimetry calculations. Kidneys are critical organ for therapy with radiolabelled octreotide.

In the inguinal or low-axillary nodal stations, planar scintigraphic images are mostly adequate for the localization of the sentinel lymph nodes. However, in the regions of the head and neck, the chest, and the pelvis, an imaging method for the more precise anatomic localization of the sentinel lymph nodes preoperatively is highly desired. SPECT/CT might have an additional value in sentinel lymph node scintigraphy (Figure 9) (12) Localization and identification of sentinel lymph nodes was more accurate by integrated SPECT/CT imaging in comparison with planar images and SPECT images, respectively (27).

CONCLUSION

SPECT/CT represents synergy rather than competition in tumour imaging (28). SPECT-CT often provides complementary diagnostic information. Both sensitivity (superior disease localization) and specificity (exclusion of false-positives due to physiological tracer uptake) are improved, and the functional significance of indeterminate lesions detected on cross-sectional imaging can be defined (29).

The incremental diagnostic value of integrated SPECT/CT images compared with SPECT alone includes improvement in lesion detection on both CT and SPECT images, improvement in the localization of foci of uptake resulting in better differentiation of physiological from pathologic uptake and consequently less false positive results and precise localization of the malignant foci. This can improve specificity of tumour imaging, for example differentiation between physiological uptake, abnormal uptake in the primary tumour or in the metastasis (Fig. 1, 2). In this respect hybrid imaging can improve the accuracy of staging and evaluation of treatment follow-up. PACS systems are available allowing correlative imaging. However a study has shown the incrmental value of fused SPECT/CT imagesover side by side SPECT and CT images. Fused SPECT/CT added additional value over side by side SPECT and CT in 65% for anatomical localisation, increased diagnostic confidence in 71%, and altered interpretation in 47% of cases (30) The use of hybrid techniques can occur at the time of initial diagnosis, in assessing the early response of disease to treatment, at the conclusion of the treatment, and in continuing follow-up of patients.

SPECT/CT fusion images affect the clinical management in a significant proportion of patients with a wide range of diseases by guiding further procedures, excluding the need of further procedures, changing both inter- and intramodality therapy and providing prognostic information.

SPECT/CT fusion images have the potential to provide important information to guide the biopsy of a mass to active regions of the tumour (Figure 6) and to provide better maps than CT alone to modulate field and dose of radiation therapy.

Advanced integrated SPECT/CT imaging allow for a highly patient-specific tumour dosimetry calculation (26).

Lymphoscintigraphy for radioguided sentinel node scintigraphy has become standard in various types of cancers. If exact localisation of the

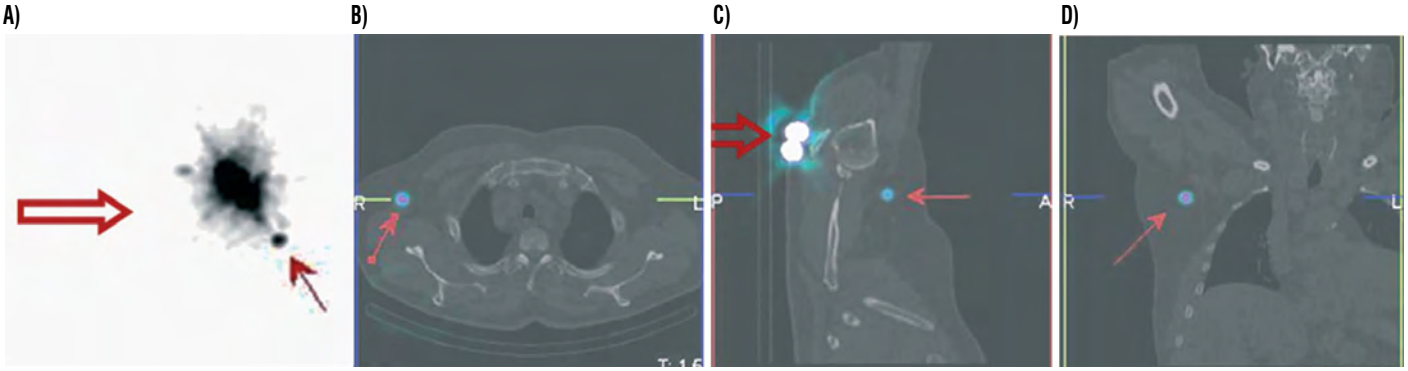

Figure 9. Sentinel node scintigraphy: (A) injection site (open arrow), sentinel node (arrow) on MIP image, (B) hybrid images in transaxial, (C), sagital and (D) coronal projections

sentinel node can be shown on a fused image this is certainly a big help for the surgeon performing biopsy.

It is expected that the role of SPECT/CT in changing management will continue to evolve in the future and that it will become fundamental component of the truly "personalized medicine" we are striving to deliver (31).

Conflict of interest

We declare no conflicts of interest.

REFERENCES

1 Schillaci O. Single-photon emission computed tomography/computed tomography in lung cancer and malignant lymphoma. *Semin Nucl Med*. 2006;36:275-85.

2 Bockisch A, Freudenberg LS, Schmidt D, Kuwert T. Hybrid imaging by SPECT/CT and PET/CT: proven outcomes in cancer imaging. *Semin Nucl Med*. 2009;39:276-89.

3 Ruf J, Seehofer D, Denecke T, et al. Impact of image fusion and attenuation correction by SPECT-CT on the scintigraphic detection of parathyroid adenomas. *Nuklearmedizin*. 2007;46:15-24.

4 Patel CN; Chowdhury FU, Scarsbrook AF. Clinical utility of hybrid SPECT-CT in endocrine neoplasia. *AJR Am J Roentgenol*. 2008;190:815-24.

5 Buck AK, Nekolla S, Ziegler S, et al. SPECT/CT. *J Nucl Med*. 2008;49:1305-19.

6 Mariani G, Bruselli L, Kuwert T, et al. A review on the clinical uses of SPECT/CT. *Eur J Nucl Med Mol Imaging*. 2010;37:1959-85.

7 Hodolic M, Fettich J, Repse S, Kolenc-Peitl P, Lezaic L, Hojker S. Factors influencing radioguided surgery of neuroendocrine tumours using 99mTc-ethylenediamine N,N'-diacetic acid/6-Hydrazinopyridine-3-carboxylic acid-D-Phe1-Tyr3-octreotide. *Nucl Med Commun*. 2008;29:311-7.

8 Taubman ML, Goldfarb M, Lew JI. Role of SPECT and SPECT/CT in the Surgical Treatment of Primary Hyperparathyroidism. *Int J Mol Imaging*. 2011;11:141-93.

9 Lawey WC, Goetze S, Friedman KP, Leal JP, Zhang Z, Garret-Mayer E, et al. Compasrison of SPECT/CT, SPECT, and planar imaging with single and dual-phase 99m-Tc sestamibi parathyroid scintigraphy. *J Nucl Med*. 2007;48:1084-9.

10 Vercellino L, Ismaili Alaoui N, Faugeron I, et al. Lingual thyroid imaging with 123-I SPECT/CT. *Eur J Nucl Med Mol Imaging*. 2011;38:1173.

11 Spanu A, Solinas ME, Chessa F, Sanna D, Nuvoli S, Madeddu G. 131I SPECT/CT in the follow-up of differentiated thyroid carcinoma: incremental value versus planar imaging. *J Nucl Med*. 2009;50:184-90.

12 Chen L, Luo Q, Shen Y, Yu Y, Yuan Z, Lu H, et al. Incremental value of 131I SPECT/CT in the management of patients with differentiated thyroid carcinoma. *J Nucl Med*. 2008;49:1952-7.

13 Grewal RK, Tuttle RM, Fox J, et al. The effect of posttherapy 131-I SPECT/CT on risk classification and management of patients with differentiated thyroid cancer. *J Nucl Med*. 2010;51:1361-7.

14 Kohlfuerst S, Igerc I, Lobnig M, et al. Posttherapeutic (131)I SPECT-CT offers high diagnostic accuracy when the findings on conventional planar imaging are inconclusive and allows a tailored patient treatment regimen. *Eur J Nucl Med Mol Imaging*. 2009;36:886-93.

15 Meyer-Rochow GY, Schembri GP, Benn DE, et al. The utility of metaiodobenzylguanidine single photon emission computed tomography/computed tomography (MIBG SPECT/CT) for the diagnosis of pheochromocytoma. *Ann Surg Oncol*. 2010;17:392-400.

16 Franzius C, Hermann K, Weckesser M, et al.Whole-body PET/CT with 11C-metahydroxyephedrine in tumors of the sympathetic nervous system: feasibility study and comparison with 123I-MIBG SPECT/CT. *J Nucl Med*. 2006;47:1635-42.

17 Hodolic M, Fettich J, Banti E, Chondrogiannis S, Al-Nahhas A, Rubello D. Diagnostics of neuroendocrine tumours. *In vivo*. 2010;24:771-4.

18 Fettich J, Hodolic M. Hynic SPECT/CT. In: Fanti S, Farsad M, Mansi L, eds. Atlas of SPECT/CT. Springer; 2011. p. 86-95.

19 Perri M, Erba P, Volterrani D, et al. Octreo-SPECT/CT imaging for accurate detection and localization of suspected neuroendocrine tumors. *Q J Nucl Med Mol Imaging*. 2008;52:323-33.

20 Wong KK, Cahill JM, Frey KA, Avram AM. Incremental value of 111-In pentetreotide SPECT/CT fusion imaging of neuroendocrine tumors. *Acad Radiol*. 2010;17:291-7.

21 Beer AJ, Eiber M, Souvatzoglou M, Schwaiger M, Krause BJ. Radionuclide and hybrid imaging of recurrent prostate cancer. *Lancet Oncol*. 2011;12:181-91.

22 Seo Y, Aparici CM, Cooperberg MR, Konety BR, Hawkins RA. In vivo tumor grading of prostate cancer using quantitative 111In-capromab pendetide SPECT/CT. *J Nucl Med*. 2010;51:31-6.

23 Filippi L, Schillaci O, Santoni R, Manni C, Danieli R, Simonetti G. Usefulness of SPECT/CT with a hybrid camera for the functional anatomical mapping of primary brain tumors by [Tc99m] tetrofosmin. *Cancer Biother Radiopharm*. 2006;21:41-8.

24 Sharf S. SPECT/CT imaging in general orthopedic practice. *Semin Nucl Med*. 2009;39:293–307.

25 Linke R, Kuwert T, Uder M, Forst R, Wuest W. Skeletal SPECT/CT of the peripheral extremities. *AJR Am J Roentgenol*. 2010;194:329-35.

26 Dewaraja YK, Wilderman SJ, Koral KF, Kaminski MS, Avram AM. Use of integrated SPECT/CT imaging for tumor dosimetry in I-131 radioimmunotherapy: a pilot patient study. *Cancer Biother Radiopharm*. 2009;24:417-26.

27 Husarik DB, Steinert HC. Single-photon emission computed tomography /computed tomography for sentinel node mapping in breast cancer. *Semin Nucl Med*. 2007;37:29-33.

28 Mariani G, Straus HW. Positron emission and single-photon emission imaging: Synergy rather than competition. *Eur J Nucl Med Mol Imaging*. 2011;38:1189-90.

29 Chowdhury FU, Scarsbrook AF. The role of hybrid SPECT-CT in oncology: current and emerging clinical applications. *Clin Radiol*. 2008;63:241-51.

30 Ingui CJ, Shah NP, Oates ME. Infection scintigraphy: added value of single-photon emission tomography/ computed tomographyfusion compared with traditional analysis. *J Comput Assist Tomogr*. 2007;31:375-80.

31 Delbeke D, Schoder H, Martin WH, Wahl RL. Hybrid imaging (SPECT/CT and PET/CT): improving therapeutic decisions. *Semin Nucl Med*. 2009;39:308-40.