# RECENT DEVELOPMENTS IN NUCLEAR MEDICINE FOR CANCER MANAGEMENT: FROM NUCLEAR MEDICINE TO MOLECULAR IMAGING

## A. Introduction to Molecular Imaging

The last decade has witnessed significant advances in medicine, particularly in the understanding of pathological processes at the molecular level, aided by the development - in parallel - of ever more sophisticated diagnostic imaging technologies. The increase of chronic diseases worldwide, including cancer, has spurred the development of a new biomedical research discipline, called Molecular Imaging, enabling the visualization, characterization, and quantification of biological processes taking place at the cellular and sub cellular levels. The images produced with molecular imaging reflect cellular and molecular pathways and mechanisms of disease present in the context of the living subject. Biologic processes can be studied in their own physiologically authentic environment instead of by in vitro or ex vivo biopsy/cell culture laboratory techniques.

Also driven by the discipline of nuclear medicine - a branch of medicine that uses radioisotopes

- labelled biologically active molecules called radiopharmaceuticals in the diagnosis and treatment of disease – these rapid developments in diagnostic methods and analysis have led to a paradigm change in the treatment of patients with cancer, from standard to personalized treatment. As a result of this change, the process of diagnosing and treating disease is shifting from a single specialist interacting with a patient to a multidisciplinary approach that retains a focus on the patient. Nuclear medicine faces a parallel evolutionary shift—from imaging function at the organ/tissue level to detecting changes at cellular and molecular levels. In this context, nuclear medicine is being coupled with other imaging modalities such as Computed Tomography (CT) or Magnetic Resonance Imaging (MRI) to improve diagnostic accuracy and optimize patient care.

One of the most striking advancements of imaging technologies has been the introduction of Positron Emission Tomography (PET), which has its foundations in the early 1930s, when Nobel Laureate Otto Warburg, a medical doctor and one of the twentieth century's leading biochemists, observed an increased use of glucose, a process called glycolysis, in rapidly growing tumors [I-1 and I-2]. Fifty years later, some first experiments showed the increased incorporation in tumors of the glucose analogue fluoro-deoxyglucose (FDG) labeled with fluorine-18 [I-3] (F18-FDG). This eventually led to the incorporation of in-vivo imaging of enhanced tumor glucose consumption using Positron Emission Tomography (PET) [I-4], for many types of cancers, involving all steps of cancer management, namely:

- Staging (assessment of the extent of disease prior to initiation of treatment),
- Response evaluation (assessment of treatment response during or after therapy),
- Restaging (assessment of the extent of disease following initial therapy or when recurrence has been confirmed),
- Detection of recurrence (assessment of the presence of cancer following clinical and/or biochemical suspicion of recurrence) and,
- Follow-up during or after cytostatic therapy (surveillance in the absence of clinical evidence of recurrence).

# B. Medical Imaging Technologies and Hybrid Imaging

Imaging modalities such as CT and MRI will remain first line modalities in the investigation of cancers. However, when a PET study is used in the diagnosis of cancer patients it can cause changes in therapeutic decisions in 30% to 40% of the cases [I-5].

Diagnosis and characterization of disease by both CT and MRI imaging is based on morphologic criteria such as size, texture and tissue attenuation. CT and MRI provide information regarding changes in organ size and tissue density, as well as their precise spatial localization and topographic landmarks. PET imaging, on the other hand, is based on the bio-distribution of a radioactive agent over time and space, enabling visualization of dynamic physiological and pathophysiological processes that define the functional characteristics of disease.

Due to inherent characteristics of nuclear medicine images and their limited resolution power, it is difficult to define the precise anatomical location of diseases, making the interpretation of studies a complex process. To overcome this limitation, the molecular and functional imaging provided by PET and the anatomical imaging provided by CT, have been merged into "hybrid imaging" using combined scanners such as PET/CT [I-6] while prototype PET/MRI scanners are already in development [I-7]. These hybrid modalities allow in a single diagnostic procedure a combined evaluation of function and structure, while obtaining the most from each modality. The introduction of hybrid imaging offers the possibility to re-examine the diagnostic process, the order in which studies are performed, as well as the construction of the therapeutic pathway (Fig. I-1).

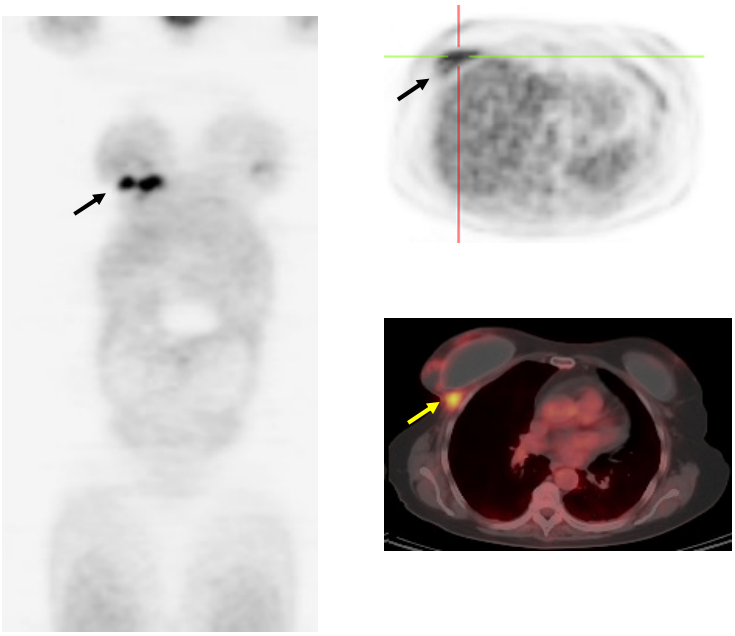

*FIG.I-1: Female 52, with recurrence of breast cancer; PET shows an area of increased uptake in the right breast, lateral to the prosthesis. The CT cannot characterize the nature of the lesion. The combined PET / CT can locate recurrence and ensure that there is no bone extension thus changing the treatment option.*

The technologies described below are key elements in the discipline of nuclear medicine.

## *B.1. PET/CT*

PET produces a three-dimensional picture of functioning processes in the human body, allowing for the evaluation of tissue metabolic activity. In PET a positron emission radionuclide – or tracer – able to track a specific biologic process at molecular level is injected into the patient. As these radioactive

tracers decay, they emit positrons, which are then detected using a PET scanner. The resulting images will help distinguish between normal and abnormal cellular/molecular activity. Positron emitters are radionuclides like fluorine-18, carbon-11, oxygen-15 and nitrogen-13, which in their non-radioactive state are normal constituents of all biologically active molecules (fluorine is a suitable substitute for hydrogen) and are therefore potentially suitable to label any molecule without altering its metabolic pathway.

A simple way to describe the tumour growth process is that tumours need to divide, multiply and invade the neighbouring structures or tissues and spread to distant sites, a process called metastasis. To grow and metastasize, tumours require energy and the utilization of glucose – the fuel used by the body to produce energy - provides the necessary elements for this activity. While normal cells use glucose, there is an increased consumption of glucose within tumour cells.

Labeled with fluorine-18, a glucose analogue like FDG is used as a tracer, both because flourine-18 is quick to decay, thus limiting patients' radiation exposure and because it is a natural indicator of cellular metabolic state, particularly increased in cancer cellular deposits and therefore easily detectable In diagnosing cancer with PET/CT, the most commonly used biologically active model is F18-FDG, a glucose analogue labeled with a radioactive element, the positron emitter fluorine-18, which allows the evaluation of glucose metabolism in normal and abnormal cells.

## *B.2. SPECT/CT*

Another hybrid imaging technology, single photon emission computed tomography (SPECT), also allows visualization of functional information about a patient's specific organ or body system. Like in PET, a radiopharmaceutical or tracer is injected into the patient. Unlike PET, SPECT utilises single photon emitters as tracers which does not require on-site dedicated cyclotrons for production. As this tracer decays, it emits gamma rays, which are then detected by a gamma camera. An essential tool in nuclear medicine, a sophisticated substitute for the X-Ray, the gamma camera can be used in planar imaging to acquire 2-dimensional images, or in SPECT imaging to acquire 3-dimensional images.

Coupled with CT, SPECT/CT has greatly improved neuroendocrine tumors diagnosis and staging using somatostatin receptor scintigraphy (SSRS) by improving detection sensitivity and localization of tumor foci [I-8]. The same is true for other tumor-seeking agents like meta-iodo-benzyl-guanidin (MIBG) and sestamibi labeled with single photon emitters such as indium-111, iodine-123 or technetium-99m. MIBG is a specific agent for neuroblastoma as well as of pheochromocytoma and other paragangliomas [I-9]. It still plays a major role in staging and follow-up of children with neuroblastoma, where it can also be used for radionuclide therapy [I-10].

As a general rule, scintigraphic images lack accurate anatomic landmarks for precise localization and characterization of findings, despite the fact that specific radiopharmaceuticals are used for assessment and diagnosis of specific disease processes. These considerations explain why morphologic (CT) and functional imaging modalities (SPECT and PET) are complementary and not competing techniques, especially if precise image registration is made possible by using a single imaging unit combining the emission based data with the transmission based data (CT, which also serves to correct the emission data for tissue attenuation) (Fig. I-2). Called image co-registration, this process determines the geometric relationship between multimodality imaging studies, in order to use information provided by one test in the context of the other modality.

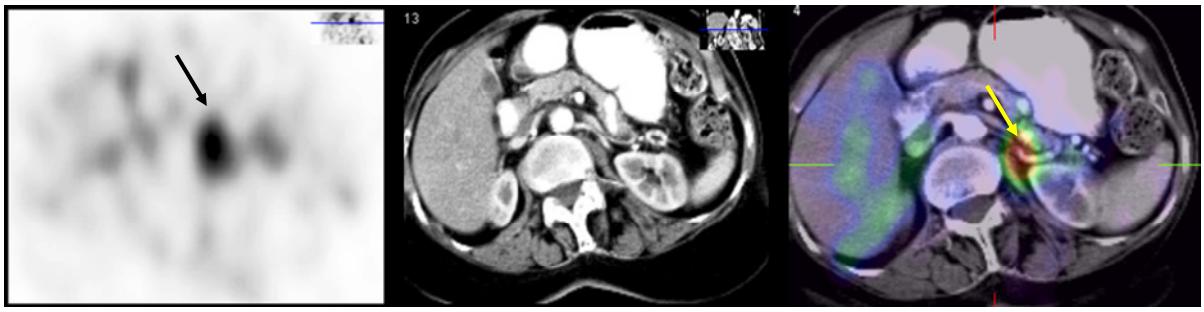

*FIG. I-2. Female 65 years old, with a neuroendocrine tumour (Pheochromocytoma).The SPECT – MIBG study shows an increased tracer uptake that is difficult to localize. The CT study shows no anatomical abnormalities. However, SPECT/CT allows one to localize the uptake in the left adrenal gland.*

Simultaneous recording of CT and SPECT allows distinguishing tumor foci from normal tissue uptake such as in the gallbladder, kidney, spleen (including accessory spleens) and excretory pathways (urinary tract and intestines). It helps also to separate uptake due to activated lymphocytes and increased vascular permeability in inflammatory changes from tumors.

## C. Role of PET/CT in cancer management

The introduction of FDG-PET (Fluorodeoxyglucose-PET) has definitively changed the therapeutic approach to patients with non small lung cancer (NSCLC) [I-11] (Fig. I-3) and plays a major role in the initial evaluation of other tumors such as lymphomas [I-12], nasopharyngeal carcinomas [I-13], carcinomas of the uterus and cervix [I-14] (Fig. I-4), and gastrointestinal stromal tumors (GIST) [I-15].

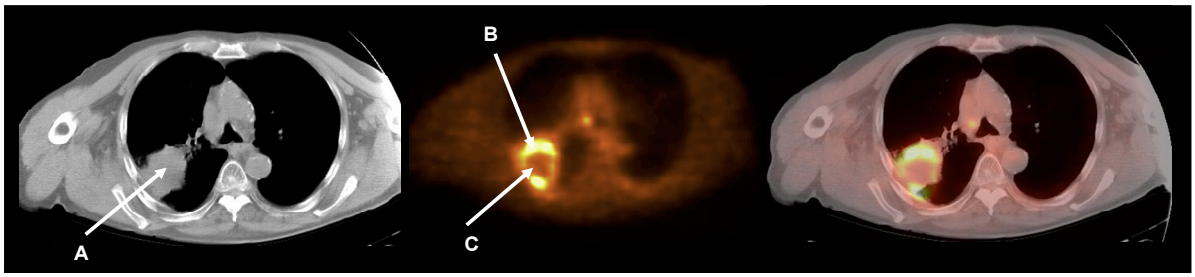


*FIG. I-3.PET (central image) and CT Images (left side image) of a patient with right lung carcinoma CT study shows an abnormal mass (A) that cannot be characterized. The PET study shows glucose uptake in the periphery of the lesion indicating the presence of viable tumour tissue (B) and no uptake in the center, indicating central necrosis. (C) Combining PET/CT (right side image) is ideal for directing the biopsy to the active edge of the lesion.*

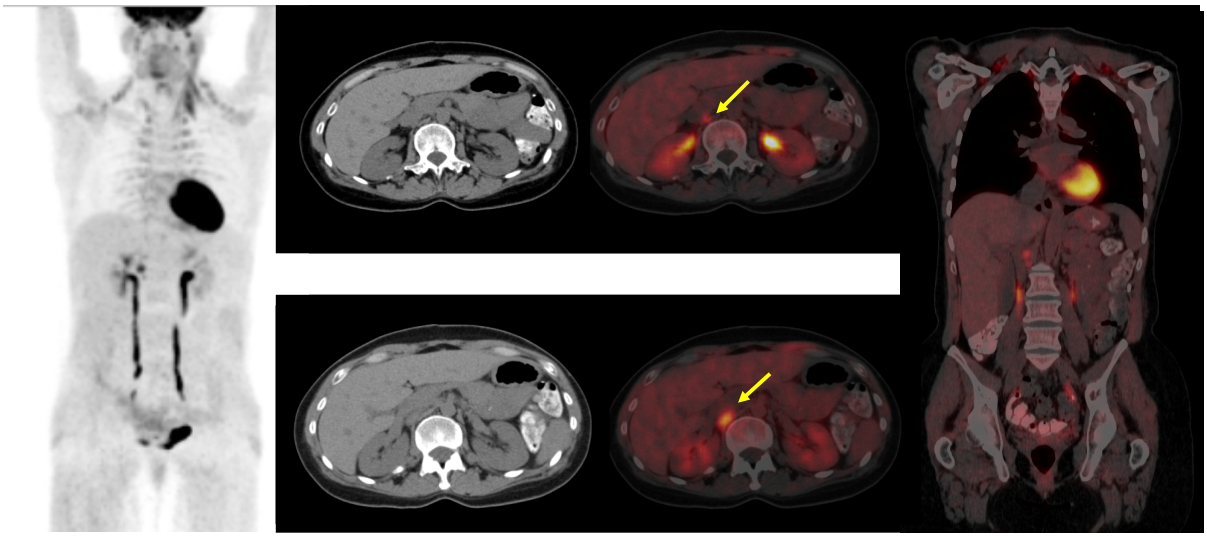

*FIG. I-4. Female 43 years old, with Ovarian Cancer who had a PET/CT study to evaluate restaging post treatment (surgery & chemotherapy). Two abnormal nodes consistent with metastatic disease were found in the lumbar region. The combination of PET and CT allows for a better localization of the disease.*

It is also currently used for the detection of distant diseases in head and neck, colorectal, ovarian and small cell lung cancer as well as in locally advanced breast cancer and melanoma. Besides determining the stage, initial PET/CT can be used to assess the degree of FDG avidity of the tumors. It has been shown that in several tumour types the intensity of FDG uptake is correlated to the aggressiveness of the tumour [I-16]. In other tumours, such as lymphomas, particularly low-grade non-Hodgkin lymphomas (NHL) or GIST, it is important to evaluate the uptake intensity before treatment. In fact, some of these tumors are not FDG avid and consequently FDG-PET is not useful for evaluating treatment responses or detecting recurrence. In these cases it is important to use other radiotracers.[1]

There is evidence that complete disappearance of FDG uptake during the early course of treatment of lymphomas independent of the presence of residual tumors on computerized tomography (CT) is an excellent indicator of favorable prognosis [I-17]. Persistent FDG uptake, on the other hand, indicates poor response and consequently a high risk disease that might need more aggressive treatment. Similar observations have been made in other tumors, in particular NSCLC [I-18].

On the other hand, many oncologists tend to no longer administer complementary radiotherapy in young patients with complete metabolic response, as assessed by PET/CT, after chemotherapy of Hodgkin's disease, especially in female patients with mediastinal involvement, to avoid late second cancers. These medical practitioners adopt the principle of precaution, because - despite the great improvements of external beam radiation therapy in recent years - the incidence of unilateral or bilateral breast cancer is significantly increased in patients having previously been treated with radiotherapy for Hodgkin's lymphoma.

## C.1. Assessing tumour response to therapy

Advances in the understanding of tumor biology have allowed for identifying targets involved in tumor proliferation, invasion and metastases that are addressed by newly developed drugs. These treatments are expensive and often have substantial toxic effects. It is therefore important to have tools to identify those patients who might benefit from treatment at an early stage. Tumor volume measurements using conventional tools like CT scanning sometimes may prove inaccurate because

[1] For an earlier overview of advances in medical radiation imaging, see Annex IV of the Nuclear Technology Review 2006.

volume changes do not occur early enough. In some instances tumors might even grow initially in spite of responding to the treatment.

Nuclear medicine methods allow imaging and quantifying of the functional state of the tumor and therefore offer excellent surrogate markers of early response assessment [I-19]. Again, the most frequently used method today is FDG-PET. Several studies have shown a rapid decrease of FDG uptake in cancer cells after treatment with small molecule inhibitors of tyrosine kinase. A relationship between FDG uptake decrease and selective inhibition of oncogenes has also been shown.

The first tumors in which the relationship between FDG accumulation and treatment response was used to guide therapy were GIST treated by the tyrosine kinase inhibitor imatinib, a drug with distinct target specificity. Dramatic decrease of FDG uptake was observed in these patients within the first days after the start of treatment. However, as soon as FDG uptake was no longer blocked, the treatment appeared no longer efficient necessitating either an adjustment of the dose or a change of the inhibitor.

This model has since been translated to other molecular therapies targeting specific processes at cellular/tissue level; in particular epidermal growth factor inhibition and inhibition of angiogenesis. These treatments have resulted in improved survival and symptom control of patients with NSCLC, but failed to improve outcomes when tested in large randomized trials. These results underline the importance of possessing a tool that allows for appropriately selecting the right patients for a therapy that is cytostatic rather than tumouricidal. This is especially true because many cancers today are considered chronic progressive diseases that need continuous cytostatic treatment. It is crucial to have methods for following these patients in order to know if they still respond to the drug, especially since these drugs need to be administered in the optimal biological dose in order to keep the balance between efficacy and side effects, usually late in development and often irreversible. In addition, due to the high costs of these new therapies, they need to be restricted to patients most likely to benefit from them. FDG-PET is the first and most widely distributed of these surrogate markers of tumor response (Fig. I-5).

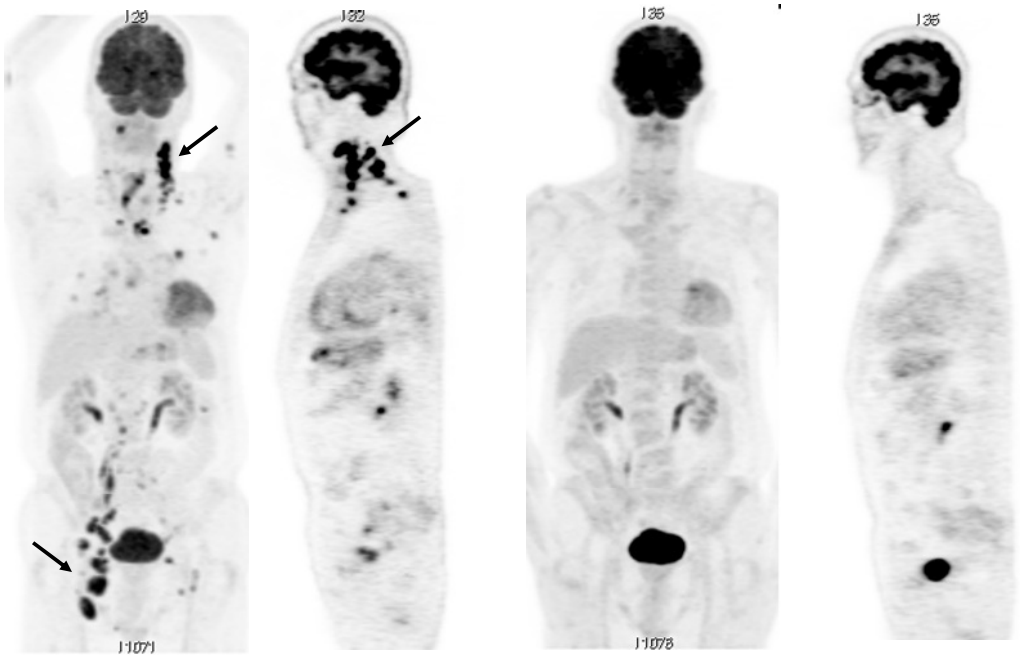

*FIG. I-5. Male 40, with Lymphoma. PET images pre-treatment show multiple sites of cancer diffusion (arrows). Images post chemotherapy show a complete response to the therapy.*

Other compounds are either in development stages or undergoing clinical testing. These include markers of cellular proliferation (F-18 fluorothymidine), amino acid transport (F18-fluoroethyltyrosine) or angiogenesis, i.e. production of new vascular tissue to ensure blood supply to the tumour. Such markers may ultimately not only serve to monitor targeted tumor therapy but also to assess target expression and heterogeneity, in order to select the most appropriate treatment for the individual patient.

Flourine-18 labeled radiopharmaceuticals and radiolabeled peptides [I-20] also play an important role in the management of patients with neuroendocrine tumours. These peptides mostly target somatostatin receptors over expressed by these tumours. They may be labeled with single photon emitting nuclides such as indium-111 or the positron emitter gallium-68. This radionuclide is particularly interesting because it is a generator product and therefore available when needed even in centers not equipped with a cyclotron. PET-images obtained with such gallium-68 labeled peptides are normally of superior quality because of the very low background in normal tissues (except kidneys and spleen), that allows the revealing of subcentimetric lesions as long as the receptor density is elevated [I-21].

## *C.2. Radioguided Minimally Invasive Surgery using SPECT/CT*

The increase in the detection of occult lesions has led to the development of new localisation methods using radiopharmaceutical products. The use of these products can be used to perform a "thrifty" (less-aggressive) surgical excision and, to simultaneously carry out the biopsy of the sentinel node in cases, for example, of breast cancer. Many studies clearly show the advantages of the radioguided surgery method i.e. its effectiveness and attractiveness to surgeons. The sentinel node technique as well as the improved localization on fused SPECT-CT imaging [I-22] has stimulated the interest of surgeons in radioguided surgery beyond sentinel node dissection. SPECT-CT has proven to be very helpful in precisely identifying sentinel nodes especially in malignant melanoma of the trunk and head and neck area where drainage is much less predictable than in the breast area or in melanoma of the limbs. Somatostatin analog uptake may be localized intraoperatively in non-enlarged lymph nodes as well as in the pancreas where no definite nodular structure had been identified preoperatively. It is routinely used in many centers for minimal invasive resection of parathyroid adenomas. It may also be very helpful in identifying residual tumor bearing neck nodes after a previous neck dissection for thyroid carcinoma. Looking to the future, nuclear medicine is now beginning to experiment with radioguided minimally invasive surgery and PET probes are currently being developed, besides gamma probes, to take advantage of the high contrast of PET radiopharmaceuticals [I-23].

# D. Targeted Radionuclide Therapy

Radionuclide therapy is the treatment of diseases by intracavitary, intravenous, oral, or other routes of administration of sealed and unsealed radiopharmaceuticals and is characterized by the selective delivery of radiation doses to target tissues and by limited toxicity and few long-term effects. The treatment may be systemic or applied loco-regionally. In the first case, it combines the advantage of being selective like external beam radiotherapy or brachytherapy with that of being systemic like chemotherapy. The basis of successful radionuclide therapy is a good and selective concentration and prolonged retention of the radiopharmaceutical at the tumour site.

Nuclear medicine offers the unique possibility to study distribution, uptake and biokinetics of trace amounts of the compound labeled with a single photon or positron emitter before using it for therapy after labeling with a beta emitter. Dosimetry has made great progress recently with the widespread availability of SPECT coupled or not to CT (SPECT-CT) that allows one to precisely compute three-dimensional radionuclide distribution over time, as well as volume measurements of tumours and normal organs [I-28].

## D.1. Bone pain palliation in metastatic cancers using radiopharmaceuticals

Radionuclide bone therapy refers to the treatment of bone metastases using specific tumour seeking radiopharmaceuticals. Unlike radionuclide tumour therapy, where the radiopharmaceutical is incorporated into or fixed to the tumour cell, this form of bone therapy targets the reactive osteoblastic reaction in the normal bone directly adjacent to the metastasis, which is generally the cause of pain [I-24]. Bone therapy can also include the treatment of primary bone tumours, e.g. osteosarcoma, where the bone-seeking radiopharmaceutical behaves like a tumour-seeking agent, targeting the tumour-produced osteoid of not only the primary tumour and its skeletal metastases, but also the extra-osseous metastases. Finally, it should be mentioned that palliative therapy of painful bone metastases with samarium-153 lexidronam [I-25] or strontium-89 chloride [I-26] offers complete or partial pain relief to a majority of patients with diffuse bone metastases, in particular from prostate cancer, and can substantially improve the quality of life of these patients.

## D.2. Radiolabeled peptides

Radiolabeled peptides are not only used for diagnosis, staging and follow-up but also for the treatment of patients with neuroendocrine tumors. Labeled with yttrium-90 or lutetium-177, somatostatin analogs have been widely used for targeted radiotherapy [I-27]. Even if these tumors are not very radiosensitive, remarkable therapeutic effects have been obtained. While complete responses are only rarely observed, most patients experience stabilization of their disease, often for prolonged time periods, as well as disappearance/improvement of neuroendocrine symptoms. These treatments are well-tolerated and can be repeated several times, though the dose to the kidneys, as the critical organ, must be closely monitored to avoid delayed kidney failure.

The example of somatostatin analogs in neuroendocrine tumours is in line with the long experience of nuclear medicine in imaging and the efficient treatment of benign and malignant thyroid disorders. Other therapeutic applications include the treatment of NHL with iodine-131 or yttrium-90 labeled monoclonal antibodies directed against the CD20 or CD22 antigens of B-cells [I-29]. A single administration of the yttrium -90 labeled ibritumomab tiuxetan in a consolidation setting after first-line therapy of follicular NHL has shown a high conversation rate of partial to complete, including molecular, response and an approximately two years prolonged progression free survival in comparison with the corresponding group of controls.

## D.3. Radionuclide therapy with Alpha emitters

Another approach is to target isolated tumor cells and preangiogenic micrometastases with monoclonal antibodies labeled with alpha emitters such as bismuth-213 or astatine-211[I-30]. Targeted high-LET (Linear Energy Transfer) alpha-emitting antibodies offer significant potential advantages in the treatment of diffuse micrometastatic or small volume disease. The interest in alpha-emitters is predicated on the extreme high radiotoxicity of alpha particles. For example, it requires only 1-5 alpha particles passages through a cell nucleus to inactivate a tumor cell in contrast to several thousand for the same level of cell kill using a beta source. This is extremely attractive when working with isolated cells, or micrometastases where the amount of targeting may be extremely small, or when using antibodies e.g. M195, for which there is only a limited number ($5 \cdot 10^4$) of antigens per cell. Further, the very short range of alpha particles (< 90 μm) means that a larger portion of the radiation energy will be deposited in the tumor cells, effectively sparing normal tissues. Promising results have been obtained in leukemia or in bone marrow ablation [I-31] or, after intraperitoneal administration, in ovarian carcinoma [I-32], but most of these therapies are still experimental and need further confirmation and research.

## *D.4. Radiotherapy Planning*

More recently, a new potential use of PET/CT has been suggested and evaluated, namely its use as an aid to the treatment of cancers using external radiation beams [I-33]. Indeed, during radiotherapy planning FDG-PET/CT has been shown to be useful to better delineate the biologically active tumor volume (Fig. I-6) and to distinguish between viable tumor tissue and non-specific changes due to previous surgical and/or radio therapeutic treatments.

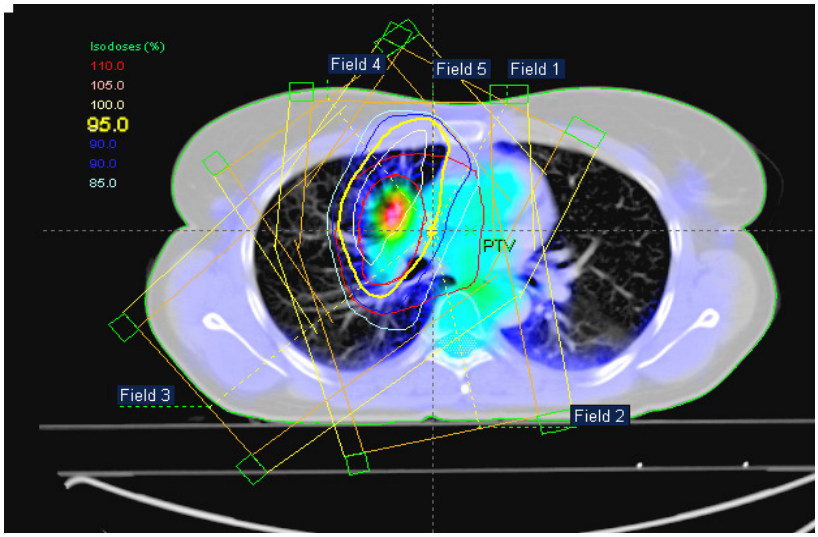


*FIG. I-6. Planning for radiotherapy fields based on images from PET/CT in a patient with advanced-stage lung carcinoma.*

To study brain tumors [I-34], FDG is most often replaced by either carbon-11 or flourine-18 labeled amino acids, as FDG is normally concentrated in the normal brain and therefore is less adequate for distinguishing tumor tissue from normal structures. PET also serves to demonstrate the poorly perfused, partially necrotic central parts of the tumor that might need an additional boost as hypoxia is known to decrease the efficacy of radiation. Several publications address the question of imaging hypoxia [I-35] before and during external beam radiotherapy to adapt the dose to the changing conditions. These are interesting approaches that are also attempting to tailor the treatment to the individual patient's needs in order to improve tumor control, while diminishing toxicity to normal surrounding structures and acute and late side effects. However, long-term results are not yet available to definitively evaluate the outcome i.e. the therapeutic efficiency or toxicity of these approaches.

# E. Conclusion

The key utilization of molecular imaging is in the interrogation of biologic processes in the cells of a living subject in order to report on and reveal molecular abnormalities that form the basis of disease. This is in stark contrast to the classical form of diagnostic imaging where documented findings show the end effects of these molecular alterations typically via macroscopic and well-established gross pathology. Molecular imaging includes the field of nuclear medicine along with various other fields that together offer an array of different strategies to produce imaging signals. Whereas nuclear medicine uses radiolabeled molecules (tracers) that produce signals by means of radioactive decay only, molecular imaging uses these as well as other molecules to image via means of sound (ultrasound), magnetism (MRI or magnetic resonance imaging), or light (optical techniques of bioluminescence and fluorescence) as well as other emerging techniques.

Molecular imaging with radiolabeled tracers along with PET/CT and SPECT/CT currently plays a pivotal role in the management of patients with cancer. It assists in choosing the most appropriate

therapy by refined staging, it evaluates the response to both chemotherapy, be it cytotoxic or cytostatic, and radiotherapy, and finally it contributes to the early detection of recurrence.

Furthermore, molecular imaging with PET/CT and SPECT/CT will strengthen personalized medicine by better characterizing the extent, the biological features and the response of the tumours. Intra-operative probes assist minimal invasive surgery for the removal of sentinel nodes and tumour-involved structures, which may present unremarkable morphological changes. In addition, it offers efficient treatment by targeted radiotherapy of thyroid diseases, neuroendocrine tumors and non-Hodgkin's lymphoma as well as pain palliation in patients with diffuse bone metastases. New approaches with alpha particles are also under investigation. Finally, the use of PET-CT for the definition of biological tumor volumes and "dose painting" in radiotherapy planning holds promise for less toxic but more efficient tumor control, although long-term confirmation is still required.

## REFERENCES


[I-1] WARBURG, O., On the origin of cancer cells, Science **123** (1965) 306-314.

[I-2] VANDER HEIDEN, M.G., CANTLEY, L.C., THOMPSON, C.B., Understanding the Warburg effect: the metabolic requirements of cell proliferation, Science **22** (2009) 324(5930):1029-33.

[I-3] KUBOTA, K., et al., Differential Diagnosis of Lung Tumor with Positron Emission Tomography: A Prospective Study, J Nucl Med. **31** (1990) 1927-1932.

[I-4] WAGNER, H., Jr., Clinical PET: Its Time Has Come, J Nucl Med. **32** (1991) 561-564.

[I-5] HILLNER, B.E., et al., The impact of positron emission tomography (PET) on expected management during cancer treatment: findings of the National Oncologic PET Registry, Cancer **115** 2 (2009) 410-8.

[I-6] TOWNSEND, D.W., Dual-modality imaging: combining anatomy and function, J Nucl Med. **49** (2008) 938-55.

[I-7] WEHRL, H.F., JUDENHOFER, M.S., WIEHR, S., PICHLER, B.J., Pre-clinical PET/MR: technological advances and new perspectives in biomedical research, Eur J Nucl Med Mol Imaging **36** (2009) 56-68.

[I-8] BOCKISCH, A., FREUDENBERG, L.S., SCHMIDT, D., KUWERT, T., Hybrid imaging by SPECT/CT and PET/CT: proven outcomes in cancer imaging. Semin Nucl Med. **39** (2009) 276-89.

[I-9] ROZOVSKY, K., et al., Added value of SPECT/CT for correlation of MIBG scintigraphy and diagnostic CT in neuroblastoma and pheochromocytoma, AJR Am J Roentgenol **190** (2008) 1085-90.

[I-10] SCHMIDT, M., SIMON, T., HERO, B., SCHICHA, H., BERTHOLD, F., The prognostic impact of functional imaging with (123) I-mIBG in patients with stage 4 neuroblastoma >1 year of age on a high-risk treatment protocol: results of the German Neuroblastoma Trial NB97, Eur J Cancer **44 (**2008) 1552-8.

[I-11] HELLWIG, D., BAUM, R.P., KIRSCH, C., FDG-PET, PET/CT and conventional nuclear medicine procedures in the evaluation of lung cancer: a systematic review. Nuklearmedizin. **48** (2009) 59-69.

[I-12] BREPOELS, L., STROOBANTS, S., PET scanning and prognosis in Hodgkin's lymphoma, Curr Opin Oncol. **20** 5 (2008) 509-16.

[I-13] YEN, R.F., et al., The cost-utility analysis of 18-fluoro-2-deoxyglucose positron emission tomography in the diagnosis of recurrent nasopharyngeal carcinoma, Acad Radiol. **16** (2009) 54-60.

[I-14] SCHWARZ, J.K., GRIGSBY, P.W., DEHDASHTI, F., DELBEKE, D., The role of 18F-FDG PET in assessing therapy response in cancer of the cervix and ovaries. J Nucl Med. **50** 1 (2009) 64-73.
[I-15] VAN DEN ABBEELE, A.D., BADAWI, R.D., Use of positron emission tomography in oncology and its potential role to assess response to imatinib mesylate therapy in gastrointestinal stromal tumors (GISTs), Eur J Cancer **38** 5 (2002) 60-5.
[I-16] SALSKOV, A., TAMMISETTI, V.S., GRIERSON, J., VESSELLE, H., FLT: measuring tumor cell proliferation in vivo with positron emission tomography and 3'-deoxy-3'-[18F]fluorothymidine, Semin Nucl Med. **37** 6 (2007) 429-39.
[I-17] MACMANUS, M.P., SEYMOUR, J.F., HICKS, R.J., Overview of early response assessment in lymphoma with FDG-PET, Cancer Imaging **7** (2007) 10-8.
[I-18] HICKS, R.J., Role of 18F-FDG PET in assessment of response in non-small cell lung cancer, J Nucl Med. **50** 1 (2009) 31-42.
[I-19] WAHL, R.L., JACENE, H., KASAMON, Y., LODGE, M.A., From RECIST to PERCIST: Evolving Considerations for PET response criteria in solid tumors. J Nucl Med. **50** 1 (2009) 122-50.
[I-20] OYEN, W.J., et al. Targeted therapy in nuclear medicine--current status and future prospects. Ann Oncol. **18 (**2007) 1782-92.
[I-21] PRASAD, V., et al., Detection of unknown primary neuroendocrine tumours (CUP-NET) using (68)Ga-DOTA-NOC receptor PET/CT, Eur J Nucl Med Mol Imaging **37** (2010) 67-77.
[I-22] UREN, R.F., SPECT/CT Lymphoscintigraphy to locate the sentinel lymph node in patients with melanoma, Ann Surg Oncol. **16 (**2009) 1459-60.
[I-23] GULEC, S.A., BAUM, R., Radio-guided surgery in neuroendocrine tumors. J Surg Oncol. **96 (**2007) 309-15.
[I-24] RICCI, S., et al., Clinical benefit of bone-targeted radiometabolic therapy with 153Sm-EDTMP combined with chemotherapy in patients with metastatic hormone-refractory prostate cancer, Eur J Nucl Med Mol Imaging **34** (2007) 1023-30.
[I-25] SINZINGER, H., WEISS, K., HILTUNEN, J., Background, reasons and benefits using the vienna protocol for the treatment of painful bone recurrences with 153Samarium-EDTMP. Anticancer Res. **29** (2009) 3393-5.
[I-26] LAM, M.G., DE KLERK, J.M., VAN RIJK, P.P., ZONNENBERG, B.A., Bone seeking radiopharmaceuticals for palliation of pain in cancer patients with osseous metastases, Anticancer Agents Med Chem. **7** (2007) 381-97.
[I-27] WEHRMANN, C., SENFTLEBEN, S., ZACHERT, C., MUELLER, D., BAUM, R.P., Results of individual patient dosimetry in peptide receptor radionuclide therapy with 177Lu DOTA-TATE and 177Lu DOTA-NOC. Cancer Biother Radiopharm **22** (2007) 406-16.
[I-28] MEREDITH, R.F., KNOX, S.J., Clinical development of radioimmunotherapy for B-cell non-Hodgkin's lymphoma, Int J Radiat Oncol Biol Phys. **66** 2 (2006) 15-22.
[I-29] MACKLIS, R.M., Radioimmunotherapy as a therapeutic option for Non-Hodgkin's lymphoma, Semin Radiat Oncol. **17 (**2007) 176-83.
[I-30] NAKAMAE, H., et al., Biodistributions, myelosuppression, and toxicities in mice treated with an anti-CD45 antibody labeled with the alpha-emitting radionuclides bismuth-213 or astatine-211, Cancer Res. **69** (2009) 2408-15.
[I-31] LUCIGNANI, G., Alpha-particle radioimmunotherapy with astatine-211 and bismuth-213, Eur J Nucl Med Mol Imaging **35** 9 (2008) 1729-33.
[I-32] DRECOLL, E., Treatment of peritoneal carcinomatosis by targeted delivery of the radio-labeled tumor homing peptide bi-DTPA-[F3]2 into the nucleus of tumor cells, PLoS One. **4** 5 (2009) e5715.

[I-33] BÖRJESSON, P.K. et al., Radiation Dosimetry of 89Zr-Labeled Chimeric Monoclonal Antibody U36 as Used for Immuno-PET in Head and Neck Cancer Patients, J Nucl Med. **50** (2009) 1828-1836.

[I-34] WEBER, D.C., et al., R., Recurrence pattern after [(18)F]Fluoroethyltyrosine-Positron Emission Tomography-guided radiotherapy for high-grade glioma: A prospective study, Radiother Oncol. **93** 3 (2009)586-592.

[I-35] ANDERSON, C.J., FERDANI, R., Copper-64 radiopharmaceuticals for PET imaging of cancer: advances in preclinical and clinical research, Cancer Biother Radiopharm. **24** (2009) 379-93.