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PET/CT Radiotherapy Planning

Part 3

A Technologist Guide

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Foreword

Giorgio Testanera

In the era of modern medicine, personalised treatment is fast becoming an essential goal for radiation therapy, and it appears likely that molecular imaging (e.g. PET-CT) will play an important role in this respect. Not surprisingly, oncologists and radiation therapists are taking a keen interest in PET-CT for pre-therapeutic staging, therapy response assessment and radiotherapy planning. This book is the last in a series of three about PET-CT and it concentrates on the role of PET-CT in radiotherapy planning. The series commenced in 2010 with *Principles and Practice*[1] and continued in 2011 with *Clinical Applications*[2]. The current book will be of value not only to radiographers and technologists working in PET-CT and radiotherapy but also to other healthcare professionals working in these fields.

I would like to extend my sincere gratitude to all those who have made this book possible. In particular, I would like to thank the authors and reviewers, without whom the book would not have been possible. I am proud to be able to welcome and thank our colleagues from ESTRO (European Society for Radiotherapy and Oncology) and SNM (Society of Nuclear Medicine, America) for their high-quality contributions. This is the first time that we have collaborated with other scientific organisations in the production of our annual book. I would also like to thank Professor Peter Hogg and Mrs. Marianne Federspiel, the editors, for the energy they have invested in organising the authors and reviewers and for the proof-reading and editing that is always required when books are written. Special thanks must be given to Siemens; Siemens have financially sponsored all three books in the PET-CT series. Finally, I remain extremely grateful to the EANM Executive Committee, EANM Executive Secretariat, Technologist Committee and all the EANM committees involved in the production of the PET-CT series of books.

With my warmest regards

Giorgio Testanera
Chair, EANM Technologist Committee

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Introduction

Peter Hogg and Marianne Kinggaard Federspiel

In 2008 approximately 13 million new cases of cancer were diagnosed worldwide and nearly 8 million deaths were attributed to it. The most common causes of cancer death were lung, stomach and liver cancer [1]. Worldwide, the incidence of cancer is a fifth higher in men than in women. As the population grows, cancer will inevitably increase, too – even if incidence rates remain the same. Over half of all cancers are diagnosed in the developing countries, and this proportion is expected to increase over time. Based on current rates, projections indicate that by 2030 there will be around 21 million new cases diagnosed annually and approximately 13 million deaths from cancer [2].

Whilst cancer rates have increased, the ability to treat cancer effectively has improved substantially owing in major part to better diagnostic procedures that permit more timely detection of cancer. The enhanced prognostic ability of diagnostic tests allows for streaming of patients into more appropriate treatment or palliation (individualised) schemes. And, of course, the methods by which cancer can be treated or managed have improved considerably. Alongside these developments, new approaches to treatment/management continue to be tested and then introduced. Thirty years ago, many patients who developed cancer saw it as a death sentence; today this is no longer the case as many cancers are curable.

Improvements in radiotherapy treatment regimens have created the need for more accurate planning. Various factors have brought about this change. For instance, there have been moves towards less radical surgical techniques, sparing healthy tissue but placing demands on the radiotherapy service to ensure that residual cancerous tissue is treated. Radiotherapy itself has evolved, too, with more targeted treatment fields being applied, again so as to spare healthy tissue and thereby help minimise unwanted effects of radiation therapy. In order to meet this goal, it is necessary to ensure that the radiotherapy field is planned as accurately as possible. Until recently, CT has played the major role in radiotherapy planning but now PET/CT has started to evolve to help define radiation treatment fields.

In 2008 [3], the IAEA released helpful information which proposed that PET/CT would likely prove valuable in radiotherapy planning. More recently, EANM selected a collection of journal papers that may also prove useful in understanding the value of PET/CT in radiotherapy planning; these can be accessed via the EANM website [4]. The philosophy which underpins the use of PET/CT is related to the fact that the combination of PET and CT data allows structural and functional information to be demonstrated and evaluated together. The combination of anatomical (CT) and functional (PET) information can give the healthcare team better insight into not only cancer distribution and physical tumour size but also metabolic activity levels.

This book, the third and final in the PET/CT series, gives an introduction and overview of PET/CT for radiotherapy planning. Knowing that the readership could include those with limited familiarity with radiotherapy, we have included background information about this. Consequently, the early chapters introduce cell biology, radiobiology, side-effects of radiation therapy and radiation tolerance doses; these are followed by an overview of external beam radiotherapy (conventional, IMRT/Rapid Arc and stereotactic). Treatment planning is then introduced. At this stage, those new to radiotherapy planning will have gained a level of understanding to help contextualise the remaining chapters, which concentrate on PET/CT for radiotherapy planning.

Whole-body FDG PET/CT scanning for radiotherapy planning is becoming the "state of the art", done on a multidisciplinary basis by qualified staff from the Radiotherapy Department and the Nuclear Medicine and PET Department [5]. Therefore we took a strategic decision to invite authors from our collaborators, ESTRO and SNMT, to contribute their expertise in this field for this Tech Guide Book. ESTRO authors, as experts in radiotherapy planning, have contributed with the chapters "Introduction to Radiotherapy", "Method and Treatment Planning" and "4D CT and 4D PET". SNMT, our American counter partner, has written about future prospects for PET/CT in radiotherapy based on the introduction of novel tracers in the chapter "New tracers".

We would like to thank all chapter authors and peer reviewers who have helped us to create this book, in close collaboration with ESTRO and SNMT, for radiation therapy technologists, radiographers and nuclear medicine technologists and guests in your departments. We hope the reader will enjoy reading and using the book.

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Section 1 – Background

Introduction to Radiotherapy

Xavier Geets

Introduction

Radiation therapy (RT) represents one of the main treatment modalities for solid malignant tumours. As with surgery, the primary objective of ionising radiation treatment is to control tumours locally, which is an essential prerequisite for cancer cure. RT can be used as the only therapeutic intervention for non-resectable, locally advanced tumours, for patients in whom a non-surgical approach is preferred and for inoperable patients. RT is most frequently delivered in combination with surgery and radio-sensitising agents such as chemotherapy and targeted therapy. The combination of surgery and RT in an adjuvant setting is employed to improve the local tumour control and therapeutic outcome.

The tremendous technical progress in engineering, computation, imaging and dose delivery has provided the basis for impressive technological advances in the field of RT during the past decade. Technologies such as intensity-modulated radiation therapy (IMRT), image-guided radiation therapy (IGRT) and adaptive radiation therapy (ART) have revolutionised the way in which ionising radiation is delivered. The technological refinements have opened avenues for new strategies that make use of the unique molecular information provided by functional imaging, including PET and MRI, in order to improve the identification and delineation of specific radiotherapeutic targets. Functional imaging can provide unique information on intratumoral biology and thus serve as guidance for dose prescription based on the spatial distribution of biological features within each individual tumour, also known as "dose painting". Dose painting is therefore a methodology which may allow for increased tumour control by escalating radiation dosages to regions with known radioresistance.

The technological developments and new concepts in the field of radiotherapy primarily rely on fundamental principles that govern the biology of normal and cancer cells, and describe the way in which these cells interact with ionising radiation. The aim of this introduction is thus to provide a meaningful background on clinical radiobiology that will help the reader throughout this book. The present chapter will cover the main aspects relating to tumour cell biology and irradiation-induced damage to malignant and normal cells and their practical repercussions for the implementation of clinical RT strategies.

This introduction has been largely inspired by the ESTRO book on "basic clinical radiobiology", which I warmly recommend for advanced reading [1].

Cancer cell biology

Normal tissues present a complex hierarchical organisation at the cellular level. They are typically made up of cells that self renew by mitotic division to ensure the development and maintenance of the organ, of differentiated and specialised cells that carry out the functional properties of the tissue and of

cells that compose the stroma (fibroblasts, inflammatory cells, cells of vascular structures etc). Complex intracellular circuitries continuously regulate cell division, growth, differentiation and death, as well as intercellular interactions, via appropriate signalling pathways, thereby ensuring homeostasis of cell number and maintenance of normal tissue architecture and function.

Long-lived populations of actively dividing cells are particularly exposed to mutations, which result from mitotic accidents and are facilitated by constant and prolonged exposure to genotoxic stresses, such as those caused by environmental factors (free radicals, tobacco, natural radiation, chemicals etc.). Fortunately, most mutations are inconsequential: they may be adequately repaired thanks to systems that ensure the genomic integrity and even if they do result in abnormal cells, these cells are usually eliminated from the pool of replicating cells, thereby preventing their uncontrolled proliferation. Despite these extremely efficient control mechanisms, oncogenic mutations can rarely accumulate and may lead to cancer. This probability increases with the number of events, and thus with time and the patient's age. Genetic predispositions that affect cell control pathways may also expose individuals to an increased risk of cancer. In the neoplastic state, the rate of mutations is often accelerated through increased sensitivity to mutagenic agents, breakdown of one or several components of the genomic maintenance machinery and a compromised surveillance system that fails to adequately monitor the genomic integrity.

During the multistep process of tumorigenesis, the accumulated genomic alterations progressively confer on cancer cells abnormal functional capabilities that collectively dictate the malignant growth. The so-called hallmarks of cancer, described by Hanahan and Weinberg [2,3], include sustained proliferative signalling, insensitivity to anti-growth signals, resistance to cell death, replicative immortality, sustained angiogenesis, tissue invasion and metastasis. These acquired functionalities allow cancer cells to survive, proliferate and disseminate, and tissue homeostasis is no longer guaranteed. Arguably the most fundamental trait of cancer cells is their ability to sustain chronic proliferation by deregulating growth-promoting signals. Many mechanisms may be involved in this process: the self-production or stimulated normal cell production of growth factors, the permanent receptor activation, the constitutive activation of signalling circuits, the disruption of negative feedback mechanisms and the loss of sensitivity to growth suppressors. Another noteworthy property of cancer cells is the unlimited replicative potential, i.e. cell immortality, which is needed to generate macroscopic tumours. In parallel, sustained angiogenesis leads to the development of tumour-associated neovasculature that helps sustain the expanding neoplastic growth. During the development of most

cancers, neoplastic cells further acquire the ability to move out of the primary lesion, invade adjacent tissues and thence travel to distant sites where they may succeed in founding new colonies.

Interestingly, accumulated knowledge demonstrates that tumours should no longer be regarded as simple masses of proliferating cancer cells but rather as complex tissues composed of distinct cell types that continuously interact together. The recruited normal cells (endothelial cells, pericytes, immune/inflammatory cells, fibroblasts and stem cells), which form the tumour-associated stroma, actively participate in the tumorigenesis process and contribute to the development and expression of certain hallmark capabilities.

In summary, cancer is a complex genetic disease that leads to the unregulated expansion of neoplastic cells mediated by specific functional capabilities acquired during the tumorigenesis process.

Radiobiology

Interaction between radiation and cells

Photon-based RT is by far the most widely used technique for the treatment of patients with radiotherapy. Photons are electromagnetic radiation produced by linear accelerators (LINAC) or gamma emitters (e.g. cobalt-60 source) with energies typically ranging from 1 to 25 MV in clinical settings. The biological effects of photons are mediated by the ionisation of molecules within the cells. Although high-energy photons cause direct ionisation, most of the biological damage results from secondary electrons produced by intracellular molecules, and more particularly by water, which represents the preponderant cell component. Each electron will cause further ionisations through the molecules with which it successively collides along its path.

Chemical cascades will, within less than one second, follow the initial physical interactions in the cell, and ultimately lead to breakdown of the chemical bonds that normally guarantee the structure and function of macromolecules. Since energy deposition is a random process, all molecules within the cell have an equal probability of being damaged by ionising radiation. However, the biological significance of the induced damage varies depending on the involved molecules. In most cases, the damage is inconsequential since it relates to molecules widely represented within the cell that can be easily replaced. On the other hand, damage induced to DNA may have severe consequences for the functionality of the irradiated cell.

When DNA is damaged, an extensive and sophisticated repair apparatus is activated with the goal of repairing DNA and preserving cellular function and integrity. The repair pathway is activated when specific molecules recognise damage to the DNA structure, including single-strand breaks (SSBs) and double-strand breaks (DSBs). This molecular interaction initiates a cascade of events,

leading to cell cycle arrest at a specific checkpoint within the cell cycle to allow for DNA repair before the cell cycle is re-entered. It is of interest that in cancer cells the damage checkpoint pathways are often disabled owing to genetic aberrations, making the cells more sensitive to radiation than competent cells.

Among radiation-induced DNA damage, the DSBs are the most complex form of damage to repair, and residual errors may persist. This can introduce small DNA deletions/insertions that jeopardise the structural genomic integrity. Consequently, inadequate repair of DSBs several hours after RT directly correlates with cell mortality.

The radiation-related cell death, which refers to the permanent loss of reproducible capacity, results from two main mechanisms:

- *Programmed cell death:* Genetically controlled pathways may actively trigger "cell suicide" in response to severe DNA damage. Different processes have been identified, such as apoptosis and necrosis, that typically lead to early cell death. Only a minority of cancer cells will embark on these pathways in response to irradiation, but noteworthy exceptions exist such as lymphoma, which can show early and major response to small doses of radiation thanks to cell apoptosis.
- *Mitotic catastrophe:* More frequently, cells fail to complete mitosis owing to the damaged DNA. This mechanism is responsible for most cell death after irradiation. The unrepaired DNA breaks or rearrangements prevent some cells from entering mitosis, and the chromosome aberrations accumulate, thus causing cells to undergo mitotic catastrophe. This form of cell death arises late compared with the initial response to damage, sometimes occurring after cells have successfully completed several mitoses.

Dose-response curves in RT

The effects of radiation on both normal and cancer tissues are classically described by means of dose-response curves which show the relative probability of response of a given tissue according to the delivered dose expressed in Gray (Gy). The tumour control probability (TCP) is usually used for assessing the tumour response, while the incidence of acute and late clinical toxicities (normal tissue complication probability, NTCP) evaluates the normal tissue response according to the absorbed dose. Owing to the random nature of radiation cell killing, the response curves have a typical sigmoid shape. Some important features that characterise these curves are listed below (Fig. 1):

- The position of the curve may vary between tumours and normal tissues. The dose leading to a 50% probability of tumour control (TCD_{50}) is often used to compare various tumour sensitivities to radiation.

- The gamma-value (γ_n) describes the steepness of the response curve. It corresponds to the increase in response expressed in % for a one percent increase in radiation dose. This value varies according to the position on the sigmoid curve: a small effect of dose variation on response is observed for the lowest and highest doses, while the steepness of the curve increases for the intermediate dose range. This has relevant clinical impacts for both normal and neoplastic tissues. According to these curves, it appears that there is no dose below which the probability of complications is non-existent. Increasing the dose improves tumour local control but at the price of increased severity, frequency or both of radiation side-effects on normal tissues. Finally, the dose range used in clinical routine is typically located within the steepest part of the dose-response curve for most locally advanced carcinomas, so that a significant gain in local tumour control can be expected thanks to moderate dose escalation RT strategies.

The relative position and shape of dose-response curves corresponding to the tumour control and a given radiation-related complication determine the therapeutic window within which the delivered dose will lead to a satisfactory probability of tumour control while keeping side-effects at a clinically acceptable level. In other words, dose-response curves guide the dose prescription with respect to the expected tumour response and normal tissue toxicities. New RT strategies and technologies thus aim at increasing the probability of uncomplicated cure.

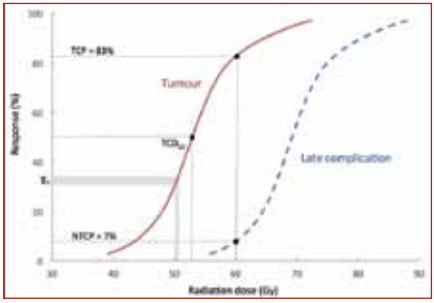

Figure 1: Dose-response curves for local control of tumour and for late complications (fictive organ at risk). According to these curves, a 60-Gy dose would lead to an 83% probability of local tumour cure, with a 7% probability of development of a late complication

Factors influencing tumour responses to radiation

Fractionation, which consists in delivering the total dose in consecutive small fractions over several weeks, is a key aspect of the clinical implementation of radiotherapy. Fractionation relies on the intrinsic capacity of normal cells to recover from sublethal radiation damage between two consecutive fractions. Thus, splitting the dose into several small fractions has only a slight impact on treatment efficacy but guards against severe late toxicities.

Another crucial parameter in radiotherapy is the overall treatment time (OTT), i.e. the time needed for completion of the whole treatment. For most tumours, the cancer cell proliferation occurring during the treatment partially compensates for the cell killing induced by radiation. The repopulation may thus reduce the global RT efficacy. This phenomenon is even more problematic at the later stage of radiotherapy, when accelerated repopulation occurs (3-4 weeks after the start of treatment). At this time, a significant part of the delivered dose is wasted to compensate for the active repopulation process. Thus, any prolonged duration of treatment has to be strongly avoided so as not to impair the treatment efficacy, or the repopulation has to be compensated for by giving extra doses. However, while shortening the OTT appears beneficial at the tumour level and has little influence on late radiation effects, it significantly worsens early toxicities by limiting the stem cell repopulation within high-turnover tissues during radiotherapy (see below).

Thus, the variable proliferation rate and cell repair capacity of late-responding tissues, acutely responding tissues and tumours underlie their relative sensitivity to fractionation and OTT (see also Table 1). The differential effect resulting from these parameters on these tissues serves as the basis for optimising radiotherapy schedules according to the total dose, the dose per fraction and the number of fractions:

- *Conventional fractionation*: This schedule uses daily doses of 1.8-2 Gy given in five fractions per week. The total delivered dose varies significantly depending on tumour histology, size and location. Conventional fractionation usually allows a high total dose to be safely delivered to the tumour, but is not necessarily appropriate if further dose escalation is warranted for control of poorly responding and/or large tumours. Increasing the total dose raises the probability of normal tissue complications and is inevitably associated with a prolonged OTT when conventional fractionation is used. Thus, part of the potential gain of dose escalation is lost as the tumour cells repopulate.

- *Hyperfractionation*: This refers to radiotherapy regimens that use a dose per fraction lower than 1.8 Gy and an increased number of fractions, often given twice daily. Hyperfractionation may be a convenient way of escalating the total dose without prolonging the OTT or increasing the risk of late normal tissue complications. Hyperfractionation using very low doses per fraction limits the damage inflicted on late-responding tissues, assuming that an interval of at least 6-8 h exists between fractions in order to allow cells to recover from sublethal damage. Clinical observations suggest that an even longer delay should be considered for neural structures like brain or spinal cord.

- *Hypofractionation*: The use of large doses per fraction (>2 Gy) theoretically leads to therapeutic loss owing to the increased risk of late complications. However, exceptions exist, and some tumors actually benefit from this approach. As an example, postoperative hypofractionated RT in breast cancer achieves comparable oncological and cosmetic results to conventional RT, and is commonly used across centres. Hypofractionation with only a few large fractions is more specifically used for palliative treatment of patients with limited life expectancy and for the treatment of small tumours with high-precision techniques like stereotactic RT. However, the volume and the nature of the irradiated tissues must always be carefully evaluated to ensure that the treatment-associated complications remain acceptable.

Other factors are known to influence the tumour response to ionising radiation. Some are related specifically to individual tumours. First, the intrinsic radiosensitivity varies amongst solid tumours. Schematically, some are highly sensitive (lymphoma, seminoma) or, on the contrary, respond poorly (glioblastoma, melanoma) to radiation, while most common tumours demonstrate intermediate sensitivity (squamous cell carcinoma, adenocarcinoma etc.). The tumour microenvironment also plays a significant role. An inadequate vascular network is a typical feature that may cause imbalance between the tumour oxygen supply and consumption and often leads to tumour hypoxia. The latter is known to worsen response to irradiation because the lack of oxygen inhibits the formation of free radicals that normally mediate most of the photon radiation damage.

Extrinsic factors, such as chemotherapy, have also been well recognised to be modulators of RT response. Chemotherapy enhances radiation effects, mainly by inhibiting the tumour cell proliferation that occurs between consecutive radiation fractions, although the direct modulation of DNA/chromosome damage and repair and the influence on tissue oxygenation also contribute to the radio-sensitisation effect. Consequently, the concomitant delivery of chemotherapeutic agents and ionising radiation often improves tumour local control, and is widely used in clinical routine despite the anticipated increase in acute toxicities.

Side-effects of radiation therapy

Irradiation of tumours is invariably accompanied by significant dose deposit within the surrounding normal tissues and is thus associated with the risk of significant side-effects.

Toxicities are commonly distinguished according to whether they are early or late radiation side-effects. This distinction relies on the time course of normal tissue response, the nature of the considered tissue, the underlying damage mechanisms and, more importantly, their clinical importance. The main characteristics of early and late side-effects are summarised in Table 1.

Early side-effects

By definition, early side-effects are observed during or shortly after RT, within the 3-month period that follows the start of treatment. They occur in tissues with a high proliferative activity, often including tissue that constitutes a natural barrier between two environments. Epidermis, oral mucosa and epithelium from the oesophagus and intestine are typical examples of early-reacting tissues with high turnover rates. These tissues are hierarchised into well-defined functional compartments: (1) stem cells, which actively divide to keep their pool constant and to produce cells that eventually differentiate,

	Early radiation toxicity	**Late radiation toxicity**
Tissue architecture	Hierarchised High turnover	Flexible Slow turnover
Tissue examples	Epidermis, mucosae of the digestive tract, bone marrow	Lung, brain, spinal cord, liver, kidney
Effect of total dose (TD)	High sensitivity	High sensitivity
Effect of fractionation	Low sensitivity	High sensitivity
Effect of overall treatment time (OTT)	High sensitivity	Low sensitivity
Time course of side-effects	During RT or soon afterwards (<3 months)	Months/years after RT (>3 months)
Natural history	Usually complete healing; rarely leads to severe late effects	Irreversible, worsening over time, potentially fatal
Treatment	Symptomatic care, prevention/ treatment of secondary complications	Supportive care, organ substitution treatment, palliative care

Table 1: Main characteristics of early and late radiation-induced toxicities

(2) transit or precursor cells, which undergo a limited number of divisions and form the amplification compartment, and (3) post-mitotic cells, which progressively mature until terminal differentiation and, eventually, cell elimination (Fig. 2).

The irradiation of such tissues predominantly causes stem cell deaths, but does not have a relevant effect on the differentiation and cell loss processes. The result is radiation-induced impairment of cell production, which can no longer compensate for the physiological loss of differentiated cells. This imbalance between cell production and loss progressively leads to tissue hypoplasia, which becomes clinically evident after a given threshold cell depletion is reached. After radiotherapy, healing of acute radiation effects relies on the compensatory proliferation of surviving stem cells within the irradiated volume or on migration from outside.

The pathogenesis of acute side-effects easily explains the observed dose-response relationship. The total dose does not influence the time course of early response, which is in fact related to the overall tissue turnover time. As an example, the dry desquamation of the epidermis typically occurs 2 or 3 weeks after the onset of radiotherapy with conventional RT. By contrast, the higher the dose and the shorter the OTT, the lower is the number of stem cells that survive the treatment. In these conditions, acute reactions are more severe and take longer to heal completely.

Early side-effects commonly cause significant short-lived morbidities. They justify optimal medical care to manage the patient's symptoms (pain, inflammation, dysphagia etc.) and to prevent or treat secondary complications such as infection (skin, mucosa) or feeding problems (oral mucositis, oesophagitis). Aggravating factors such as tobacco, alcohol, a spicy diet or mechanical constraints that cause additional trauma to the damaged tissues should be avoided whenever possible.

Acute reactions may require a brief interruption of treatment to allow partial recovery. However, they are rarely life-threatening and often resolve completely within a couple of weeks after completion of therapy.

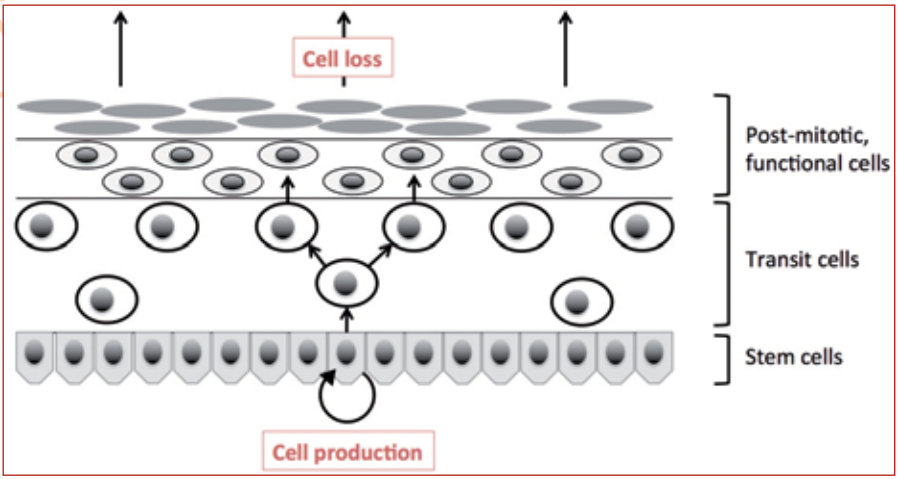

Figure 2: Schematic view of turnover tissues. Stem cells self-renew and give rise to transit cells, which undergo a limited number of divisions (amplification compartment). These cells ultimately mature and differentiate into functional cells, which are eventually lost. The epidermis represents a typical example of a high-turnover tissue

Late side-effects

Late side-effects have a multifactorial pathogenesis, are generally irreversible and typically worsen over time. They become clinically manifest only after a latent period of months or years following RT. Late effects arise from tissues that are without a clear separation between proliferating and functional cells and are characterised by a reduced proliferation capacity compared with proliferative (high cell turnover) tissues. Depending on demand, proliferating cells may be recruited into the functional population, and vice versa, to preserve organ integrity and function.

The pathogenesis of late effects is highly complex. Essentially, radiation progressively depletes proliferating cells that are continuously recruited from the functional population to compensate for the cell loss. As a result, a critical depletion of functional cells may occur and translate into the impairment of organ function. The compensatory accelerated cell division paradoxically accelerates the radiation-induced cell death (cascade effect). Finally, vascular damage (endothelial cell death), fibrosis (increased production of collagen by activated fibrocytes) and chronic inflammatory response furthermore aggravate late damage.

The dose-response relationship of late-responding tissues differs significantly from that of acutely responding organs. Increasing the total dose shortens the latent period prior to the occurrence of chronic damage and accelerates the rate at which the severity of clinical changes worsens. In addition, late reactions are highly sensitive to fractionation. This reflects their slow proliferation rate, which limits their ability to compensate for radiation-induced cell killing. Fractionation using low radiation doses in sufficiently time-spaced fractions allows most irradiated cells to recover from sublethal DNA damage and thus limits the extent of cell depletion.

The late effects are differently expressed depending on the functional architecture of a given organ. Broadly speaking, one can consider that organs are composed of functional subunits ensuring their global function. These subunits can be organised either in parallel or in series. In organs with a predominantly parallel structure, such as lung, kidney and liver, each functional subunit works independently. In this case, radiation damage has clinical repercussions only when the surviving units can no longer sustain the physiological activity of the individual organ. Radiation oncologists should thus pay particular attention to the organ volume receiving doses above a threshold that is known to cause irreversible damage to subunits. On the other hand, in organs with a mainly serial structure, such as spinal cord and intestine, the global function relies on the integrity of each individual subunit, and any localised damage potentially results in a clinical side-effect. For serial organs, the risk of complications is thus mainly driven by the highest doses ("hot spots") rather than by the global dose distribution within the whole organ. A typical example is the spinal cord, for which segmental and limited lesions suffice to dramatically impair the nerve influx conduction. Although most organs actually present a mixed organisation of serial and parallel structures, such volume models are useful for determination of dose constraints for various organs when the RT treatment is being planned and evaluated.

Cancer related to radiation exposure is a dramatic late complication of radiotherapy. DNA damage, which underlies the anti-neoplastic properties of ionising radiation, also exposes normal cells to the risk of malignant transformation after a latent period of years (mainly leukaemia) or decades (mainly solid tumours). Although radiation-related cancers may theoretically concern any type of organ, certain tissues and cell types exhibit a higher risk of malignant transformation than others. Bone marrow (acute and chronic myelogenous leukaemia, acute lymphocytic leukaemia), the thyroid gland, the lung and the female breast are among the most sensitive organs. Since the incidence of secondary cancers rises over the lifetime of the individual, with a long latent period, radiation-induced tumours are mainly a concern when RT is given at young ages, and especially during the paediatric

period. The assumption that low to moderate doses preferentially expose patients to cancer risk compared with high doses is still a matter of debate, but it no longer seems corroborated by observations. Efforts should therefore be made to keep the integral dose delivered to the whole patient as low as possible, and hadron therapy, which uses charged particles (e.g. protons, carbon ions), appears particularly promising in this respect.

Late toxicity has always been considered the main limiting factor for the clinical implementation of high-dose RT strategies. Indeed, most late complications are definitive, severe and significantly impair the patient's quality of life. As no treatment is available that will efficiently heal the deficient organ, only supportive care can be offered. As examples, radiation may cause lung fibrosis with subsequent respiratory insufficiency, requiring permanent oxygen supply, and radiation-induced renal failure may require permanent dialysis or kidney transplant. Moreover, late toxicities entail the risk of life-threatening complications: myocardial infarction, intestinal obstruction or perforation, vascular rupture, cerebrovascular accident, terminal respiratory insufficiency and secondary radiation-induced cancer are usual causes of radiation-related death that can occur several years after completion of RT. The optimum dose in curative RT is therefore the dose that gives the highest probability of cure at an acceptable level of severe sequelae.

Dose constraints in radiotherapy

Since the frequency and severity of radiation-induced toxicities probabilistically correlate with the delivered dose to organs at risk, the radiation oncologist community has been trying to establish dose constraint recommendations for decades. These derive from animal experiments, clinical observations and, most importantly, large clinical trials. The dose constraints usually relate to a dose-volume histogram (DVH), which summarises a 3D dose distribution into a graphical 2D format. The volume referred to in DVH corresponds to either a target or a healthy organ. Several useful values can be extracted from a DVH to evaluate the risk of RT complications, according to the recommendations of the International Commission on Radiation Units [4,5] (Fig. 3):

- The mean absorbed dose (D_{mean}) and the V_D, which correspond to a relative or absolute volume that receives at least the dose D, are especially useful metrics for reporting doses for parallel-like normal structures. As previously mentioned, the risk of toxicity mainly depends on the distribution of the total dose within these organs.

- The maximal absorbed dose (D_{max}) is often reported for serial-like structures since toxicities are mainly driven by the "hot spot" dose within the organ. More recently, the use of the near-maximum absorbed dose ($D_{2\%}$), which is the dose received by 2% of the organ of interest, has been suggested instead of D_{max} to provide a more reliable metric than a single computation point.

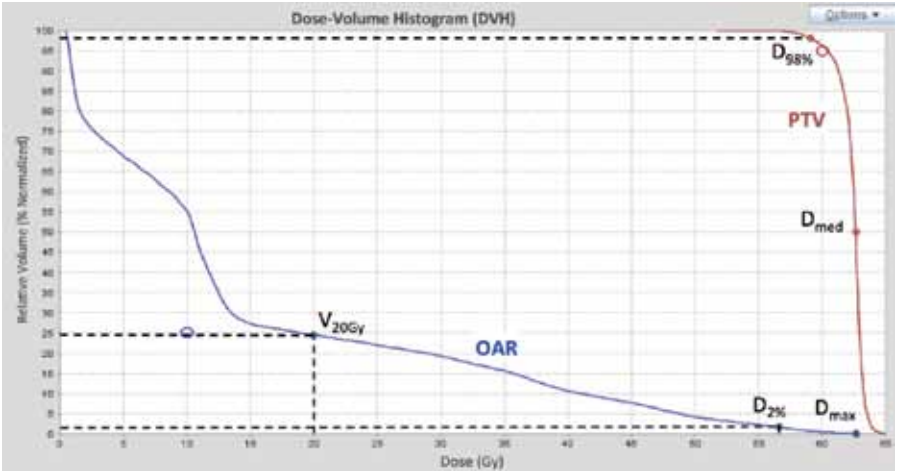

Figure 3: Dose-volume histograms for the planning target volume (PTV, red line) and a fictive organ at risk (OAR, blue line). Some metrics usually used when reporting doses are illustrated: V_{20Gy} (volume receiving at least 20 Gy), D_{max} (maximum absorbed dose), $D_{2\%}$ (near-maximum absorbed dose), $D_{98\%}$ (dose received by at least 98% of the volume) and D_{med} (median absorbed dose)

Several aspects must be considered when documenting and reporting normal tissue complications in RT:

First, the severity of any toxicity should be graded according to standardised international classification systems. Among these, the RTOG/EORTC [6] and CTCAE v3.0 [7] are the most commonly used scoring methods, allowing a reliable and reproducible comparison between investigators, institutions and clinical trials. Schematically, complications are scaled from 0 to 5, gradually going from no toxicity to side-effect-related death (Table 2).

Grade	Severity	Description
0	No reaction	No toxicity
1	Mild reaction	Toxicity that spontaneously heals without any medical intervention or interruption of oncological treatment
2	Moderate reaction	Toxicity that can be treated on an ambulatory basis; no modification of the RT required
3	Severe reaction	Toxicity that frequently requires intensive care and hospitalisation; dose reduction or treatment interruption sometimes required
4	Life-threatening	Toxicity that requires immediate hospitalisation for intensive care; cessation of the RT required
5	Death	Death owing to side-effects

Table 2: Scoring of side-effects

Secondly, the clinician has to distinguish between acute and late toxicities, since their management and prognosis deeply differ. As previously mentioned, the irreversible and progressive nature of late complications confers on them a noteworthy importance for guiding the dose prescription and delivery, and further careful assessment should be carried out during follow-up.

Thirdly, the probabilistic nature of radiation-related events has to be considered, a defined dose level leading to a certain risk of a particular grade of toxicity for each organ. The recommended dose constraints for healthy tissues thus aim at keeping the incidence and severity of complications at an acceptable level, which is set according to the involved organ and the clinical impact of its potential dysfunction. As an example, the near-maximum dose to the spinal cord should typically not exceed 50-54 Gy (2 Gy/fraction) to keep the incidence of disabling myelitis very low (<0.5%). By contrast, constraints to the skin are less restrictive since late toxicities mainly have a cosmetic impact.

Last but not least, dose constraints are highly sensitive to fractionation (mainly for late effect) and to a lower extent to the OTT (mainly for acute effect). Most dose recommendations have been formulated for classic fractionation schedules (1.8- to 2-Gy fractions). Fortunately, mathematical models are available for adapting the dose constraints according to the fraction dose. However, these models poorly predict the radiation effects for very high dose fractionation (>8 Gy/fraction), such as is employed in stereotactic RT, and data collected from clinical trials should be used instead to develop valid recommendations.

An exhaustive review of the radiation-related toxicities has been recently presented in a special issue of the International Journal of Radiation Oncology Biology Physics, dedicated to Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC) [8]. Some illustrative dose constraints derived from this review are reported in Table 3 for biologically equivalent dose in 2-Gy fractions.

Organs	Toxicities		Dose constraints for late toxicities
	Acute	Late	
Brain	Intracranial hypertension Headache Asthenia	Somnolence syndrome Cognitive impairment Brain necrosis Cerebrovascular disease	$D_{2\%}$ <72 Gy (5% risk at 5 years of radiation necrosis for partial irradiation)
Spinal cord	Lhermitte's sign	Progressive myelopathy (hemiplegia, transverse myelitis, paraplegia etc.)	$D_{2\%}$ <50 Gy (0.2% risk of myelopathy for full cord cross-section)
Ear	Otitis externa Dizziness Labyrinthitis	Hearing loss	D_{mean} <35-45 Gy
Optic nerve/ chiasm		Visual impairment (visual loss and bitemporal hemianopsia)	$D_{2\%}$ <55 Gy (<5% risk of radiation-induced neuropathy)
Heart	Pericarditis	Constrictive pericarditis Cardiomyopathy Ischaemic heart failure Valvulopathy Arrhythmia	V_{25Gy} <10% (<1% risk of cardiac mortality at 15 years)
Lung	Radiation pneumonitis	Radiation pneumonitis Lung fibrosis	D_{mean} <20-23 Gy V_{20Gy} <30-35%
Liver	Venous thrombosis Radiation-induced hepatitis	Fibrosis Atrophy Cirrhosis	D_{100} <28-30 Gy if whole-liver RT D_{mean} <28-32 Gy if partial-liver RT (<5% risk of radiation-induced liver disease)
Kidney		Nephropathy Renal failure	D_{mean} < 18 Gy V_{28Gy} < 20% V_{20Gy} < 32% V_{12Gy} < 55%
Intestine	Diarrhoea Abdominal pain	Fibrosis Stenosis Intestinal obstruction Bleeding Fistulae	V_{15Gy} <120 cc (bowel itself) V_{45Gy} <195 cc (peritoneal space)

Table 3 continued on page 22

Organs	Toxicities		Dose constraints for late toxicities
	Acute	Late	
Oesophagus	Acute oesophagitis	Stenosis Chronic ulceration Fistulae	V_{60Gy} <30% V_{50Gy} <30% if chemo V_{45Gy} <40% V_{20Gy} <45%
Rectum	Softer or diarrhoea-like stools Pain with cramping Ulcerations	Stricture Diminished compliance Decreased storage capacity	V_{75Gy} <15% V_{70Gy} <20% V_{65Gy} <25% V_{50Gy} <50%
Parotid gland		Xerostomia	Unilateral sparing (D_{mean} <20 Gy) of parotid gland whenever possible D_{mean} <25 Gy (both parotid glands)

Table 3: Examples of acute and late toxicities, and dose constraints for late effects

If constraints are essential for guiding the dose prescription, they have to be carefully interpreted in the light of several confounding factors, which makes their practical implementation problematic in daily routine.

First of all, recommendations may differ between studies and institutions. Such differences partially reflect the difficulty in accurately describing probabilistic and multifactorial events like side-effects. They also relate to methodological biases in the studies on which recommendations are based, such as the method of assessing and reporting toxicities and the heterogeneity of the considered patient populations and radiotherapy techniques. On the other hand, RT technologies are evolving so fast that the available data on toxicity often refer to obsolete techniques. For example, following the introduction of rotational IMRT for treatment of lung cancer, it has recently come to light that the increased volume of lung receiving low doses (V_{5Gy}) inherent to this technique is significantly correlated with the risk of radiation-induced pneumonitis [9].

Moreover, the tolerance to radiation is obviously decreased by any pre-existing disease or surgery altering the organ function. Diabetic retinopathy, chronic renal failure, chronic obstructive pulmonary disease, neurodegenerative disease, pre-existing hearing loss, cutaneous scleroderma and other conditions promote organ breakdown in the event of further irradiation. Aggressive measures have to be taken to even better spare the diseased tissues, and the dose levels that

are usually considered to be tolerable should be lowered according to the severity of the prior organ dysfunction. Genetic diseases associated with an alteration in the repair of DNA damage (such as xeroderma pigmentosum and ATM mutation) also expose the patient to increased risk of severe complications during and after RT.

External factors may also modulate the response of healthy tissues to radiation or may cause additional damage to that induced by RT. Chemotherapeutic agents are known to potentiate the effects of radiation on healthy tissues, especially when they are given concomitantly. As most drugs act on proliferating cells, they aggravate the cellular depletion induced by radiation at the level of rapidly renewing tissues. Increased acute toxicity is anticipated in this situation and has been confirmed in several clinical trials. Moreover, some drugs have a specific toxicity for tissues within the irradiated volume, such as bleomycin (lung toxicity), doxorubicin (cardiac toxicity), cisplatinum (renal toxicity) and neurotoxic drugs, including platinum agents and vincristine (neural tissue toxicity). In this setting, some combinations should be avoided whenever possible, or the radiotherapy and/or chemotherapy should be adapted on the basis of accumulated knowledge in order to avoid unacceptable late toxicities.

Surgery is another aggravating factor. It promotes inflammatory reactions and tissue fibrosis and may impair the lymphatic drainage when extended node dissection is performed; these factors act cumulatively with the radiation effects. Severe cutaneous fibrosis, permanent lymphoedema and wound healing delay are often reported when perioperative RT is performed.

Finally, management should be adapted according to the general condition and specific oncological situation of the patient. Indeed, the radiation oncologist should always balance the potential benefit of the treatment against the risk of complications. In some cases, the clinician may decide, in agreement with the patient, to exceed the recommended dose if the patient's survival is threatened. On the other hand, short, hypofractionated RT favouring quality of life is often the preferred option in patients with a short life expectancy who are unlikely to experience late toxicities.

Conclusion

The fundamental principles of radiobiology described in this chapter have governed all developments since the birth of RT. Recently, the emergence of highly conformal radiation techniques has allowed for much better sparing of healthy tissues, while the tumour biology can now be characterised by functional imaging in a non-invasive way. The technological refinements offer new opportunities for modification of treatment plan design and dose delivery so as to better accord with the radiobiology of solid cancers and normal tissues.

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Section 2 – Radiotherapy

Treatment Planning

Bob Smulders and Lotte S. Fog

Introduction

Following the discovery of X-rays by Wilhelm Conrad Röntgen in 1895, the treatment of cancer patients with radiation started almost immediately, in 1896 [1]. In the same year, Henri Becquerel discovered radioactivity, which led to the discovery of the isotopes of polonium and radium by Pierre and Marie Curie-Skłodowska in 1898. The first treatment with radium was performed in 1901. In the early days, external radiation therapy planning was done by visual inspection of patients with superficial tumours. With the introduction of cobalt-60 machines and medical accelerators, which have a higher X-ray energy, more deeply seated tumours could be treated. Also diagnostic X-ray machines were introduced to image the tumour. In the early days of radiotherapy planning, the administered dose distribution was calculated and drawn manually. With the introduction of computers, these calculations were automated. As computers became more powerful, computed tomography (CT) data from the patient were used for tumour identification and radiotherapy planning. Calculation algorithms were developed to incorporate CT densities to take into account tissue density differences inside the patient. Radiotherapy treatments became more conformal and accurate. Soon, new algorithms were developed in order to computerise the process and to identify the optimal solution for the individual patient, giving rise to the term "intensity-modulated radiation therapy". Nowadays, linear accelerators are equipped with an X-ray tube to verify the pre-set radiation position more clearly. The X-ray tube is used as diagnostic 2D images or 3D cone beam CT images.

In principle, there are three methods of cancer treatment using radiation. The first is external radiation therapy, in which a radiation beam is administered externally to the patient with a sufficiently high energy to penetrate to the depth of the tumour. The beam can be produced by a machine containing a radioactive source emitting radiation (cobalt-60) or by a machine with accelerated particles alone or accelerated particles that collide into a high-density target, causing X-rays (bremsstrahlung). The second method is brachytherapy, in which naturally radioactive materials are inserted directly into or near to the tumour. The third method is the form of cancer therapy administered in nuclear medicine, termed systemic radioisotope therapy. This involves the injection either of radioisotopes with the chemical properties to ensure their absorption by a certain gland instead of other body organs, or of isotopes attached to a certain molecule or antibody that ensures targeting of the tumour. This chapter will not elaborate on this third method. The majority of radiation therapies are delivered as external beam treatment.

Radiation modalities

In radiation therapy, different kinds of radiation modality can be employed. The types of radiation commonly used are photons, electrons, protons, neutrons and light ions, which display different reactions with matter, regardless of energy.

When a beam of photons (or electrons) generated with a medical accelerator enters a homogeneous media, such as water, the absorbed dose of the photon beam varies with depth, as shown in Fig. 1.

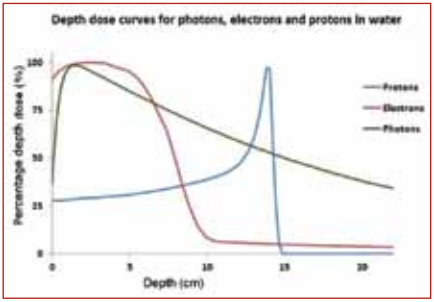

Image courtesy of P. Munck af Rosenschöld, Department of Radiation Oncology, Rigshospitalet – Copenhagen University Hospital, Copenhagen, Denmark

Figure 1: Percentage depth dose curve of protons, electrons and photons in water.

The forms of radiation most commonly used for cancer treatment are photons and electrons. The behaviour of absorbed dose in relation to depth for photons and electrons has an impact on the design of treatment plans (Fig. 1). Because most tumours are situated deep within patients, use of a single beam is not recommended. Such an approach would cause healthy tissue in the path of the beam to receive a higher dose than the tumour at depth, and the patient would suffer severe complications. Therefore, treatment plans entail multiple beams from different entrance angles, ensuring that the total dose to the tumour is sufficiently high while the dose to the area surrounding the tumour is kept low. Electron radiation is commonly used for superficial tumours while photon radiation is used for deep-seated tumours. Proton therapy is becoming increasingly popular owing to the fact that the majority of the absorbed dose is deposited at a specific depth (Fig. 1), which ensures that healthy tissue receives a lower overall dose. The deposition depth can be changed by altering the energy of the proton beam. However, the cost of a proton accelerator is much higher than that of an accelerator producing photons and electrons [2-4]. Furthermore, proton therapy is more sensitive to patient movement and setup uncertainty since the absorbed dose of a proton beam is very sensitive to different tissue densities, which can cause the tumour to be missed. Proton therapy is especially to be preferred in infants and younger adults owing to the decreased risk of secondary cancer and side-effects [5].

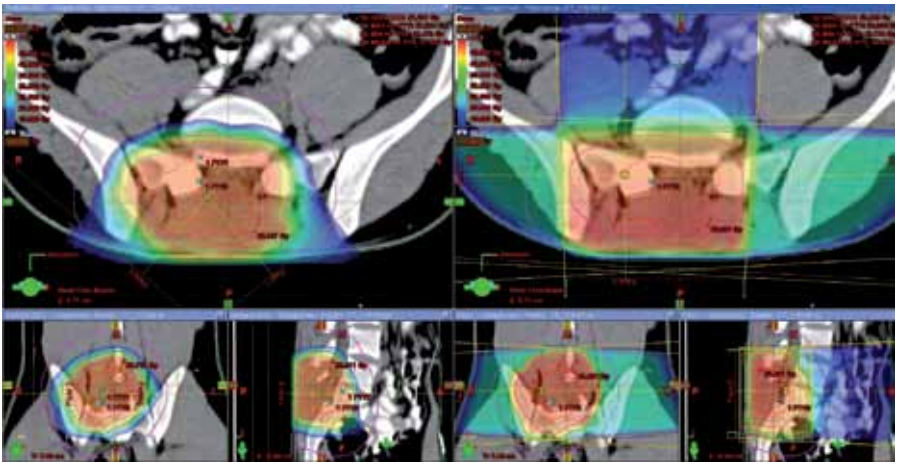

Image courtesy of Department of Radiation Oncology, Rigshospitalet – Copenhagen University Hospital, Copenhagen, Denmark

Figure 2: Comparison of dose distributions with protons (left) and conventional photons (right). The prescribed tumour dose is 48 Gy and the lowest dose shown with colour wash is 10 Gy.

Figure 2 shows a comparison of a dose distribution in an adolescent patient. The prescribed absorbed dose to the tumour was 48 Gy. The left-hand side of the figure shows a two-field proton treatment plan while the right-hand side shows a three-field photon treatment plan. The dose distribution is shown in colour wash and the lowest dose shown is 10 Gy. It is evident that with the conventional photon treatment plan, the area receiving the lower doses is far greater, which increases the risk of secondary cancer later in life.

Medical accelerators

The machines most frequently used to irradiate tumours are medical accelerators for photons and electrons. Electrons are accelerated close to the speed of light through an accelerator tube using electromagnetic waves. The electrons either leave the accelerator (through the flight tube, where the electrons are bent 90°) directly (electron radiation) or collide with a high-density material, producing photon radiation (Fig. 3). The penetration depth in tissue can be changed by varying the energy of the beam.

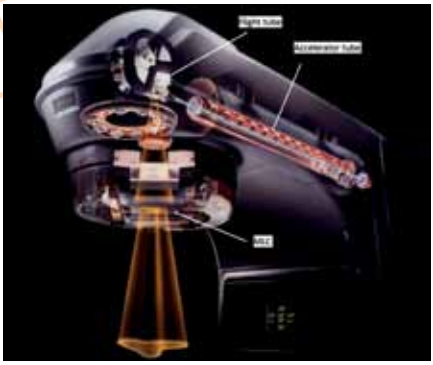

Figure 3: Inside a medical accelerator. Electrons are accelerated in the accelerator tube from right to left and smash into a high-Z material, producing X-rays (in orange).

Most accelerators are equipped with seven different electron radiation energies and two photon radiation energies. The accelerator tube is mounted on a gantry so that the patient can be irradiated from different angles. The gantry has a radius of rotation of 100 cm measured from the spot where the radiation leaves the flight tube and the rotational centre. This rotational centre is called the isocentre. The isocentre is often conveniently placed at the centre of the tumour so that the gantry can be rotated around the patient without the need to move the patient during treatment (Fig. 4).

Figure 4: Positioning of the patient on the treatment couch, where the tumour is situated in the isocentre of the accelerator.

After the radiation leaves the flight tube, it passes through the accelerator head, where the radiation is collimated by the collimator jaws and a multileaf collimator (MLC). The MLC consists of small leaves able to move independently in order to shape the beam in the form of the tumour (Fig. 5). Some medical accelerators are equipped with a wedge situated in the radiation head in order to shape the dose distribution of a photon beam so that a high dose is created at one end of the beam and a low dose at the other end. Other accelerators are able to create this effect by closing or opening the collimator jaws during radiation.

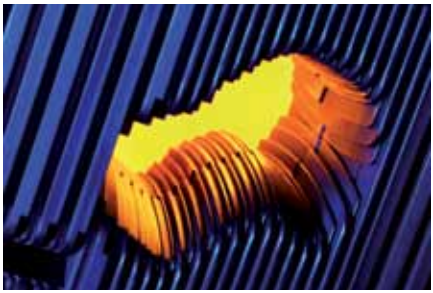

Figure 5: MLCs shaping the beam so that it conforms to the shape of the tumour.

Brachytherapy: rationale and a brief history

Brachytherapy (from the Greek word *brachys*, meaning "short distance") is a form of radiation therapy where a radiation source is placed inside or next to the area requiring treatment. Brachytherapy typically uses radiation of an average energy around 100 times less than that of external beam radiation, with typical penetration depths measured in millimetres rather than centimetres. Brachytherapy has a clear advantage over the more commonly used external beam therapy in that the dose outside the tumour can be kept very low. On the other hand, the access required to insert the source into the area near the tumour may present some difficulties.

Brachytherapy was pioneered in 1901 in Paris. Radioactive sources were inserted directly by radiotherapy staff until the 1970s, when afterloaders (remotely controlled machines that allow staff to be positioned outside the treatment room when the source is inserted) became commercially available. By the 1990s, CT and MR images were being commonly used in planning brachytherapy.

Brachytherapy can be intracavitary (e.g. for cervical or oesophageal tumours), interstitial (e.g. for tumours in the head, neck, prostate, cervix, penis or extremities) or intraluminal (for tracheal or oesophageal tumours) (Fig. 6).

Figure 6A: An interstitial gynaecological applicator.

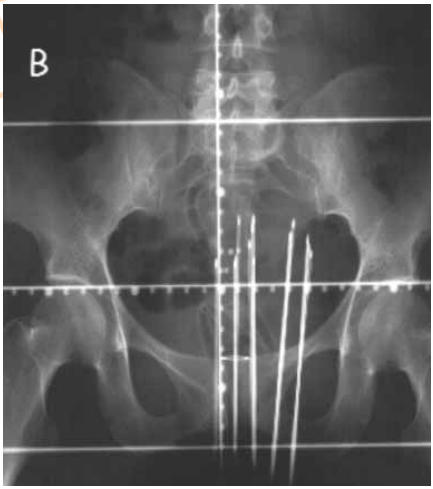

Image courtesy of Professor S.A. Engelholm, MD, DMSc, Head of the Department of Radiation Oncology, Rigshospitalet – Copenhagen University Hospital, Copenhagen, Denmark

Figure 6 B: A CT image showing the applicator positioned in a patient.

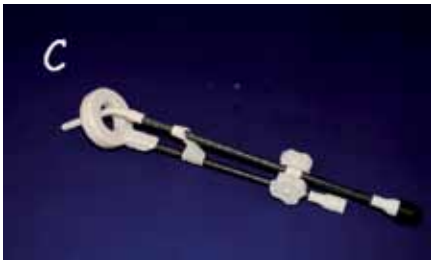

Image courtesy of Department of Radiation Oncology, Rigshospitalet – Copenhagen University Hospital, Copenhagen, Denmark

Figure 6 C: An intercavitary gynaecological applicator.

Brachytherapy is divided into low, medium or high dose rate depending on the strength of the source used for treatment. Side-effects in the healthy tissue surrounding the tumour are reduced when a low dose rate treatment is used; however, continuous irradiation for several days presents practical problems for both the patient and the clinic. In practice, fractionated high dose rate treatments (delivering treatments in three to seven fractions) or pulsed dose rate treatments (delivering pulses of radiation dose every hour for 10-50 h) are entering common use.

Curative radiation therapy

The intention of curative radiation therapy is to completely cure the patient from cancer or to prolong the life of the patient significantly. These treatments are usually fractionated in long fractionation schemes, utilising the therapeutic ratio as described in Section A. This therapeutic ratio identifies the point at which healthy tissue recovers faster than tumour tissue at a certain absorbed radiation dose. The fraction dose is in the range of 1.8–2.2 Gy. The total dose to solid tumours varies from 50 to 80 Gy, while for lymphomas it ranges from 20 to 40 Gy. Usually, these schemes involve 5 days treatment and 2 resting days each week. Some studies have shown, however, that for head and neck tumours the optimal week comprises 6 days of treatment and 1 resting day [6]. In order to perform curative radiation therapy, the dose distribution has to be homogeneous in the tumour area, as described in the ICRU guidelines [7]. Some cancers have a high risk of dissemination via lymph node systems, and adjacent areas may then be irradiated simultaneously at a lower dose. This is called the integrated boost technique, e.g. 68 Gy to the tumour and 50 Gy to surrounding high-risk lymph nodes.

Palliative radiation therapy

Palliative radiation therapy primarily provides pain or other symptom relief rather than having a curative aim. It is typically delivered in fewer fractions than curative therapy (and with a greater dose per fraction). The main reasons for this are that the patient may not be sufficiently physically fit to attend treatment sessions to receive a large number of fractions, and that speedy pain relief is a higher priority than the risk posed by late side-effects.

PET is often used to detect distant metastases prior to radiation therapy, and since the presence of distant metastases indicates a need for palliative rather than curative treatment, PET data are often referred to when assessing treatment intent. A review of the current literature found that, "in 10–26% of cases, FDG-PET changed the intent of treatment from radical to palliative, because of the detection of distant metastases or locally advanced tumour, not suitable for radical treatment" [8].

Radiotherapy treatment planning

Imaging modalities

In order to visualise the tumour and other anatomical/physiological features, different image modalities can be used, the most common being CT, MRI and PET. Each has a different way of visualising anatomy and physiological features. CT is based on X-rays and maps the density of the body. If the tumour has a similar density to the surrounding tissue, it will not be clearly detectable on a CT scan. MRI makes use of the property of nuclear magnetic resonance to image the nuclei of atoms inside the body of the patient. In comparison with CT, MRI offers better visualisation of soft tissue. With PET it is possible to visualise tumours using a tumour tracer combined with a diagnostic radioactive substance. PET also allows visualisation of metastases which are not visible with the other modalities.

These modalities have different advantages and disadvantages. CT is always the basis for the dose distribution calculation in radiotherapy planning. It is therefore important to fuse images or perform image registration between other imaging modalities and the CT scan (Fig. 7), thereby allowing the physician to delineate on another modality where the tumour is best visible and then to translate it to the CT scan. Image registration can be based on bony structures or soft tissue. If the patient is scanned in a PET/CT or PET/MRI scanner then the registration can be based on the mutual spatial axis. It is of paramount importance that the patient is immobilised in the same way on all scans, otherwise the anatomy will be shifted, rotated and stretched.

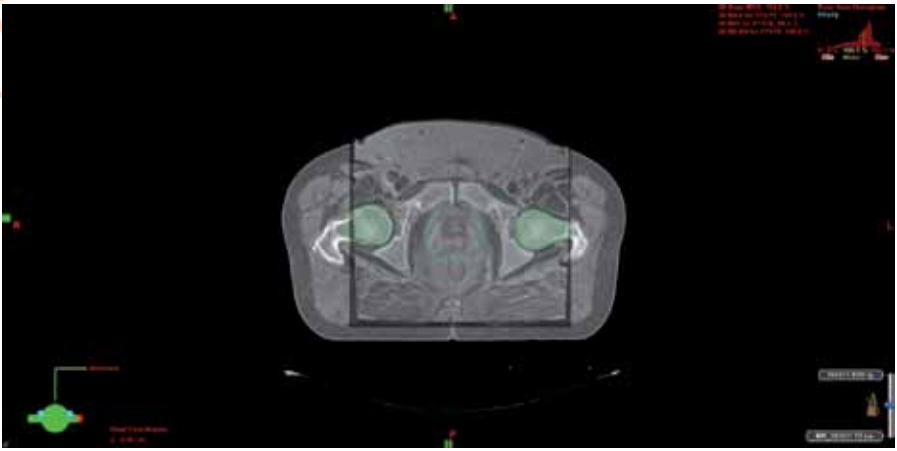

Image courtesy of Department of Radiation Oncology, Rigshospitalet – Copenhagen University Hospital, Copenhagen, Denmark

Figure 7: An example of MRI and CT image registration.

In this section the following radiotherapy planning techniques are considered:

- Conventional radiotherapy planning
- Intensity-modulated radiation therapy (IMRT)/volumetric-modulated arc therapy (VMAT)
- Stereotactic radiation therapy
- Brachytherapy

Conventional radiotherapy planning

Radiotherapy planning is usually done on a treatment planning system (TPS). The TPS is a computer program interactively simulating the treatment of a cancer patient. This programme contains a library of the hardware of the treatment machine and the dosimetric characteristics of the radiation beam. The program runs on a network of powerful computers.

In the TPS, a three-dimensional CT scan is used as a basis for calculating the absorbed dose in the patient. The tissue densities in the patient are expressed in CT numbers and are used in the TPS to take into account the difference in dose absorptions of different densities. On the CT scan, the physician delineates the tumour (gross target volume, GTV), with or without the aid of different imaging modalities such as MRI and PET. Additional margins are included (clinical target volume/planning target volume, described in Section C) around the delineated tumour to take into account, for example, microscopic disease and delineation and set-up uncertainties.

Due to the depth dose characteristics of a photon beam, the photon treatment plan typically consists of multiple beams from different irradiation angles. The angles are chosen in such a way that the most sensitive organs and/or tissues are avoided. The isocentre (or the centre of rotation) of the accelerator is typically placed in the centre of the tumour. The MLC of each field is shaped to the form of the tumour in the beam's eye view, which is the view from the accelerator head through the MLC to the tumour at the chosen beam angle (Fig. 8).

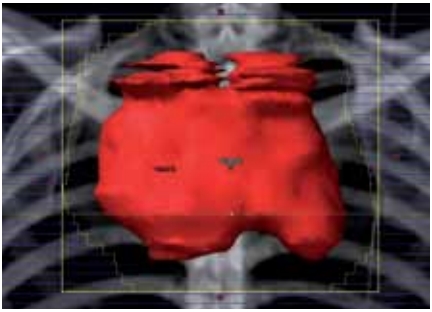

Image courtesy of Department of Radiation Oncology, Rigshospitalet – Copenhagen University Hospital, Copenhagen, Denmark

Figure 8: Beam's eye view of a radiation beam.

An additional margin is included to allow for penumbra effects (dose build-up from the outside to the inside of the beam) (Fig. 9).

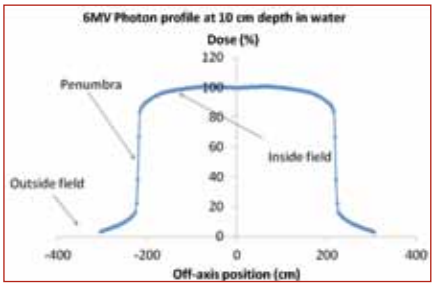

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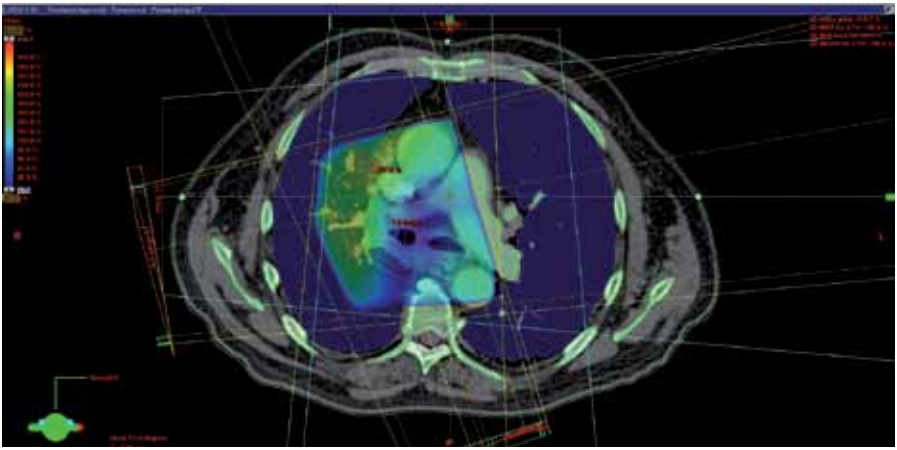
Figure 9: A beam profile of a 6-MV photon beam in water

To obtain a qualitatively good treatment plan, the guidelines of the ICRU [7] are followed. These guidelines state that the PTV has to be covered by at least 95% of the prescription dose and that the maximum dose should not exceed 107% of the prescription dose. Radiation dose to organs at risk can never be completely avoided owing to proximity of tumours to these organs. Organs at risk have a tolerance dose that depends on the dose per fraction, but the dose must be kept as low as possible. Usually a juggling act is necessary between target coverage and dose to organs at risk, and a compromise/sacrifice has to be made.

Therefore, the treatment plan is individualised for each patient according to the tumour location. The number of irradiation fields and irradiation angles varies. Furthermore, the tumour's position and the patient's anatomy influence the irradiation intensity of each treatment angle with a view to obtaining a homogeneous dose distribution as described by the ICRU. These intensities or beam weights are adjusted manually in conventional radiotherapy planning, depending on tumour depth from each beam angle and difference in tissue densities between the surface and the tumour. The curvature of the patient's body and the variations in depth of an elongated tumour also influence the dose distribution; a wedge with adjustable wedge angles can be used to compensate for these effects. The conformal treatment plan usually contains three or four different beam angles (Fig. 10).

IMRT/VMAT

Often the tumour is located very close to the organ at risk (or to several organs at risk) and/or the treatment plan requires multiple dose levels or relates to different tumour sites. Conventional treatment planning becomes very difficult in such circumstances. One solution is to intensity modulate the treatment plan. Intensity modulation is based on the idea that the radiation intensity throughout every field is varied in such a way that the dose distribution conforms to the shape of the tumour and high dose gradients bend around organs at risk and healthy tissue [9,10]. This is often done using a computer and a smart optimisation algorithm. There are two types of intensity modulation: "forward planning" and "inverse planning".



Courtesy of Radiation Oncology, Rigshospitalet – Copenhagen University Hospital, Copenhagen, Denmark

Figure 10: A conventional plan treating a lung tumour with three beams. The beams were chosen to reduce the dose to the other lung and the spinal cord.

Forward planning. Forward intensity modulation means that the beam weights of beams with pre-set field shapes are optimised with a computer algorithm. This algorithm has pre-set organ at risk and target constraints. When a constraint is exceeded, a penalty is calculated. The height of the penalty depends on the extent to which the constraint is exceeded. The sum of all penalties for all constraints is calculated. Users can also pre-set individually the importance of each constraint (Fig. 11).

The algorithm optimises the beam weights to obtain the minimum penalty sum. Often the dose algorithm used is a simplified form of the ultimate dose distribution calculation in order to speed up the calculation process. When the optimal solution is found, the final dose distribution is calculated with the original algorithm. This method is used for treatment plans which are slightly more complicated than conventional planning.

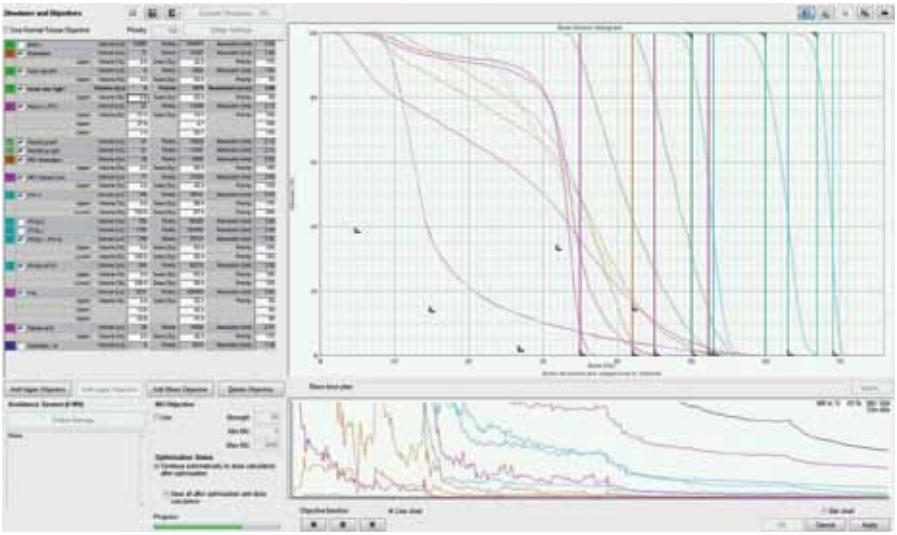


Image courtesy of Department of Radiation Oncology, Rigshospitalet – Copenhagen University Hospital, Copenhagen, Denmark

Figure 11: The optimisation module of a treatment planning system. On the left-hand side is an overview of the constraints used and at the bottom on the right-hand side are the penalties for different organs at risk and the target. The black curve is the sum of all penalties. The penalties decrease when the optimiser finds a better solution.

Inverse planning. In this type of planning, the algorithm finds the optimal solution for beam shapes and beam intensities from scratch, using only the pre-set constraints of the organs at risk and the target (Fig. 11). Here, too, the simplified form of the ultimate dose distribution algorithm is used. Inverse planning is used for two types of delivery technique: static beam IMRT and volumetric modulated arc therapy (VMAT), where the gantry is rotated during dose delivery. Both techniques use a "dynamic" MLC to deliver the desired dose distribution or intensity profiles, meeting the dose constraints of the organs at risk and the target. These intensities are defined by looking through the beam's eye view in one gantry angle, the choice of angle (static beam IMRT) depending on the overlap of organs at risk with the target.

Inverse planning of static beam IMRT entails a pre-set beam arrangement with different gantry angles selected by the user. (Nowadays, algorithms are available to identify these optimal beam angles.) Usually this arrangement consists of five to seven different gantry angles. Two alternative methods of delivery can be used. The first is based on the static MLC. Using this technique, from every gantry angle the intensity profile is delivered by a number of superimposed, partially overlapping, irregularly shaped MLC fields (segments). The technique is also called "step and shoot", the radiation being shut off between segments. In the second method, the "sliding window" technique, the leaves are moving during irradiation, creating an intensity modulation pattern. A different algorithm is needed to calculate the MLC movement in order to deliver the desired intensity. This method induces a smoother and faster dose delivery (Fig. 12 A).

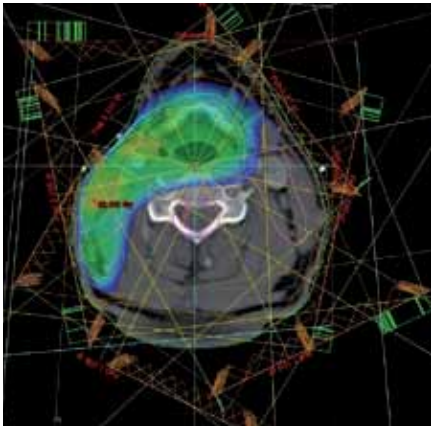


Image courtesy of Department of Radiation Oncology, Rigshospitalet – Copenhagen University Hospital, Copenhagen, Denmark

Figure 12 A: The dose distribution of a "sliding window" IMRT of a head and neck treatment.

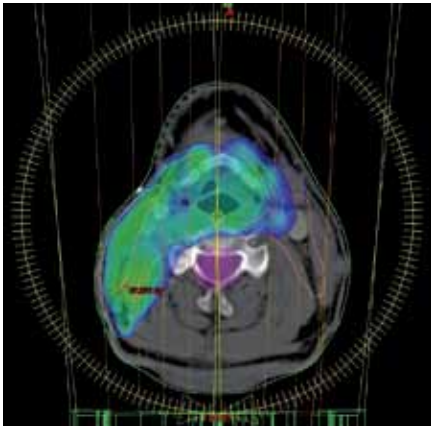


Image courtesy of Department of Radiation Oncology, Rigshospitalet – Copenhagen University Hospital, Copenhagen, Denmark

Figure 12 B: The dose distribution of a VMAT technique of a head and neck treatment.

Inverse planning of dynamic arc IMRT or VMAT was introduced by Otto [11]. The principal idea of the optimisation algorithm is that the arc is divided into multiple static beams (mostly 360°) and the intensity profile of every beam angle is optimised in the same way as for static IMRT. A different algorithm interpolates the intensity or MLC movement from one beam angle to the next. In order to achieve a smooth and fast delivery, an attempt is made to keep the rotational speed of the gantry constant, but the dose rate (delivered dose per minute) is optimised during delivery. At gantry angle intervals where the organs at risk are absent or almost absent in the beam's eye view, the accelerator will deposit more dose by using a higher dose rate. The treatment time using the VMAT technique is reduced by a factor of 1.5–3 compared with static IMRT. The dose distribution is comparable with IMRT (Fig. 12 B).

Stereotactic radiation therapy

Rationale and brief history. In a stereotactic radiosurgery, a single, large dose of radiation is delivered to a small, well-defined, stereotactically localised lesion [12,13]. Key to stereotactic treatments are the requirements regarding accuracy in patient positioning and treatment delivery (which are stricter than for conventional radiation therapy) and tumour size (typically the tumour diameter must be <4 cm since delivery of large doses to large volumes results in unacceptable side-effects).

While the first stereotactic treatments were single-fraction treatments to brain lesions and typically required use of a metal frame fastened to the patient's skull with screws, the past few decades have seen significant changes in the application of the stereotactic technique:

- Delivery of fractionated treatment (this technique is called "stereotactic radiation therapy" and aims to reduce the equivalent dose to the healthy tissue). Fractionation is particularly beneficial when treating lesions close to critical structures such as the brain stem and optic nerves
- Treatment of lesions outside the brain (e.g. lung and liver).
- Frameless fixation. This is less invasive for the patient, and modern frameless techniques result in a positioning accuracy as good as that obtained with traditional frame-based techniques.

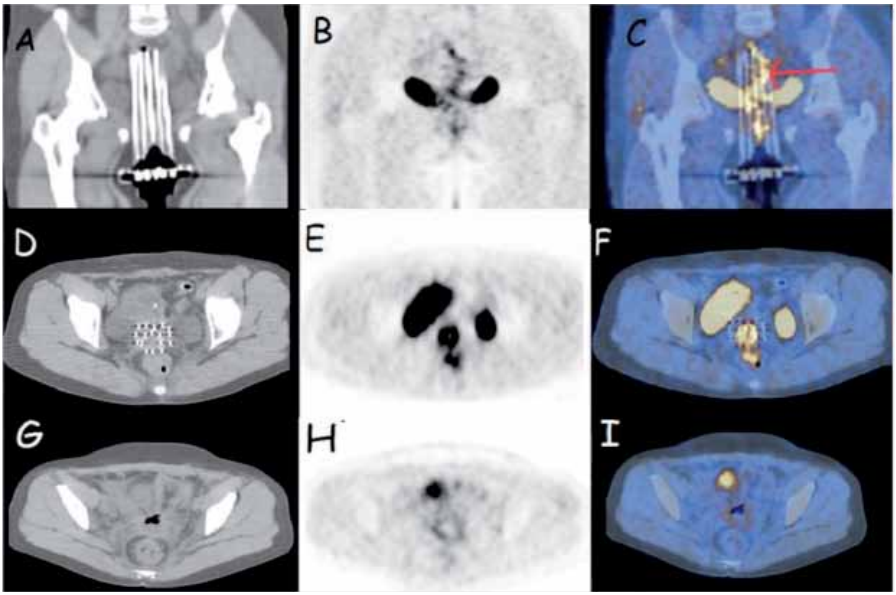
Use of PET data in planning stereotactic treatments. FDG PET imaging of brain tumours suffers from the drawback of significant glucose uptake both in the tumour and in the normal brain tissue. In an attempt to obtain more informative PET images, a range of new PET tracers have been investigated recently. Particularly promising is *O*-(2-[^{18}F] fluoroethyl)-l-tyrosine or FET, which has been found to be superior to FDG for biopsy guidance and treatment planning in patients with cerebral gliomas (although gliomas are not typically treated stereotactically) [14].

Use of PET data to evaluate stereotactic treatments. Co-registered MRI and FDG PET data have been found to be more useful than either modality alone in distinguishing between radiation necrosis and recurrent brain metastasis [15].

Brachytherapy

Use of PET data in treatment planning. No guidelines explicitly recommend the use of PET images in brachytherapy planning, and lack of availability has limited the use of PET in the past. However, with recent research indicating its value, and the emergence of new PET tracers which open up new imaging possibilities, the use of PET in brachytherapy treatment planning is becoming more widespread.

For cervical cancer, several studies have shown that FDG PET has the potential to optimise tumour coverage [16] (Fig. 13). In particular, PET-CT has the potential to show lymph node metastases in both the pelvis and the para-aortic area in patients with advanced cancer.



Images courtesy of Professor S.A. Engelholm, MD DMSc, Head of Department of Radiation Oncology, Rigshospitalet – Copenhagen University Hospital, Copenhagen, Denmark

Figure 13A-I: CT, FDG-PET and PET-CT coronal (A, B and C) and transverse (D, E and F) images of a cervical cancer patient used for brachytherapy treatment planning. The needles (in white) can be clearly identified on the CT images; the bladder (in grey) and the tumour (indicated by the red arrow in C) can be identified on the PET images. CT, FDG-PET and PET-CT (G, H and I) images 8 weeks after completed brachytherapy and external beam radiation therapy. The active area on the PET scan is the bladder. No tumour uptake could be seen.

In contrast, surgical exploration remains the most accurate method of status assessment in patients with early stage disease [17]. PET-CT has also been described as a useful tool in 3D-based adaptive brachytherapy.

For brachytherapy treatments for brain tumours, the picture is more mixed: PET with rubidium-82 has been used to distinguish necrotic tissue from tumour recurrence after interstitial brachytherapy in patients with malignant gliomas [18]. On the other hand, other authors [19] found that while one year after brachytherapy with iodine-125 seeds, the glucose metabolism had not changed, the decline in methionine uptake was significant. A limiting factor in the use of PET scans in brachytherapy treatments of brain tumours has been that both the tumour and the healthy brain tissue display high FDG uptake. However, recently developed PET tracers such as FET [20] may well overcome this limitation.

For liver cancer, only limited work has been reported on the use of PET with brachytherapy. However, PET has been found to play a role in predicting survival after brachytherapy [21].

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Section 3 – PET/CT in Radiotherapy Planning

3.1 Practical Positioning and Immobilisation

Elisabeth Abrahamsson

Introduction

When performing a PET/CT scan, it is of utmost importance that the patient lies still for the entire study. This requires that the patient is positioned as comfortably as possible and is well stabilised. A PET/CT scanning session, even with a modern scanner, will typically take at least 12-15 minutes. The PET images will be attenuation corrected, reconstructed and fused with the CT images; therefore the patient must not move between the two procedures. The PET/CT scan can be used for precise tumour delineation and planning of the radiation therapy, on condition that the patient lies identically during the scanning session and the treatment session.

When the scan is used as the basis for radiation therapy (so-called therapy PET/CT), it demands higher standards of absolute accuracy and reproducibility. Modern radiotherapy offers sophisticated treatment options, such as intensity-modulated radiation therapy (IMRT), dose painting, stereotactic radiotherapy and volumetric-modulated arc therapy (VMAT). These techniques provide an opportunity to tailor the target areas with small margins and thus reduce the dose to radiosensitive organs. Radiation therapy is often delivered in many fractions, or alternatively in a few fractions with a high dose (stereotactic technique).

The position of the patient and the target area is verified prior to the radiation therapy. Image verification of the target position is referred to as image-guided radiation therapy (IGRT). IGRT can be performed with different imaging modalities and at different frequencies, ranging from a single 2D image at the first treatment fraction to daily volumetric imaging. With the more sophisticated IGRT modalities it is possible to achieve very precise verification of the target positioning. Therefore it is very important (and time consuming) to ensure that very careful preparations and precise positioning are performed.

It is absolutely essential that within the department, standards and guidelines exist for the positioning technique and immobilisation options applied for the PET/CT scanner unit and treatment unit accelerators. This is especially important if the PET/CT scanner unit is geographically located in another department. All immobilisation devices must be identical and the documentation must be standardised and unambiguous.

Guidelines must be written or be digitally available, depending on the department's routine. There should be a responsible editor for reviewing, and a quality manager to check that all materials are intact and that the guidelines on positioning and marking are observed. Procedures for the marking routine on the patient depend very much on the local facility.

The department must establish a rationale for how the therapy PET/CT scan can be implemented in the planning process. Different methods can be used, e.g. first a low-dose whole-body PET/CT scan for staging, followed by a diagnostic (full CT dose) therapy PET/CT scan over the target area for planning, or only one diagnostic therapy whole-body PET/CT scan for both staging and planning. With the latter method, unexpected results such as metastases could appear, and the treatment plan could consequently be changed.

The combination of two specialties, nuclear medicine (PET/CT) and radiotherapy, makes the therapy PET/CT scan (see definition below) a multidisciplinary task and places high demands on the involved staff. It is recommended that personnel with professional credentials from each specialty collaborate as a team for this task.

The following sections describe the factors and considerations relevant to positioning and immobilisation of patients for external beam radiation therapy, and provide examples of fixation devices, marking and documentation. The term *"therapy PET/CT scan"* means a scan session with the patient in the treatment position and the scan used for tumour delineation and radiotherapy planning. The patient position is reproducible for the daily set-up at the treatment accelerator.

For further reading, the reader is referred to references 1–4.

Considerations and challenges regarding positioning

Many factors affect the positioning and fixation of a patient. Before performing a therapy PET/CT scan, it is important to investigate and consider what difficulties and special care need to be taken into account for each individual patient. Some examples:

- General health
  The patient may have difficulties in lying down due to pain, dyspnoea, coughing, nausea, agitation, anxiety or claustrophobia. The patient may be demented or mentally disabled.

- Age
  The patient may be a small child needing anaesthesia, a toddler who can only lie still with some support, an adult patient without major problems or an elderly person with reduced mobility.

- Weight
  A very thin patient may have difficulty lying on a hard couch, while an obese patient can be difficult to position or fit in a standard immobilisation device.

- Respiration
  Respiration causes the target area to move. The patient may have difficulties in breathing or breathes irregularly.

- Organ motion
  Varying amounts of content in the stomach, the intestines or the bladder contribute to movement of the internal organs and thus the target.

- Clothes
  The patient may wear different clothes and/or shoes from day to day, or the clothes may be rumpled under the patient.

- Underlay
  Different kinds of blankets, sheets or mattresses may be positioned between the scanner and the treatment equipment, and different kinds of pillow may be used.

- Overlay/couch top bending
  There may be variable bending/flexing of the overlay/couch top at the scanner and the treatment machine. Different geometry!

- Laser light
  The laser light can be out of alignment or varies between the scanner and the treatment equipment.

- Treatment area
  Some anatomical areas are difficult to immobilise, causing the whole process to be complicated and very time consuming.

- Fixation device
  Different standard fixation devices may be used at the scanner and the treatment unit.

- Placement of fixation devices
  Fixation devices may not be placed in the same position when using the PET/CT scanner and the treatment equipment.

- Incorrect positioning
  The patient is not positioned according to the standards of the department or the documentation.

- Documentation
  Information about the patient's positioning or fixation is missing or difficult to interpret.

- Skin marks/tattoos
  Markings or tattoos are missing or hard to see. Previous tattoos enhance the risk of mistakes.

- Staff
  The process is dependent on staff skills, experience and accuracy.

- Environment
  How are the temperature and the lighting in the room? Is the atmosphere pleasant, friendly, trustworthy and professional? Is there enough time?

- Disease progression after the therapy PET/CT scan
  In patients with a fast-growing tumour or progression of lymph node disease, a long interval between the therapy PET/CT scan and the first radiation treatment course may entail changes in the shape of the tumour and the skin surface, and the fixation device may no longer fit.

How is appropriate and identical positioning of the patient achieved at the scan and at the treatment session?

Patient-related factors

Collaboration and communication with the patient. A patient in whom a course of radiation is planned has to participate in a series of studies, investigations and preparations before treatment can begin. This can certainly be stressful, both physically and mentally. Good communication is very important so that the patient is informed about the entire process, verbally and in written form. The simultaneous preparations for a PET/CT scan and for radiotherapy are quite complex, and it is a good idea to have relatives or a friend present at the information session.

The construction of an individually tailored immobilisation device or testing of a standard immobilisation device must always be performed before the patient is injected with the radioactive tracer. In this situation, it is important that patients are provided with detailed factual information to enable them to understand why they must lie in a certain way or why they might be lying with a mask over their face. Patients must also know how long they will have to lie on the scanner couch and what the staff will do to help them. Most patients are very motivated to cope, even in an uncomfortable position or in an unpleasant immobilisation device, when they understand the significance and importance of the demands being placed on them. At this time one can also recognise whether the patient is anxious or claustrophobic.

Safety provision for the patient. The patient should feel safe and secure. Good fixation and positioning means that the patient need not be nervous about incorrect positioning during the scan. The patient often feels calmer if there is something to hold onto, like a grip ring for the hands. This is, however, not always possible during a therapy PET/CT scan.

A similar set-up procedure in the scanner room and later at the treatment unit gives security! Don't hold technical discussions in the presence of the patient, and if this is necessary, explain and try to include the patient.

If possible, offer a call bell so that the patient can ring for help during the scan. Pay particular attention to monitoring of the patient during and after the administration of intravenous contrast. Inform the patient of the audio and visual surveillance.

Comfort provision for the patient. Positioning of the patient and the use of various immobilisation devices are primarily intended to ensure proper treatment, but a further aim is to make the patient as comfortable as possible so that he or she is able to lie still and relax. Very thin patients may have difficulty lying directly on the hard bed. If possible, depending on the target area, "padding" or a mattress should be used, but only if its positioning is reproducible on the treatment couch. Many patients are afraid of falling off the table and need support for this. Ensure that the room temperature is comfortable and that the lighting is not too bright. Take into account privacy when the patient is undressed. Play music in agreement with the patient or an adventure story for children. If possible, inform the patient during the scan session how much longer it will take to complete the scanning sequence.

Health care of the patient. The patient should be palliated for pain before the therapy PET/CT scan: a patient in pain cannot relax properly. Patients who find it difficult to breathe when they lie down can be provided with oxygen during the scan session. If the patient has a tracheostomy, it should be cleaned before scanning if necessary; equipment for this purpose must always be available when scanning patients with a tracheostomy. When a patient has nausea, anti-nausea medication should be considered. In anxious or claustrophobic patients, a thorough explanation of the process is essential and, if possible, the patient should be allowed to inspect the scanner and perhaps have a test run through it. If the patient still thinks it could be a problem to relax, an anti-anxiety medication can be offered in good time before the scan; this need should be clarified before the tracer injection. Analgesic cream or spray for the skin or the mucous membranes may be used when required.

Paediatric care. Paediatric patients range from infants to young adults and their needs are very different. Very small children often need anaesthesia. For toddlers and schoolchildren it is important to explain in detail what will be happening, covering aspects such as noise, lights, smells, how they will feel and whether it will hurt (Fig. 1). Showing the procedure with a teddy or a doll can be a good way to explain the process. It is important to have time and patience, to prepare as much as possible and to collaborate with the parents and staff from the ward. To avoid FDG uptake in the brown fat, which can influence the description of the study, the child should be prepared with warming blankets at least half an hour before injection of the FDG. Alternatively, a beta blocker may be given an hour before the FDG injection. Uptake in brown fat is common up to the age of 20 years, especially in very thin patients. More information on PET/CT radiotherapy planning in children is provided in Sec. 3.3 PET/CT Radiotherapy Planning in Children.

Courtesy of Rigshospitalet, Copenhagen University Hospital

Figure 1: "Rigo" coming to the PET/CT scan – an illustration for paediatric information.

Technical/mechanical-related factors

PET/CT gantry. If possible, a PET/CT scanner with an extra-large gantry opening should be used. Currently a scanner with a 760-mm diameter gantry opening is commercially available. This provides good space for immobilisation devices and for placement of the arms above the head (Fig. 2).

Courtesy of Siemens AG

Figure 2: Siemens Biograph mCT PET/CT scanner.

CT overlay. The usual standard CT top/mattress must be replaced with a flat therapy top, a carbon fibre CT overlay, to achieve the same geometry as at the radiotherapy couch top. The CT overlay must be strong and not sag in the extended PET scan position, be lightweight for easy attachment and be compatible with the entire variety of patient positioning and fixation accessories used in the department (Fig. 3).

Figure 3: Therapy couch top

Immobilisation devices. It should be possible quickly and accurately to transfer an immobilisation device and place it on the CT overlay and the treatment couch. The same standard positioning and fixation system, including pads and other small accessories, should be used at the PET/CT scanner and the treatment unit. The standard fixation system should be used alone or as a supplement to an individually constructed fixation device. Fixation devices should ideally be easy to handle, durable and easy to clean and store. These qualities are especially important when the radiation therapy is given in many fractions. The immobilisation device should also be of a material that gives minimal attenuation for imaging and does not interfere with the skin-sparing benefits of a high-voltage linear accelerator.

Documentation. Description and documentation of the patient's positioning, skin marks and tattoos should start at the construction of the immobilisation device, be continued at the therapy PET/CT scan and be included in the patient's treatment chart.

Instruction and training. Guidelines, optimally in digital version documents, must be available regarding the positioning and use of immobilisation devices. These guidelines must be continually updated, and new staff must be instructed and trained in the department's practice.

Quality control. There must be regular quality control of the PET/CT scanner and the external laser system for alignment.

Coordinate systems and planes

External laser system

An external laser system at the PET/CT scanner is absolutely necessary to achieve precise patient alignment. The coordinate system in the three axes is used for the treatment set-up and to mark the external reference points on the patient's skin and on the immobilisation device. The alignment system is important for reproducing the positioning from the therapy PET/CT scan to the treatment unit and for defining the treatment geometry. Several commercially available laser systems can be used for this purpose (Fig. 4).

Courtesy of LAP IsoMark System

Figure 4: IEC 1217 coordinate system.

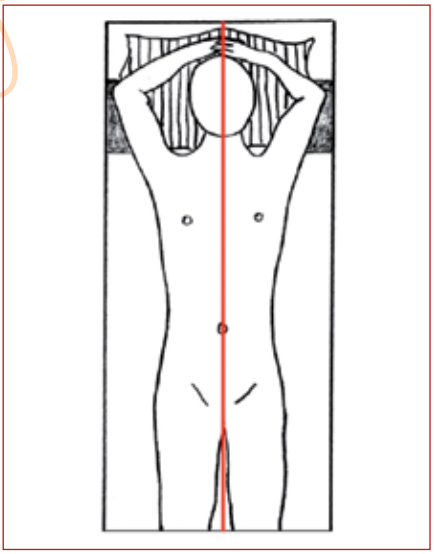


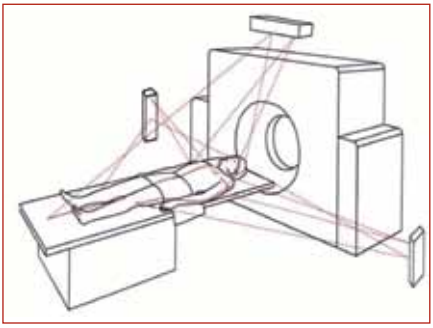
Figure 5: Positioning of the patient exactly in the middle of the longitudinal laser beam

Positioning procedure using an external laser system

- Prepare the overlay with the appropriate fixation materials.
- Prepare the patient and recommend voiding immediately prior to the scan.
- Remove metallic objects, prostheses, clothing and shoes depending on the scanning and target area.
- Position the patient on the couch and check that the patient is properly positioned in the fixation devices:
- Ensure that the patient lies exactly in the middle of the longitudinal laser, which is at 0 mm. Checkpoints are in the supine position: midway between the eyes, the sternum, through the middle of the pubic bone and between the feet (Fig. 5). To avoid errors in rotational isocentre, it is important that the entire patient, and not only the target area, is lying in the middle longitudinal line, and is not twisted or rotated.
- Move the bed with the patient in the full length of the target region.
- Move the bed with the patient in the vertical plane to an appropriate height in the gantry so as to achieve optimal resolution for the scan (Fig. 6).
- Move the mobile laser in the vertical plane (height), to the isocentre of the target region.
- Draw skin marks on the patient and/or place marks on individual immobilisation devices for the three coordinates x, y and z, to define the reference isocentre.
- If warranted by the treatment area, mark different set-up points or alignment points in addition to the above-mentioned reference isocentre.
- Set metal pins on the marks defining the isocentre so that they are visible on the CT scan (Figs. 7 and 8).

- Move the patient into the gantry so that the isocentre position corresponds to the internal scanner laser. Set the length position of the scanner couch to 0.
- Move the patient to the scan start position.

With this method the coordinates for the isocentre are defined in "the target region" based on an estimate and the corrected final isocentre will first be established during the dose planning process.



Courtesy of LAP IsoMark System

Figure 6: Patient positioned with the LAP laser coordinates.

Figure 7: Metal pins and wire for marking

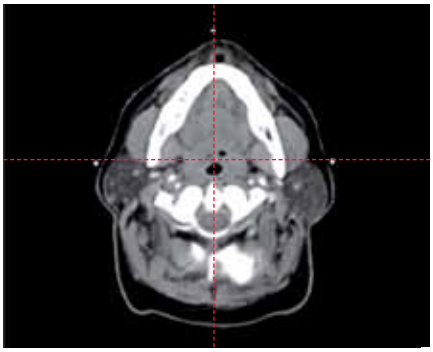


Figure 8: Metal pins defining the isocentre

The isocentre

The isocentre refers to the centre of gantry rotation, i.e. the gantry of the treatment machine (linear accelerator) can rotate 360° around this designated point. By using radiation therapy treatment techniques with two or more fields assigned to the same target, an isocentric technique is usually applied, i.e. the patient and/or the isocentre is at the same position for all the treatment fields. Typically, the distance from the linear accelerator's radiation source focus to the axis of gantry rotation is 100 cm; this distance is referred to as the focus axis distance (FAD) (Fig. 9 A, B)

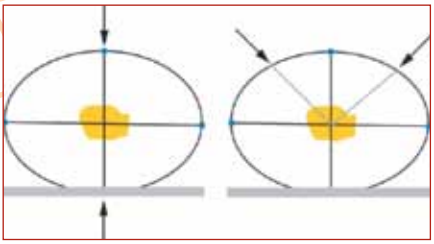


Figure 9 A, B: Examples of the isocentric treatment technique

Marking external reference points

To ensure proper alignment and reproducibility throughout the treatment, it is necessary to have set-up marks on the patient and/or any immobilisation devices. The marks should be established at the time of the therapy PET/CT scan.

Marking the patient

With a good immobilisation device it is not always necessary to use marks on the patient. For example, a good mask as an immobilisation device for treatment in the head and neck area can give sufficient fixation and thus make it unnecessary to mark the patient.

Marks versus tattoos

Marks can be drawn on the patient with a surgical marker or permanent ink. With this method there is always a risk that the marks will disappear or become indistinct during treatment; this risk is especially high when the patient sweats or showers, but loss of marks may even occur with normal wear. If the marks need to be continually redrawn during the treatment period or even before the first treatment, there is a greater risk of "displacement".

A good alternative is small tattoo dots on the skin. The tattoos must be as unobtrusive as possible and be done under hygienic conditions. The patient must be informed of the purpose of the tattoo and of the fact that it is permanent but can be removed surgically or by laser surgery 3 months after the completion of treatment. The tattooing is designed to ensure permanent proper alignment, which is a comfort for many patients as they need not concern themselves with the fact that the marks may disappear. If the patient refuses tattooing, this should always be respected.

One can choose to tattoo at the therapy PET/CT scan session or wait until the first treatment session. This depends on local circumstances and procedure.

For the tattoo, one can use a small blood sample lancet and black ink (Fig. 10a). This gives a very small, tiny and discreet dot in the skin. There are also other tools for tattooing on the market. The tattoo is made with a single quick, small prick in the middle of a drawn and recorded cross (Figs. 10b, 11). After the tattoo, the drawn cross must be removed with an alcohol swab, and it has to be confirmed that the tattoo can be seen. If it is too small, it can be necessary to repeat the tattoo. Tattoos are usually so small and discreet that only the radiation therapy staff knows that they are there. This method eliminates the need to have visible drawings on the skin.

Figure 10A: Tools for the tattooing.

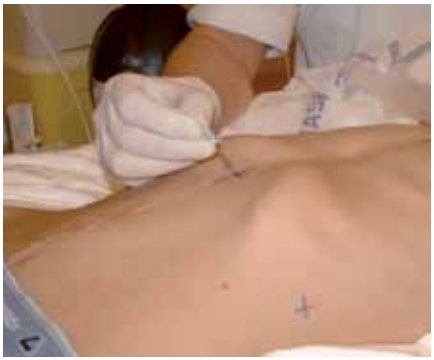


Figure 10B: Tattooing the isocentre

Before the drawn markings or crosses are removed from the patient's skin with an alcohol swab, they need to be photographed and the images inserted in the patient's treatment schedule chart.

It is a good idea for the department to have specific rules on how to perform tattoos. It is not always possible to place skin marks in the relevant area, e.g. in the presence of loose, movable skin or skin folds, in the breast area or in an obese patient. In these circumstances it is important to use reference points as an extension of the isocentre and to place the skin marks in a more suitable area.

An example of tattoos on the chest

Three tattoos at the midpoint of the crosses for location of the reference isocentre

One extra mark within the cross for positioning

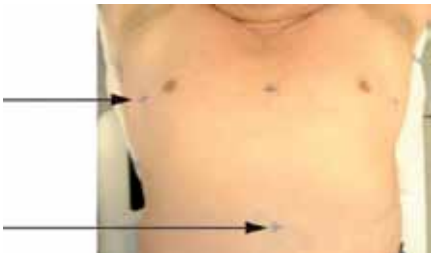


Figure 11

Documentation

It is important that all markings and tattoos are clearly and unambiguously marked. It is helpful to use photographs and colour codes to facilitate understanding of the different marks. In our experience it is always useful to mark the isocentre blue and the reference marks red on the photographs and fixation devices (Fig. 12).

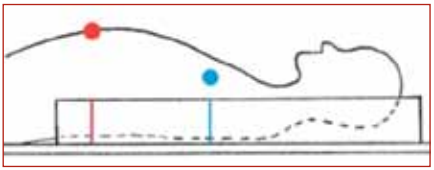


Figure 12 A: Marking of the isocentre (blue) and the reference/alignment marks (red)

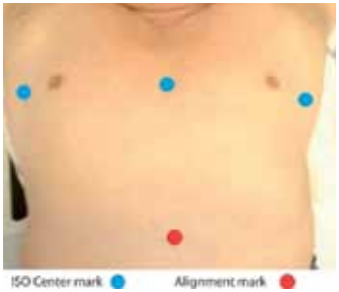


Figure 12 B: An example of tattoos on the chest

Set-up target 1		
Positioning:	Supine	
Arms:	Up	
Fixation:	Standard	
	Knee and feet	F angle 15°

Table 1: Documentation of the patient's positioning

In addition to photographs, details of the patient's positioning must also be documented, including recording of the type of fixation, angle, etc. (Table 1).

The first treatment session

How is use made of the marks from the therapy PET/CT scan? When the patient comes to the first treatment session, he/she will be positioned and aligned according to the same principles as at the therapy PET/CT scan session. The staff at the treatment unit can see in the pretreatment documentation chart which marks are the reference marks and which are the isocentric marks, and will use them for alignment with the laser systems.

Sometimes the reference isocentre from the therapy PET/CT scan is not adequate and the final plan may involve new marking of an isocentre for the treatment. In this case, after the positioning set-up, the couch will be moved in the appropriate direction and the distance (in mm) will be noted in the treatment plan (Table 2). After image verification of the new set-up, the staff at the treatment unit may, if necessary, apply some new marks/tattoos for subsequent treatment purposes. This must be clearly documented.

Couch adjustments – from reference to treatment	+/-
x (lateral)	mm
y (vertical)	mm
z (longitudinal)	mm
Couch reference height	mm

Table 2: Documentation of couch adjustments

Hospitals and departments throughout the world have different procedures for handling such changes. In some departments, designated alignment points are established at the first treatment session and the final marks for the isocentre are made at this time.

Today, several systems are available to the treatment unit for image guidance and target verification at the initial set-up and for target verification and automatic positioning during the treatment. A relatively simple system is the Electronic Portal Imaging Device (EPID), which uses the treatment beam for imaging. IGRT modalities using X-rays of diagnostic quality can either be gantry mounted and orthogonal to the treatment beam (e.g. On Board Imager from Varian), or stand alone but be fixed in the room (e.g. ExacTrac from BrainLab). In addition to planar 2D images, gantry-mounted IGRT devices can produce volumetric 3D images, referred to as cone beam CT (CBCT). In contrast to 2D imaging, CBCT provides soft tissue information as well.

All image guidance is performed with the patient on the treatment couch in the treatment position.

Positioning for head and neck treatment

Radiation treatment of the head and neck area is usually given as fractionated radiation therapy (a number of treatments) to achieve better tumour control and decrease the risk of side-effects. It is often necessary with small margins to avoid radiation of radiosensitive tissues, such as the eyes or the spinal cord.

This type of treatment requires experienced staff to position and immobilise the patient in order to make the treatment as accurate as possible. A secure means of immobilisation in this region is use of an individually tailored mask over the face and head. A piece of perforated thermoplastic material is softened in a hot water bath. After softening it should immediately be stretched and moulded over the patient's external surface, and after about 10 minutes it is hardened. The mask must not be stretched too much as this will make it weaker. The mask will keep its form unless warmed again. The face mask is not uncomfortable to wear as it has a coating to prevent it sticking to the skin or hair (Fig. 13).

The face mask is attached to a base plate of carbon fibre, positioned on top of the CT overlay plate. The best fixation is achieved if the mask not only covers the face and neck but extends from the skull and includes the shoulders. This is especially important in preventing shoulder retraction if the patient has a short neck. It should be possible to release the mask quickly in cases of emergency, vomiting, coughing etc.

Many accessories can be applied on the base plate. A head support should be provided to ensure correct angulation of the head and sometimes the head or chest needs to be elevated. The mask covers the entire face and usually has no openings. However, it is possible to make holes for the eyes, nose or mouth if needed. When treating oral cavity cancer, nasal cavity cancer, or jaw cancer, the patient may need to lie with the mouth open to reduce the dose to the oral mucosa, the lips or the teeth. To keep the mouth open, the patient receives a bite block in the mouth.

Courtesy of CIVCO Medical Solutions

Courtesy of CIVCO Medical Solutions

Figure 13a: Thermoplastic in hot water bath. Figure 13b: The mask is moulded over the patient's head. Figure 13c: Patient with a headrest and a mask on a baseplate.

An extra airway can be placed through the device, which is of value since many patients find it difficult to breathe through the nose. Sometimes a bite block is used to push the tongue up or down in the oral cavity to avoid it being irradiated.

When irradiating the nose, the nostrils often need to be filled with wax or similar tissue-equivalent material to ensure delivery of the full dose to the skin surface. It is important for the dose calculation that this measure is taken before performing the therapy PET/CT scan.

Similarly, if the patient has a tumour that is near to or on the skin surface, it can be necessary to increase the skin dose. Photon irradiation with high energy has a skin-sparing effect so that the highest dose is delivered just under the skin. By placing a bolus material of wax, flab (fat) or other tissue-equivalent material on the skin, it can be ensured that the tumour surface will receive the full dose. The bolus material must be correctly placed and fit tightly; again, very importantly, *it must be in place* before performance of the therapy PET/CT scan.

For treatment of the mouth and neck region, all dentures and dental bridges must be removed and the patient must have a thorough dental examination before the therapy PET/CT scan. The patient must lie straight in the supine position, arms down along the side, and normally in a horizontal plane and with a head support that fits.

For treatment in the neck region, all clothing on the upper body must be removed and it must be confirmed that the patient is positioned in the standard position in the middle of the longitudinal laser plane, starting from the top of the head and proceeding to the toes.

Since the CT overlay of carbon fibre is very hard, it can be a good idea to put a thin mattress in the extension of the base plate. A standard knee fix cushion should be used (Fig. 14).

Courtesy of CIVCO Medical Solutions

Figure 14A: Different models of headrests.

Courtesy of CIVCO Medical Solutions

Figure 14B: Knee fix cushion.

Positioning for treatment of the thoracic and the upper abdominal region

The most common diseases irradiated in this region are breast cancer, oesophageal cancer, stomach cancer, lymphomas and lung cancer. A breast board of carbon fibre, with arm supports, various headrests and an angulation system for individual set-up, is a good choice for immobilisation in this area. Such a board is especially effective for breast cancer. Many kinds of fixation device are commercially available for this purpose (Fig. 15).

Courtesy of CIVCO Medical Solutions

Figure 15: Breast board.

For all radiation treatments it is important that the patient is positioned in a standard supine position with the entire body straight through the longitudinal laser plane from head to feet. Except for breast cancer (where often only one arm is raised), the arms are raised above the head or placed down beside the body, depending on the target area. The patient must not be wearing any clothing on the upper body. The chin must be raised if submental, submandibular and neck lymph nodes are to be included within the target area. For comfort and stability, a knee cushion should be used. Fixation may be achieved with a standard immobilisation device that can be adjusted according to the needs of the individual case, or one can create a customised immobilisation device using a vacuum cushion, i.e. a plastic bag filled with small polystyrene beads (Fig. 16). The cushion is shaped around the patient's body so that it matches exactly the patient's contour, and air is then evacuated from the cushion. The cushion retains its shape until the vacuum is broken. If the construction of the immobilisation device is not successful or the patient does not feel comfortable, the device can be altered before the therapy PET/CT scan. To ensure correct placement of the vacuum cushion, it can be positioned over a shell of Styrofoam or other material with minimal scanner attenuation. Vacuum cushions can be cleaned and re-used many times and are both environmentally friendly and inexpensive. A disadvantage is that vacuum devices require a lot of storage space. ISO centre and alignment marks should not be drawn directly on the vacuum cushion surface, as it will be recycled; instead removable tape should be used.

It is generally routine for the patient to be asked to breathe normally during the therapy PET/CT scan, as well as during the treatment sessions. However, for breast cancer and lung cancer it is optimal to irradiate with respiratory gating to minimise the normal lung tissue dose. This can be performed as a gated PET acquisition or an additional 4D CT scan.

Patients with tumours in the stomach should fast and are asked to drink two glasses of water immediately before the therapy PET/CT scan. It is important to *repeat the same procedure exactly* (fasting and water) every day before radiation treatment so as to ensure that the stomach has the same size every time.

When using FDG as the PET tracer, all patients are required to fast before tracer injection and the therapy PET/CT scan. It is important that the patient tries to achieve the same anatomical conditions every day, for example by avoiding consumption of a large meal prior to the radiation treatment.

The standard treatment for lymphoma has recently been changed at our facility, especially for Hodgkin's lymphoma. Patients who previously had large radiation fields, so-called mantle fields, will today be treated with chemotherapy. After chemotherapy an additional radiation treatment can be given to a limited area of disease. These areas must be prescribed from the *pre-chemotherapy PET/CT scan*, and it is therefore important that at the first PET/CT scan for staging, the patient is scanned in the therapy position with the correct immobilisation device. This scan will be used for delineation and planning of the radiation treatment and with this method one can compare and define the target areas more precisely.

Figure 16: Vacuum cushion for fixation

Positioning for treatment of the lower abdomen and pelvic region

The most common diseases which are irradiated in the lower abdomen and pelvic region are gynecological, colorectal and prostate cancer.

The patient should not wear trousers or any clothes which can tighten or pull the skin. The patient should void the bladder immediately before the therapy PET/CT scan and before every treatment. The patient can be positioned prone or supine. For irradiation of colorectal and anal cancer, patients are often immobilised in a prone position, which allows for a reduction in the skin build-up effect from the high-voltage accelerator when using simple treatment techniques. For the prone position a commercial "belly board" can be used or an individually tailored immobilisation device can be constructed. However, the reproducibility of the prone position is often questioned; many elderly patients find it difficult to lie in a prone position, and the prone immobilisation of obese or very thin patients is very uncertain. In these cases, it is more secure and reproducible to position the patient in a supine position. Furthermore, the introduction of VMAT treatments means that the prone position is no longer relevant. The patient should lie straight in the standard position, with the longitudinal laser through the head to the feet and with the arms lifted above the head (Fig. 17). A standard pillow can be used, but it is important that this type of head support will not change its shape and that the same type of pillow is used throughout the department. The knees and feet need to be immobilised when the pelvic area is to be treated. An individual immobilisation device can be constructed or a commercially available device for fixation of the knees and feet can be used (Fig. 18). Whichever type of devise is chosen, it must have an option for individual adjustment and can be reproduced on the therapy PET/CT and the treatment couch. Documentation regarding the positioning must be reported.

As the patient is fasting for the ^{18}F-FDG scan, he or she should not consume a large meal before the treatment session. It is not possible to avoid organ motion in the intestinal region, but one should aim to achieve the most consistent situation possible. Light respiration is preferable.

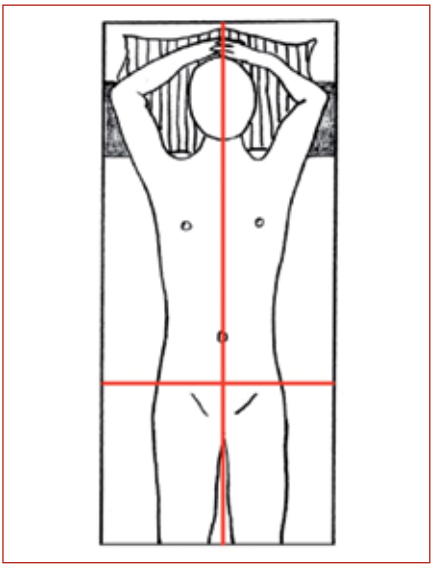


Figure 17: Patient in the standard position, with the isocentre in the pelvic region

Courtesy of CIVCO Medical Solutions

Figure 18: Fixation system for the knees and feet.

Paediatric positioning

Children range from babies to teenagers; they have different body sizes and different needs and therefore individualised approaches are required. The basic rules regarding positioning and immobilisation are also applicable to children. It is, however, often necessary to scan and irradiate smaller children under anaesthesia in order to achieve absolute accuracy. The safest immobilisation method is a thermoplastic mask covering a large part of the body. A vacuum pillow can be used as a base for the mask or, rarely, can be used alone. Dealing with children requires preparation, time and patience. Often it is a good idea to let the parents be a part of the process and be allowed in the scanner room (but sometimes this is not the case!). Older children and teens often prefer not to have their parents with them. It is important the parents understand the purpose and importance of markings and tattoos.

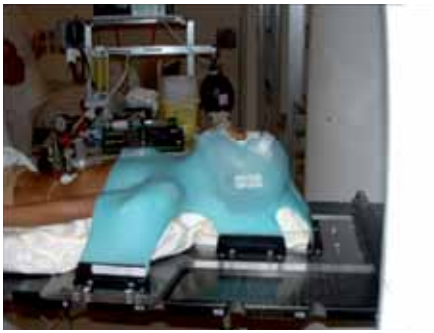


Figure 19 A, B: Child with a thermoplastic mask fixation

Figure 20: Child positioned in a vacuum pillow fixation

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3.2 Use of PET/CT in Radiotherapy Planning

Anne Kiil Berthelsen and Annika Loft

Fifty percent of patients diagnosed with cancer in the Western world will receive radiotherapy as part of their treatment [1]. Many patients can be cured by radiotherapy and others will be relieved of the symptoms caused by their malignant disease. Compared with surgery, chemotherapy and immunotherapy, radiotherapy is an inexpensive treatment method [1].

Correct target definition with inclusion of both macroscopic and microscopic disease in the target volume and sparing of as much normal tissue as possible is the main challenge in curative radiotherapy, particularly with highly conformal treatment methods. Modern radiotherapy techniques such as intensity-modulated radiotherapy (IMRT), intensity-modulated arc therapy (IMAT) and cranial/extracranial stereotactic radiotherapy (SRT) demand even more precise tumour definition and delineation. The aim is to define the tumour in all three dimensions as precisely as possible. If the defined tumour volume is too small, some of the malignant tissue might not be irradiated. If, on the other hand, it is too large, a higher radiation dose will be delivered to the normal tissue, increasing the risk of complications.

The use of PET/CT in radiotherapy planning for cancer patients has increased rapidly since it was introduced in 2001. Today, PET/CT is used for various clinical purposes, including diagnosis, staging, follow-up, and planning of radiotherapy, as well as for research. For many tumours, FDG PET has been shown to be superior to CT in detecting malignant tissue. Target delineation by PET/CT is now used for most patients with head and neck cancer, lung cancer, oesophageal cancer, stomach cancer, colorectal cancer, anal cancer, cervical cancer, lymphoma and sarcoma. FDG is the most commonly used tracer for this purpose.

It is mandatory that the PET/CT scan is carried out in the exact treatment position, e.g. with confirmation of the correct position using an external laser positioning system. A flat table-top should be used with the patient carefully positioned in an immobilisation device. At our institution, we prefer to use a scanner with a large gantry opening (preferably 78 cm).

The therapy FDG PET/CT scan is very similar to a clinical FDG PET/CT scan. The patient should fast for a minimum of 6 h prior to FDG injection; thereafter the patient must remain physically still, typically for 60 min. If it is needed for the CT scan, oral contrast can be given during this time.

The most crucial part of the procedure is positioning. The patient is positioned on the couch or table and immobilised in a fixation device, often individually produced prior to the scan. Intravenous contrast is very important for delineation of the tumour and the

at-risk organs and may be administered automatically via an i.v. injection pump. Only currently accepted contraindications to intravenous contrast media should exclude its use.

The scanner that we use operates in 3D mode and data are reconstructed using AW-OSEM (attenuation-weighted ordered subsets expectation maximisation) with the CT data used for attenuation correction of the PET data. The PET data are reconstructed into 2-mm image slices in three planes. The CT scan is reconstructed with a 2-mm slice thickness and PET images are matched. The CT rotation speed is 0.5 s and the mAs is regulated dynamically using DoseCare (Siemens mCT). The patient must remain in the same position during CT and PET scanning so that correct fusion of the images can be automatically applied at the workstation.

After the scanning, the patient's isocentre alignment marks should be tattooed on the patient's skin or permanently marked on the immobilisation device so that the exact body positioning can be reproduced at subsequent treatment sessions.

Whole-body scans are always performed for radiotherapy planning owing to the possibility of detection of unknown metastatic disease or new primary cancers which may change the treatment planning.

The treatment planning process is carried out as effectively as possible (so that there is a short period between the scan and the start of treatment) by an interdisciplinary team of qualified staff including mould technicians, nuclear medicine physicians and technologists, radiologists and radiation technologists, radiation oncologists, physicists, and dosimetrists.

The process starts with a thorough interpretation of the PET/CT scan, optimally done by a nuclear medicine physician together with a radiologist. At this time, any PET-positive tumour(s) are identified, the gross tumour volume (GTV) is drawn, and the CT scan with the PET-defined regions of interest is then transferred to the RT dose planning system (Fig. 1 and Fig. 2, blue lines). A radiologist and a radiation oncologist may then define the final GTV – a process involving clinical information gained by physical examination, previous imaging studies (e.g. previous CT, MRI, ultrasound), and information from invasive diagnostic methods including surgery or laboratory findings (Fig. 2, red lines).

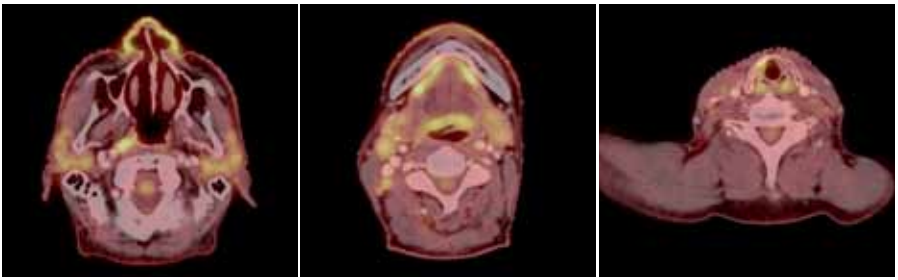

Figure 1 A–C: Transaxial fused PET/CT images of a patient with nasopharygeal cancer with lymph node metastases. Note the small lymph nodes of 4 mm defined by PET

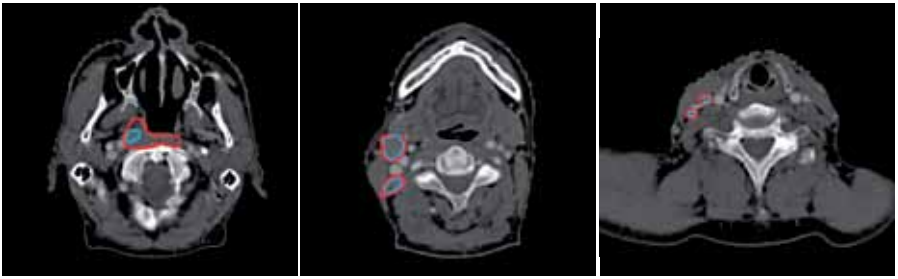

Figure 2 A–C: Transaxial CT images (same as above) showing the GTV delineated on PET/CT (GTV PET, blue lines) and the final GTV (red lines).

The oncologist then adds clinical target volumes (CTVs), which are areas potentially containing microscopic disease. These areas are irradiated with a lower dose than the GTV. Several CTVs receiving different doses for macroscopic and microscopic disease are commonly used in, for example, the head and neck area.

Movement of the tumour within the body, e.g. due to respiration, is also included by adding another volume, the internal target volume (ITV). This is also defined by the oncologist. The dosimetrist adds margins compensating for set-up uncertainty and movement during treatment, yielding the planning target volume (PTV).

Finally, organs at risk (eyes, spinal cord, kidneys etc.) are delineated. The dose plan is calculated by dosimetrists and physicists in collaboration and at this point the patient's treatment can be commenced (Fig. 3).

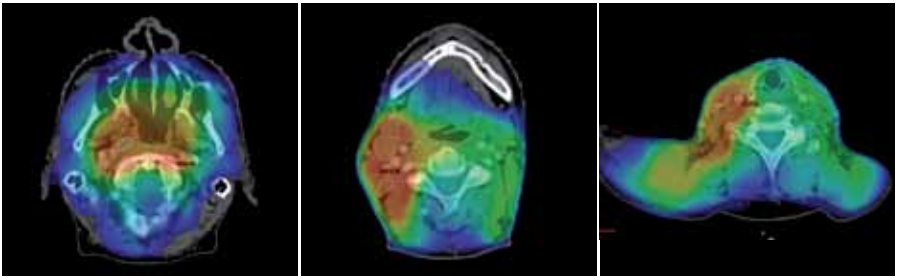

Figure 3 A–C: Dose plan

Our institution's method of target definition, which involves a nuclear medicine physician performing the tumour delineation, the PET-GTV, together with a radiologist and, subsequently, a radiologist delineating the final GTV in collaboration with a radiation oncologist, is working very well. The radiation oncologist's confidence level regarding target determination is greatly increased when CTVs are defined (after GTV definition) together with the radiologist, as compared with independent delineation of all volumes. We also feel that this form of teamwork makes the target definition more exact. We base our target definition on the visual assessment of PET/CT in order to ensure inclusion of PET-negative tumours, at risk of being excluded with target definition based on standardised uptake volume (SUV), and also to obtain anatomical correlations with the FDG uptake.

The many important advantages and positive clinical implications of PET/CT scanning for radiotherapy dose planning are: (a) improved definition of the primary tumour; (b) detection of existing regional lymph node metastases prior to radiotherapy; and (c) the fact that whole-body PET/CT scanning yields findings that change the intended treatment in up to 30% of patients [2]. This significant impact may be related to the previous crude definition of a CT-visible lymph node below 1 cm in diameter as non-malignant. PET/CT studies have demonstrated that lymph nodes below 1 cm in diameter can be PET-positive and may contain metastases [3,4]. Several studies have shown improved conformity in target definition when using PET/CT instead of CT alone [5–7].

In our effort to improve PET/CT imaging techniques for radiotherapy dose planning, we use high-quality CT with i.v. and oral contrast media and a slice thickness of 2 mm. Some PET centres perform the PET/CT scans with low-dose CT.

This type of scan cannot be used for radiotherapy planning, as low-dose CT does not allow precise tumour delineation or definition of organs at risk.

Use of PET/CT for radiotherapy planning will, most likely, soon be required to substitute for CT scans for treatment techniques like IMRT, IMAT, SRT and also proton therapy. PET/CT frequently leads to modifications in the previously defined tumour size and staging (regional and distant metastases) and may disclose other synchronous malignancy. This sometimes leads to a change in treatment modality with, for instance, addition of concomitant chemotherapy or surgery, cancellation of radiotherapy or even a switch to other treatment strategies. A number of studies have also reported on the detection of synchronous cancers when using whole-body PET/CT for radiotherapy planning [8,9].

New tracers, e.g. for prostate cancer and brain tumours, will undoubtedly increase the use of PET/CT for radiotherapy planning. Another factor that will further increase the use of PET/CT is the ability of new tracers to deliver information on prognostic parameters such as hypoxia and tumour cell proliferation [10,11]. We believe that it is of great importance to find new tracers for inherent tumour radiosensitivity, which seems to be a significant prognostic factor for local control in carcinoma of the cervix and head and neck cancers, as previously described [12,13].

We are convinced that the close, but logistically demanding, collaboration among nuclear medicine physicians, radiologists and radiation oncologists will prove cost-effective when compared with single-expert decisions. Such a joint approach allows the radiation oncologist to focus on the crucial definition of correct and precise CTVs.

Whole-body FDG PET/CT scanning for radiotherapy planning will soon become state of the art, as supported by the IAEA expert report 2006–2007 [2]. The potential benefit for patient survival remains to be documented. However, performance of a controlled study on radical radiation therapy with up-front techniques comparing treatment results in groups of better and less accurately staged patients may present ethical problems.

References Section 3.2

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3.3 PET/CT Radiotherapy Planning in Children

Charlotte Birk Christensen, Lise Borgwardt, Annika Loft and Anne Kiil Berthelsen

PET/CT is increasingly being used in the planning of radiotherapy with a curative intent and to a much lesser extent within the palliative setting, as described elsewhere in this guide.

Guidelines or recommendations for radiotherapy planning with PET/CT in adults have been outlined [1,2], but to date no guidelines are available for paediatric treatment planning. The use of PET technology in the radiotherapy setting in children is far from widespread, so very little information is available regarding paediatric protocols. To a certain extent it is possible to transfer the knowledge obtained from adult protocols to the paediatric setting, but it is crucial that the use of PET/CT for radiotherapy planning in children is performed using scanning protocols designed for the paediatric patient. Differences in cancer pathogenesis and in vulnerability to radiotherapy and the resulting late side-effects are specific to the paediatric patient. Generally, relatively few children require radiotherapy treatment planning in each institution.

The overall survival rate in paediatric malignancy is about 75% and it is therefore essential to consider the long-term effects when planning the child's treatment regimen. Treating children with radiotherapy inevitably involves irradiation of healthy tissue – sometimes of a substantial volume. Depending on the site of the tumour, this may lead to a significantly increased risk of late side-effects, e.g. secondary cancers, and equally important, impairment of the patient's quality of life. Reduced cognitive function, loss of hearing/vision, growth retardation, hypothyroidism, loss of reproductive function, or even fatal heart and lung complications can all be treatment side-effects [3]. Use of PET/CT in the planning of radiotherapy potentially allows the reduction of late side-effects without compromising tumour control through improved tumour/target delineation and may permit delivery of a modified radiotherapy dosage based on metabolic response [4].

In this chapter we shall focus on the use of PET/CT in radiotherapy planning in children with both solid and haematological cancers, discussing patient preparation, sedation and the various diagnostic groups that seem to benefit from PET/CT-based radiotherapy planning [5,6].

It is essential to display patience, flexibility and empathy when working with children and equally with their parents. The parents are often more concerned than the child being treated, and a well-informed and reassured parent can positively affect their child/your patient and provide a safe and secure ambience. Often, several different professional groups and departments are involved in the scanning procedure, i.e. technologists, nurses, physicians and sometimes anaesthetists. Informative and continuous communication and a well-structured, organised environment are basic requirements for an examination at all times, but especially when the patient is a child.

Pre-examination procedures

Information

The child and parents should be given a thorough explanation of the scan – including both scanning principles and scanning technique. This information should be given in advance, in writing, and again verbally at the scan session to ensure relaxed compliance and thus reduced anxiety in both the child and the parents.

The pre-examination procedure also covers moulding of foams and other immobilisation devices according to the treatment, and considerations concerning need for anaesthesia and/or premedication (see also "Immobilisation devices", Sec. 3.1. Practical Positioning and Immobilisation).

The prescribing physician should assess the need for premedication with either beta-blockers (β_3-antagonist) or benzodiazepines in order to prevent undesirable activation of brown fat tissue. Brown fat activation is seen especially in older children and can cause difficulties in PET interpretation. In some institutions, premedication with a beta-blocker or benzodiazepine is standard procedure in the clinic when conducting a paediatric PET/CT scan and is not reserved only for PET/CT scans performed in the radiotherapy planning setting. In our experience, in some cases it is possible to reduce activated brown fat tissue by keeping the child warm for half an hour before tracer injection by use of extra blankets and clothing.

It is recommendable that the patient has an i.v. access before arriving at the PET facility. In selected cases with difficulties in establishing an i.v. access, use of a previously placed central venous catheter for tracer injection is acceptable as long as the suspected site/sites of disease are distant from the catheter line and the catheter is well flushed after tracer injection with an isotonic saline solution.

Patient preparation

Fasting. Children should fast for 6 h (4 h for infants) prior to an FDG scan. Children undergoing general anaesthesia or sedation should also fast for 6 h following intake of a meal, for 4 h following breast feeding and for 2 h following water intake. Children not having anaesthesia or sedation should drink water to maintain good hydration and reduce radiation exposure of the bladder. Infants not having anaesthesia or sedation should be injected with the tracer as close to the next meal as possible. A meal may be given 30 min after tracer injection at the earliest.

Tracer injection. ^{18}F-FDG is injected intravenously 1 h before the PET scan. Paediatric dosage is frequently calculated as 3 MBq/kg. The patient should be kept warm and avoid exercising, talking or chewing gum during the FDG uptake period.

PET/CT

PET/CT scan of a child in the radiotherapy planning setting is basically performed in the same way as with adults, utilising the ALARA principles regarding both the FDG dosage and the CT scan, with application of available optimisation procedures.

A flat table top and fixation materials which are identical to those used at the accelerator should be employed for the PET/CT scan (see also Sec. 3.1.). Distraction with music or taped storytelling can be helpful in aiding the immobilisation of the child. Any diapers should be changed immediately prior to the scan.

Indications for PET/CT radiotherapy planning

As stated above, there are currently no official guidelines on the use of PET/CT in the radiotherapy planning setting for paediatric malignancies. Taking into consideration the increasing evidence that use of PET/CT in radiotherapy planning is beneficial in adults with malignancies, it is most likely that use of PET/CT in radiotherapy planning for paediatric malignancies will soon follow. However, the special radiation hygiene requirements of the paediatric patient should always be taken into consideration. Since 2003, our institution has routinely used PET/CT in the radiotherapy planning regimen. Below, we shall outline our experiences and practices. PET/CT for radiotherapy planning of brain tumours will be addressed in Sec. 3.4. PET/CT-Based Radiotherapy Planning in Brain Malignancies.

The referring paediatrician consults the radiation oncologist when a child is a candidate for radiotherapy as part of their primary treatment or, as is more often the case, part of the postoperative/post-chemotherapy treatment. A PET/CT scan can be considered when the tumour type is known to be FDG avid and metabolic mapping of the disease can provide additional information to that acquired with CT and/or MRI scan. The potential advantages of using a PET scan are: (a) more accurate definition of the primary tumour, (b) detection of non-enlarged but involved lymph nodes and (c) improved conformity in target definition. Together, these benefits can potentially result in increased tumour control and decreased incidental irradiation of healthy tissues, thereby decreasing adverse side-effects.

Tumour delineation

In all settings the scan is interpreted by a nuclear medicine physician and an oncology radiologist in consensus to delineate the gross tumour volume (GTV-PET). The contouring is done by the nuclear medicine physician by visual analysis as no accepted iso-contouring procedure or activity cut-off value is available at the moment. After delineation of the GTV-PET, the volumes and the associated CT scan are transferred to the dose planning system at the Department of Radiotherapy, where the final treatment plans are decided (Fig. 1).

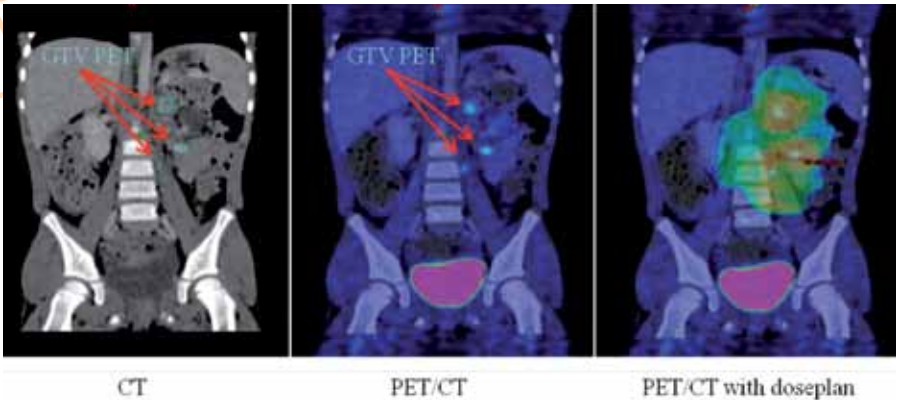

Figure 1: Example of PET/CT-based radiotherapy planning of a paediatric tumour (sarcoma). The identification of the tumour is difficult on the CT scan (left), while PET shows a few FDG-avid regions in the abdomen (delineated using a blue curve). These regions, and a margin deemed sufficient, are included in the subsequent radiation therapy plan showing the dose distribution in temperature scale/colourwash (right).

Hodgkin's lymphoma

This is the most frequent indication for PET/CT radiotherapy planning in children. A baseline staging PET/CT is performed on a flat table top with the patient in the treatment position, followed by a conventional PET scan after two and four cycles of systemic chemotherapy. If additional irradiation is indicated, i.e. when there is continued FDG avidity after two cycles of chemotherapy, a radiotherapy planning PET/CT on a flat table top, again with the patient in the treatment position, is performed. The baseline and the radiotherapy planning scans, including their GTV-PETs, are fused. The final GTV is modified according to shrinkage and FDG avidity of the tumour due to treatment [7].

Nasopharyngeal carcinoma

A similar approach is used in children with nasopharyngeal carcinoma, and may be supplemented with pre-chemotherapy MRI. In these patients the final GTV is modified according to the actual anatomy.

Other solid tumours

This group consists primarily of patients with bone and soft tissue sarcomas, Wilms' tumour and neuroblastomas. A PET/CT radiotherapy planning scan is performed and the GTV-PET is delineated from this examination. In some situations, especially for palliative treatment of solid tumours, an initial PET/CT scan may be digitally fused with the actual CT radiotherapy planning scan.

Conclusion

The integration of PET/CT in radiotherapy planning provides additional information that opens new perspectives for the optimisation of the treatment of paediatric haematological and solid tumours, especially concerning minimisation of radiation to organs at risk and subsequent reduction of the risk of secondary cancer and of late side-effects affecting quality of life.

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Section 3 – PET/CT in Radiotherapy Planning

3.4 PET/CT-Based Radiotherapy Planning in Brain Malignancies

Irina Götz and Timo S. Spehl

Radiotherapy in the brain: What are the primary targets?

The most common group of intracranial tumour masses are metastases of peripheral tumours, mostly lung, breast and renal carcinomas and melanomas; such metastases account for approximately 30-40% of all detected cerebral lesions [1]. Brain metastases can be found in ca. 20% of all patients with lung cancer, as well as in 7% of all patients suffering from melanoma or renal cancer and 5% of all patients with breast cancer [2].

The remaining ca. 60% of lesions comprise a heterogeneous group of various types of primary tumour of the brain, which develop mostly from glial cells and virtually never metastasise. Primary brain tumours are commonly graded into four categories (according to WHO criteria), ranging from I (benign) to IV (very aggressive). The most frequent primary brain tumour, accounting for 20% of all intracranial tumours [1], is glioblastoma multiforme (WHO grade IV), which has a very poor prognosis. One example of a benign brain tumour is meningioma (WHO grade I-II), which originates from the arachnoid "cap" cells in the arachnoid villi in the meninges. Meningiomas generally do not infiltrate the brain tissue, but, depending on their size and location, they can lead to pressure-related neurological symptoms.

Radiation therapy is, alongside neurosurgery and chemotherapy, an integral part of the therapy for brain tumours. Problematic locations mean that not every tumour can be completely removed by surgery without residual neurological deficits. In such cases, primary radiation therapy is a promising option. On the other hand, in most cases, tumour cells that are not visible during the operation can infiltrate the margins of healthy brain around the tumour, so that adjuvant radiation to prevent recurrence is mandatory. Only a few chemotherapeutic agents can penetrate the blood-brain barrier (BBB) in sufficient amounts to achieve a therapeutically effective concentration in the tumour.

Why is exact delineation of healthy and tumour tissue so important?

For effective tumour control, it is often necessary to administer high doses of radiation to the tumour. Simultaneously, the neighbouring structures must be spared from radiation damage. With recent technical advances in radiation therapy such as intensity-modulated radiation therapy (IMRT), this goal is becoming more and more feasible. Thus, at the same time, very sensitive and specific diagnostic methods are required to enable exact tumour delineation.

Standard morphological imaging methods like computed tomography (CT) and magnetic resonance imaging (MRI), enhanced with contrast agents, have been employed with great success over the years. Particularly MRI, with its unequalled spatial resolution and accuracy, is irreplaceable in radiation therapy planning. However, it is not tumour specific. Diagnostic criteria in MRI-based tumour imaging are generally the extent of contrast enhancement, which is representative of the breakdown of the BBB [3].

A disruption of the BBB can also occur as a result of recent operations or radiation therapy. Additionally, there are sometimes large tumour parts where the BBB is not yet affected, and that show no secondary tumour features such as cerebral oedema and compression of other brain structures. In these cases, the contrast enhancement in T1-weighted MRI sequences underestimates the tumour mass and these parts consequently escape sufficient therapy. Another diagnostic challenge arises in cases of recurrence, which is common in higher grade brain tumours but also occurs in 9% of WHO grade I meningiomas after surgical resection [4]. Often, post-therapeutic changes, which can develop over a long time span, are visible on MRI/CT. In cases of contrast enhancement, it is frequently impossible to differentiate between post-therapeutic changes and true tumour recurrence. Morphological changes on MRI that resemble tumour progression but cannot be confirmed as such by histology or clinical course are described as pseudo-progression. There is, however, also a phenomenon called pseudo-response, when medication such as steroids or VEGF inhibitors lead to a reconstitution of the BBB. Contrast enhancement then decreases on MRI, but the actual tumour mass remains unaffected or even grows larger [5].

Common PET tracers in neuro-oncology applications

The PET tracers most frequently used to detect (malignant) brain tumours are radiolabelled amino acids such as ^{11}C-methionine (MET) and ^{18}F-fluoroethyl-L-tyrosine (FET). These amino acids are avidly taken up by tumour cells due to an overexpression of amino acid transporters in their membrane (upregulation) [6, 7]. Healthy brain cells express only a small number of these transporters. Thus, amino acid-based PET/CT is tumour specific and, compared with MRI, can differentiate more precisely between malignant tumour tissue and an unspecific breakdown of the BBB. Unlike CT and MRI, PET/CT is a functional, not a morphological imaging method.

The two above-mentioned amino acid tracers are considered equally sensitive and specific in clinical practice [8]. ^{11}C-MET was used earlier and has been more intensively researched, but its short half-life of 20 min necessitates on-site radiochemical synthesis, thus limiting its clinical availability. ^{18}F-FET has a half-life of 109 min, allowing a satellite-based strategy with shipment to outlying facilities. In consequence, ^{18}F-FET can be used in nuclear medicine departments that do not have a cyclotron unit at their disposal. Another advantage of ^{18}F-FET, compared with ^{11}C-MET, is the possibility of grading tumours into low and high grades based on differences in tracer kinetics – a concept that appears promising but requires further research [9]. It must be mentioned, however, that in most countries amino acid-based PET tracers have still not been approved as radiotracers by national authorities.

The best known PET tracer, ^{18}F-2'-fluoro-2'-deoxyglucose (FDG) has become irreplaceable in clinical practice in the imaging of extracranial tumours.

However, owing to the high normal FDG uptake of brain tissue (especially grey matter), it is of limited use in brain tumour diagnostics and is used only in special situations (e.g. cerebral lymphomas) [10]. Recent studies have shown that 3',4'-dihydroxy-6'-[^{18}F]fluoro-L-phenylalanine (DOPA), an amino acid-based tracer that has mostly been used in the imaging of phaeochromocytoma (a neuroendocrine tumour of the adrenal gland), is more accurate than ^{18}F-FDG in the imaging of low-grade brain tumours, can better distinguish recurrence from radiation necrosis [11] and is comparable to ^{11}C-MET in diagnostic accuracy [12].

Long experience has been gained with somatostatin receptor scintigraphy, and the somatostatin analogue ^{68}Ga-DOTATOC (DOTA^{0}-Phe^{1}-Tyr^{3}-octreotide) is used as a PET tracer for the diagnosis of meningiomas. DOTATOC binds as a ligand to somatostatin receptors (SSTR) which are overexpressed by meningiomas, glomus jugulare tumours and certain neuroendocrine tumours (for which DOTATOC can also be used therapeutically when combined with ^{90}Y or ^{177}Lu). This tracer is very helpful for detection of infiltration of bone structures by base of skull meningiomas and infiltration of the sagittal sinus by falx meningiomas [13].

Other tracers like ^{18}F-3'-deoxy-3'-fluorothymidine (FLT) that visualise cell proliferation are currently under research and might prove to be a valuable tool in response assessment, but are not yet used in clinical practice.

Possible uses of PET/CT in radiation therapy planning

Modern PET imaging is almost always performed in combination with a (simultaneous) CT scan for attenuation correction and improved anatomical localisation. In radiotherapy planning for brain tumours, it is mostly used to delineate the actual tumour volume and in cases of recurrence, when MRI alone cannot differentiate between true and pseudo-progression. However, it is often also a crucial method in patients with brain metastases, serving to distinguish therapy-related changes from true recurrence.

In low-grade gliomas, diffuse infiltration of brain tissue is very common, so that they cannot be fully delineated on MRI. These tumours do not affect the BBB, so contrast enhancement may be completely lacking. Instead, a diffuse increase in T2-weighted signal is seen, which is representative of cerebral oedema. In these cases, a PET/CT scan can help delineate the actual tumour volume and differentiate between tumour tissue and concomitant oedema. Low-grade lesions can also show "hot spots", where an increase in malignancy and, hence, an "upgrading" of the tumour has taken place [9]. Detection of hot spots is crucial for stereotactic biopsy taking (since the maximum degree of malignancy determines the subsequent therapy) and radiotherapy planning. Recent radiotherapy techniques enable so-called dose painting, in which a circumscribed region within a predefined target volume can be irradiated with a higher radiation dose (dose escalation).

High-grade gliomas are always recurrent (Fig. 1). In cases of re-irradiation, amino acid-based PET/CT is necessary to differentiate between therapy-related changes from the initial treatment and true tumour recurrence. The target volume delineated only on MR images can vary extremely depending on the observer or it can gravely underestimate the real tumour dimensions [14] . In these cases, amino acid-based PET/CT should be performed to gain crucial additional information. Correct delineation of the tumour based on a PET/CT scan has consequences not only for the performance of therapy but also for its outcome. In a study of 44 patients suffering from recurrent high-grade glioma, a statistically significantly longer survival was demonstrated in patients who were re-irradiated using ^{11}C-MET PET in the treatment planning in comparison to patients treated on the basis of MRI/CT alone [15].

A standard therapy in cases of cerebral metastasis is whole brain irradiation. However, attempts are being made to avoid irradiation of the whole brain owing to the attendant toxicity and to use more sophisticated methods such as (stereotactic) radiosurgery, which provides excellent disease control in patients with limited brain metastases [16]. The radiosurgery often needs to be performed repeatedly because of new metastasis. It is of great importance to differentiate between local recurrence and treatment injury in patients with metastases. Here, too, amino acid-based PET/CT imaging improves diagnostic accuracy for brain metastases, and it has been shown to be helpful in the differentiation of recurrence and radionecrosis [8]. Whole brain irradiation with an integrated concomitant local boost offers a combined strategy encompassing both of the aforementioned methods. It offers an acceptable dose to the whole brain and simultaneously delivers an increased dose to the metastases.

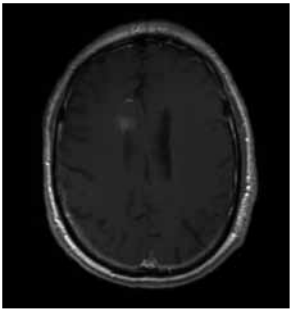

Figure 1 A: Pathological contrast enhancement in MRI imaging in a patient with suspected recurrence of glioblastoma multiforme

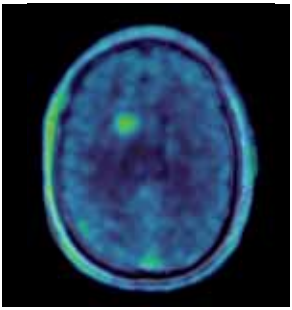

Figure 1 B: Fused images of FET-PET and MRT for better anatomical correlation

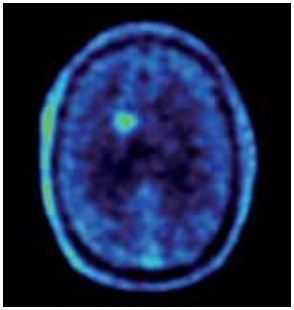

Figure 1 C: FET PET image of the same patient, confirming this suspicion by increased amino acid uptake

Meningiomas are frequently located near structures that show a high physiological contrast enhancement, including the sella and the tentorium cerebelli; this makes it difficult to determine the actual tumour size on contrast-enhanced MRI alone. In addition, very sensitive brain structures lie in the vicinity of the sellar region, such as the optic nerve, which must be spared from higher radiation doses to avoid loss of sight. In such cases, an ^{11}C-MET or ^{68}Ga-DOTATOC PET/CT scan can help to determine the actual tumour volume and reduce damage to unaffected organs [17].

There are various other situations in which a PET/CT scan becomes mandatory, e.g. when patients have a pacemaker or internal defibrillators and cannot be placed in the magnetic field of an MRI scanner. In such circumstances, combined PET/CT imaging is superior to CT imaging alone for radiotherapy planning.

How is radiotherapy planning performed?

After the indication has been set, a face mask is customised individually to each patient. Which model is chosen depends on the planned radiotherapy. In conventional three-dimensional radiotherapy, the mask is less tightly adjusted than in stereotactic radiosurgery or IMRT, where higher single doses are applied. For a single radiosurgical procedure, an invasive system such as a Riechert stereotactic head ring is often used to avoid head movement and dislocation.

Modern procedures increasingly rely on image-guided radiation. During treatment, the patient's position is monitored and verified by additional X-ray or CT scanners (e.g. cone-beam CTs), which make it possible to abandon external fixation masks and increase patient comfort.

After the mask has been attached to the patient's head, a planning CT scan is performed, which serves as a basis for the calculation of tissue density and the radiotherapy plan itself. CT scans are, however, of limited use in the display of subtle brain structures. Therefore, an additional MRI scan and, for the above-mentioned indications, a PET/CT scan need to be obtained. It is of great importance that these scans can be co-registered with the planning CT. With the improvement of planning software it is possible to perform co-registration, e.g. on the basis of bone structures, which do not change significantly during the planning procedure.

With this information provided, the target volume (PTV) can be defined, which includes the macroscopic tumour tissue (gross tumour volume, GTV), the putative microscopic invasion (clinical tumour volume, CTV) and a safety margin that depends on the radiation technique and precise patient placement (Fig. 2).

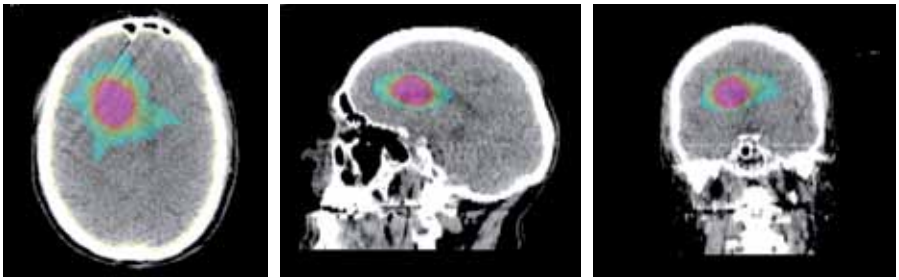

Figure 2 A–C: Radiation plan for the recurrent glioblastoma multiforme shown in Fig. 1, based on the FET PET and MRI scans in Fig. 1 A and B

Tumour delineation

Tumour delineation can be done visually or by calculating the uptake of the questionable lesion in relation to healthy brain tissue (e.g. the contralateral hemisphere). European guidelines have determined cut-off values for various clinical settings, depending on the situation and the tracers that are used [18]. For example, the current cut-off value for differentiating neoplastic brain tissue from healthy surrounding tissue with ^{18}F-FET has been set at 1.6 [18]. With the help of various commercially available software packages it is possible to automatically delineate tumour tissue using isocontour maxima, which can be set manually, so that all brain parts exceeding a certain preset uptake value are automatically delineated. However, physiological tracer accumulation must be carefully taken into account. ^{18}F-FET signal is physiologically increased, for instance, in the venous sinuses of the brain, which can mimic extension to the contralateral hemisphere in the case of sinus sphenoidalis. ^{11}C-MET signal is increased in, for example, the lacrimal gland. Hence, PET/CT-based delineation of brain tumour requires a certain diagnostic expertise.

Disadvantages of PET/CT, and future concepts

PET/CT, unlike MRI, does entail a certain radiation exposure. However, the subsequent use of much higher doses in radiation therapy in most patients places this into perspective.

The resolution of PET is limited and significantly lower than that of MRI (approximately 5-8 mm in PET and 1 mm in MRI, in each case depending on the hardware used). Modern PET scanners with sophisticated image reconstruction kernels offer a spatial resolution of up to 3 mm, but as in all reconstruction algorithms, increased resolution comes at the expense of a decreased signal-to-noise ratio.

Owing to the lower resolution, tumour margins may seem fuzzy on PET scans. Modern guidelines also recommend using monochromatic scales (like grey scale or hot metal), while multicolour scales such as rainbow scales can lead to bias when tumour delineation is performed visually. With the introduction of PET/CT with simultaneous CT image acquisition, the disadvantage of lower spatial resolution is alleviated to some extent. Even better results are expected from PET/MRI scanners, which offer great advantages in brain scanning owing to the possibility of combining exact morphological information with functional or molecular imaging offered solely by PET scanners [19]. In addition, radiation exposure can be significantly decreased when the CT image is replaced by an MR image. MR images can also be used for attenuation correction for simultaneous PET scans, although not all problems have been solved yet. PET/MRI scanners may offer greater patient comfort because all necessary information can be obtained in one scan, and the possibility of error is decreased since the necessity of co-registration is reduced from three (PET/CT, planning CT, MRI) to two images (PET/MRI and planning CT) .

Current recommendations

According to current neuro-oncology guidelines (AWMF; S1 level), amino acid-based PET/CT is not recommended for primary diagnosis of cerebral lesions. It is, however, recommended when MRI is inconclusive and in certain specific clinical settings. In post-therapeutic care, the situation is comparable [20].

In radiotherapy planning, PET/CT scans are a valuable additional imaging technique in clinical practice to improve localisation of malignant tissue; furthermore, in many studies they have been proven to help increase inter-rater agreement in target volume planning [17].

It is to be expected that PET/CT-based imaging will become more and more important, not only in general oncology but also particularly in neuro-oncology.

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Section 3 – PET/CT in Radiotherapy Planning

3.5 Radiation Protection for PET/CT Radiotherapy Planning

Susanne Svalling and Karin Stahr

The term "radiation protection" relates to the actions necessary to reduce the radiation dose to individuals, whether members of the general population, staff working daily with ionising radiation or patients. The recognition that ionising radiation can damage living tissue led in 1928 to the formation of the International Commission on Radiation Protection (ICRP), with the purpose of establishing guidelines for radiation protection. ICRP is an independent organisation that continuously monitors all aspects of radiological usage and provides regulations for radiation protection and practices.

Personal dose monitoring

Monitoring of personal radiation dose is based primarily on the external exposure to the body. All staff working in a facility where ionising radiation is utilised are required to wear personal dosimeters: TLD (thermoluminescent dosimeter), OSL (optically stimulated luminescence dosimeter), film badge, and/or electronic dosimeter (Fig. 1).

Figure 1: Personal radiation dosimeters

When planning therapy, it is recommended that dosimeters should be worn at chest height owing to the working height of the bed with the patient in the therapy planning position. It is essential for accurate monitoring that these dosimeters are worn every day and always in the same predetermined position.

Electronic dosimeters are based on a solid-state detector that is able to show integrated dose or dose rate and can be adjusted to alarm limits. Film badges utilise conventional X-ray theory. The film is placed in a holder which allows for the film to differentiate between types of radiation. This film is sensitive to radiation exposure as ionisation causes the silver ions to precipitate. It is then developed and increasing colour on the film is proportional with the volume of radiation the film has received. The films are evaluated each month and the staff's personal results are recorded, monitored by certified personnel and archived.

When considering the available measures necessary for minimisation of radiation exposure, Section 2 ("Best Practice in Radiation Protection") of the book *Best Practice in Nuclear Medicine, Part 2: A Technologist's Guide* is an excellent reference source.

There are three basic standard concepts of radiation protection: shielding, time and distance (STD). Sufficient shielding when working with positron emitters is a very difficult, impractical and expensive method owing to the sheer size and density of the shielding materials required for these high energies. Therefore, time management and distance from the source of exposure become very important for radiation exposure reduction.

The amount of radiation exposure increases and decreases depending upon the time spent near the source of radiation, and exposure is reduced fourfold when the distance to the source is just doubled (Fig. 2). Therefore, provision of relevant information to the patient prior to the FDG injection is paramount. Staff should try to avoid staying near the patient unnecessarily after injection. It is recommended that the scanner room be prepared prior to the arrival of the radioactive patient, including preparation for i.v. contrast administration. If the patient needs assistance, a wheelchair may be used to transport the patient to the scanner room, but it must be ensured that an adequate distance is kept from the patient because he or she will already have been injected with the radioactive tracer.

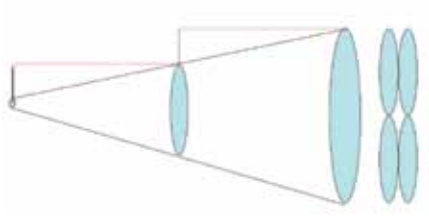

Figure 2: Doubling the distance between the body and the radiation source will reduce the radiation exposure by a factor of 4

Pretreatment regimen for the radiotherapy patient

It is important the patient has a well-structured day for the PET/CT planning session. It is essential to prepare the immobilisation device and to provide complete information about the entire sequence before the injection of the radioactive tracer.

First appointment

The patient's first appointment begins in the mould or fixation department, where the immobilisation device is made to fit the individual patient. A mask is used for head/neck cancer and a vacuum-form body immobiliser for lung, stomach and colorectal cancer. For patients with cancer of the ovary, penis or testicle, outer/extremity fixation is employed. It is important for the staff to familiarise themselves with the immobilisation devices and to understand how they are used for the various types of cancer as they differ greatly. Such knowledge will enable staff to minimise the time spent near the radioactive patient when positioning the patient in the scanner.

Second appointment

At this appointment, the patient receives explanations both of the PET/CT scanning procedure and of the way in which their scan will be integrated into the treatment plan. It is very important to ensure that the patient is as well informed and prepared as possible at this stage, and if questions arise then it is preferable to answer them *before* the tracer injection. It is at this point that the interviewer can observe the patient to identify potential problems during the therapy PET/CT. There is also an opportunity to provide suitable medication if the patient suffers from claustrophobia.

The injection procedure should be optimised by ensuring good intravenous access before the activity is handled. The dose to the staff can be further reduced by using an automatic system combining safe dispensing and infusion of ^{18}F-FDG (Fig. 3).

Figure 3: MEDRAD Intego automated injection machine

Planning process at the scanner

1. Identification is confirmed with the name and/or unique personal number. A further short explanation of the scanning should then be provided, encompassing why it is necessary and how it will be done. It is important to be familiar with the patient's medical history prior to the patient's arrival as this ensures the treatment region is clear to all staff members.

2. It is very important to inform the patient that he or she must lie perfectly still throughout the scan. It is particularly important to ensure that patients with head and neck cancer understand that they must lie perfectly still with their fixation mask on during the entire scanning. The mask is uncomfortable but it will prohibit

any movement so the radiation therapy can be given as accurately as possible. Even when working with patients who may be lying uncomfortably, it is essential to remember to keep a reasonable distance from the radioactive patient.

3. Before the patient's arrival in the scanner room, the contrast for CT scanning should be prepared. When the patient is positioned on the couch, the contrast is connected to the patient's i.v. catheter. The patient receives the i.v. contrast immediately prior to the CT scan.

4. The patient arrives at the scanner room 50 min after ^{18}F-FDG injection, and must be positioned on the scanner table using the fixation equipment designed for the individual patient.

5. There should always be two people to position the patient. They must constantly maintain a sufficient distance, and they need to work efficiently. When the planning procedure is complete, photographic documentation of the layout is suggested, which remains in the patient's file.

6. As soon as the patient lies on the couch to be positioned at the correct height in the scanner, the staff must stand in an appropriate position (Fig. 4). It is advisable to stand near the patient's feet rather than at the head or torso whenever possible (Fig. 5). The other option is to control the height of the couch from the operating console.

Figure 4 A: Correct position for the member of staff. Figure 4 B: Incorrect position

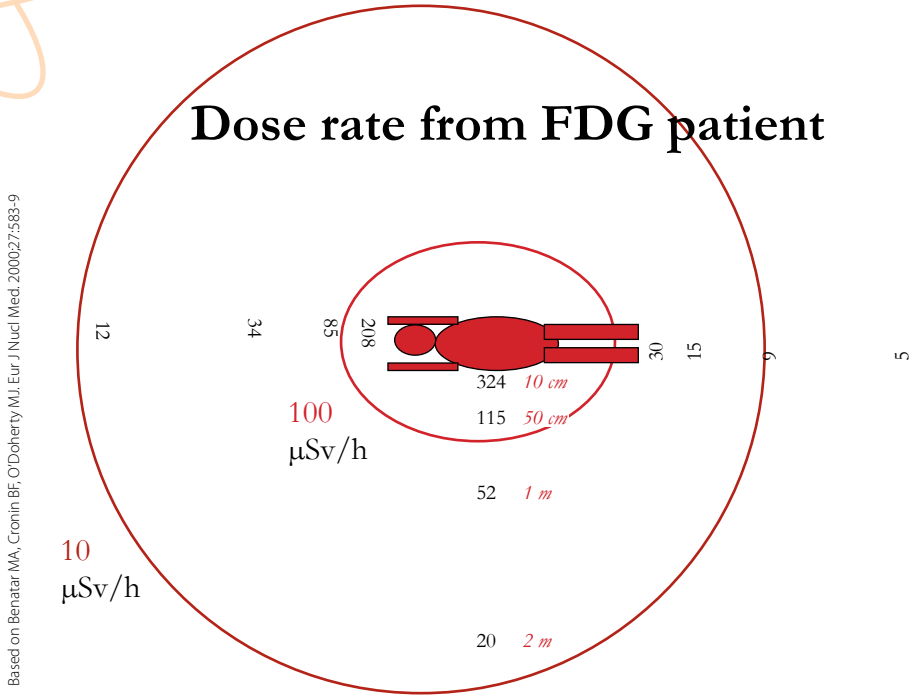

Figure 5: Dose rate from a patient injected with FDG (µSv/h after injection of 300 MBq or ~45 min after injection of 400 MBq). It can be seen that it is advisable to stand near the patient's feet rather than at the head or torso whenever possible.

7. Once the PET/CT scan has been done, the staff may tattoo the patient. Patients can receive between one and five tattoo dots. When the tattooing has been completed, the i.v. catheter is removed.

8. Patients may leave the scanner room and their PET/CT scan can now be incorporated into the treatment planning process.

Summary

A summary of the planning process is shown in Fig. 6. All nuclear medicine technologists, radiographers and radiotherapy nurses must be experienced and well trained when undertaking PET/CT radiotherapy planning, and should be competent in all phases of working with a radioactive patient. This will result in dose reduction for all staff members working in this unique environment.

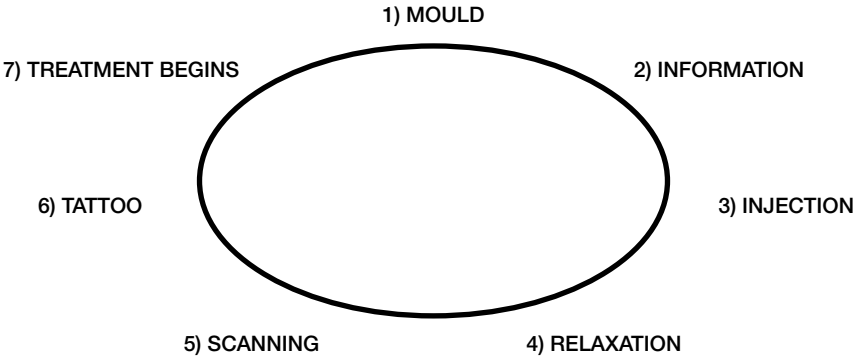

Figure 6: Summary of the planning process

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Section 4 – Future Possibilities for PET/CT in Radiotherapy Planning

4.1 New Tracers

Scott Holbrook, Sherry Reuter and Aaron Scott

In addition to advances in instrumentation, the continued development of radionuclides and biomarkers designed to target specific characteristics of a tissue or disease will enhance the detection, treatment and monitoring of the course of therapy. The ability to non-invasively image cellular characteristics, including membrane receptor expression, cellular processes (such as proliferative activity), protein synthesis, apoptosis (programmed cell death) and hypoxia, may serve as a platform for personalised cancer therapy. This approach is often termed 'theragnostic' imaging, where diagnostic and tumour characteristics are combined to yield important information that permits optimisation and individualisation of therapy.

^{18}F-Fluorodeoxyglucose (FDG) has been the radiotracer historically utilised for detection of disease and treatment planning by PET/CT. FDG is a glucose analogue and is therefore a marker for cellular glycolytic metabolism. Most cancer cells exhibit an upregulated glycolytic activity following genetic mutation and altered biochemical status to meet their requirement for energy and building blocks for cell proliferation. Cancer cells often overexpress cell surface glucose transporters (GLUTs) responsible for the transport of glucose across the cell membrane and hexokinases responsible for further metabolisation of glucose in the glycolytic pathway. Unlike dietary glucose, FDG cannot progress further through the metabolic pathway and becomes irreversibly trapped in the intracellular space, where its location can be detected following the positron emission from ^{18}F.

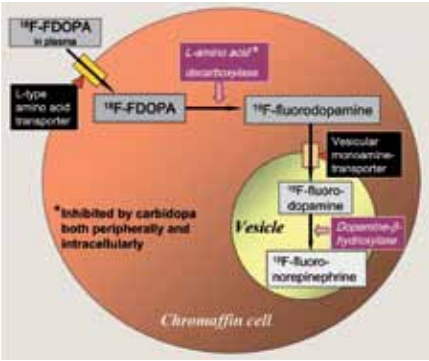
While the role of FDG PET is well established for many cancers and FDG will probably continue to play a major role in the future, there are situations where alternative radiotracers would be more desirable. These include circumstances where imaging is complicated by metabolic disorders, recent treatment with chemotherapy and radiotherapy, inflammatory and infectious conditions and co-existing diseases. Physiological accumulation of FDG in, for example, brain tissue, is another example of non-malignant tissue accumulation that makes the distinction between normal physiological and pathological uptake difficult and warrants the development of alternative tracers for detection of disease and planning of therapy. Additionally, glucose metabolism varies significantly between different cancers and for some malignancies the uptake of FDG may be similar to that in the surrounding tissues.

Against this background, more disease-specific tracers are emerging and their roles as radiotracers are constantly increasing. New radiotracers can be roughly divided into those that optimise tumour detection, those used for tumour delineation and staging of patients, and those that

provide information for evaluation, optimisation and individualisation of therapy. Tracers for the individualisation of therapy may include tracers with the ability to determine non-invasively whether cancer cells over-express or have functional receptors for certain signalling pathways. This is an important clinical issue when planning treatment in patients with newly diagnosed breast carcinoma, since determining whether the cancer expresses functional oestrogen receptors (oestrogen receptor-positive breast carcinoma) is indicative of whether the patient is likely to benefit from treatment with hormone receptor-targeting therapies. ^{18}F-Fluoroestradiol is an example of a PET imaging agent which can provide important quantitative non-invasive biological information on breast carcinoma cells' oestrogen receptor status.

Neuroendocrine tumour imaging

Neuroendocrine tumours are not defined by primary locations but rather by endocrine metabolism. They are often small, rarely present with metastases and are not particularly hypermetabolic. While these neoplasms are relatively rare, their prevalence has increased over the last decade. Conventional imaging using CT and MRI has proven insufficient for diagnostic purposes. Additionally, many neuroendocrine tumours do not express increased glucose metabolism, rendering FDG PET imaging useless. Instead, alternative radiotracers have been developed to take advantage of the unique attributes of these tumour types.



Reproduced from Minn et al. [8]

Figure 1: Intracellular transport of ^{18}F-FDOPA via the large neutral amino acid transporter.

^{18}F-FDOPA is transported intracellularly in neuroendocrine tumour cells via the large neutral amino acid transporter (Fig. 1). L-DOPA is a precursor of catecholamines, such as dopamine and adrenaline, and the abundant production of these hormones is a hallmark of neuroendocrine tumours. It is the overproduction of these hormones that leads to the traditional signs and symptoms (flushing and diarrhoea) associated with neuroendocrine tumours. The intracellular concentration of ^{18}F-FDOPA is directly proportional to the increased activity of amino acid decarboxylase, an enzyme responsible for decarboxylation of amino acids and their conversion

to serotonin, dopamine and adrenaline [1]. ^{18}F-FDOPA PET has been found to be more accurate than conventional somatostatin receptor imaging with ^{111}In agents for imaging of neuroendocrine tumours in numerous studies. Figure 2 shows phaeochromocytomas demonstrated by ^{18}F-FDOPA PET/CT but not by MIBG scintigraphy.

Effective radiolabelled somatostatin receptor imaging agents for identifying neuroendocrine tumours have been developed for PET imaging. The promising tracers include the chelating agents DOTA, DOTATOC, DOTATA and DOTANOC, labelled with generator-produced ^{68}Ga. The ability to image lesions via receptor imaging is dependent on the concentration of receptors available for interaction with the radiotracer (expressed on the cell surface and not internalised) and the affinity of the radiotracer for the receptor. Although there are at least five known somatostatin receptors, sst2 is usually overexpressed and thus a target for therapies and imaging agents for neuroendocrine tumours. While some studies show ^{68}Ga-DOTATATE to have a higher in vitro affinity for sst2 receptors, it appears to offer no advantage over ^{68}Ga-DOTATOC and ^{68}Ga-DOTANOC in vivo [2].

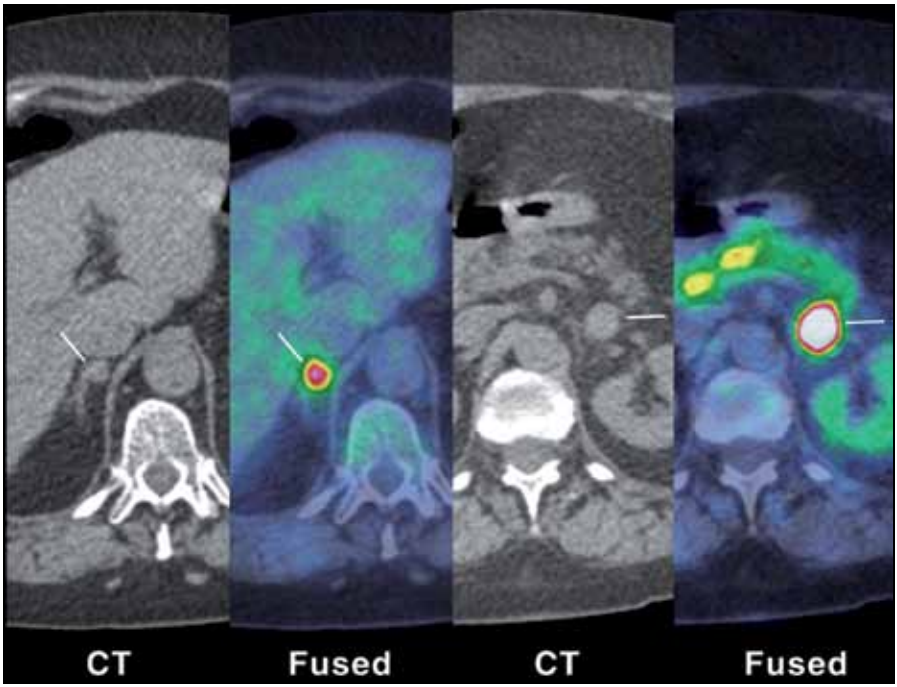


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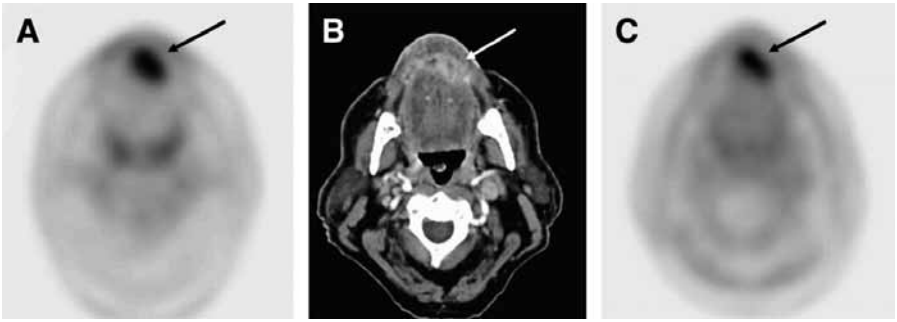
Figure 2: Phaeochromocytomas demonstrated with ^{18}F-FDOPA PET/CT (white lines) but negative on MIBG scintigraphy. A para-aortic nodal metastasis measuring 6 mm (not shown) was also found on ^{18}F-FDOPA imaging. Diagnosis of all three tumours was confirmed at surgery. Uptake of ^{18}F-FDOPA is low in the dorsal and normally functioning part of right adrenal.

Radiolabelled amino acid tracers

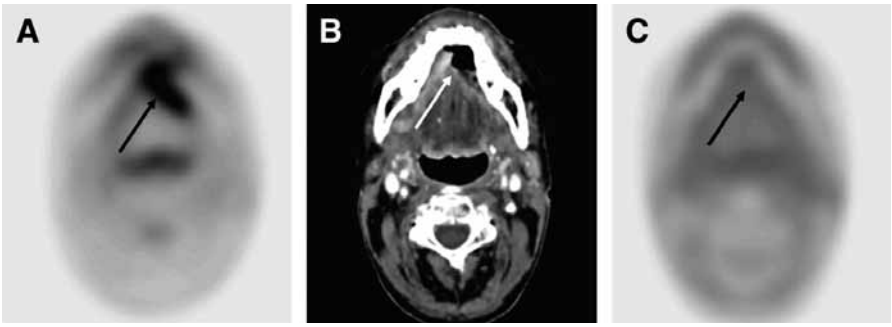
As previously stated, a high glucose metabolism in the surrounding normal tissues may complicate the use of FDG for the purposes of staging and tumour delineation. FDG uptake in surrounding tissues is, for example problematic for the detection of brain tumours and also squamous cell carcinomas in the head and neck region [3]. Radiolabelled amino acids have shown great promise in the evaluation of brain and head and neck malignancies as they are not avidly taken up by tumour-surrounding tissues.

Early studies of ^{11}C-methionine for imaging cancers of the head and neck and brain reported a high sensitivity and specificity. Methionine is a useful amino acid for detection of malignancies, which often exhibit up-regulation of protein synthesis. ^{11}C-Tyrosine has also been used for cancer imaging. Tyrosine, an amino acid, also serves as a marker for up-regulation of protein synthesis. However, the relatively short half-lives of ^{11}C-labelled isotopes (approximately 20 min) make them unsuitable for widespread distribution and routine clinical use. The clinical use of radiolabelled amino acids has recently been improved by the introduction of ^{18}F-labelled analogues such as ^{18}F-tyrosine. Studies comparing FDG with ^{18}F-tyrosine have shown that FDG may exhibit greater sensitivity but that ^{18}F-tyrosine can offer increased sensitivity, particularly when distinguishing between inflammatory and malignant lesions. This may be especially important when evaluating patients after radiotherapy of cancers in the head and neck region. The sensitivity and specificity of FDG PET for detection of squamous cell carcinoma of the head and neck has been reported to be approximately 93% and 79%, whereas ^{18}F-tyrosine exhibited a sensitivity and specificity of 75% and 95% [3]. ^{18}F-tyrosine PET imaging may therefore supplement and complement FDG for the imaging of for some cancers and regions. Figures 3 and 4 demonstrate two examples of oral cavity cancer.



Reproduced from Paulet et al. [12]

Figure 3A–C: ^{18}F-FDG PET (A), CT (B), and ^{18}F-FET PET (C) images of a 72-year-old man with squamous cell carcinoma of the oral cavity (arrows). The tumour exhibits increased uptake of ^{18}F-FDG (SUV, 8.0) and ^{18}F-FET (SUV, 3.6).



Reproduced from Paulet et al. [12]

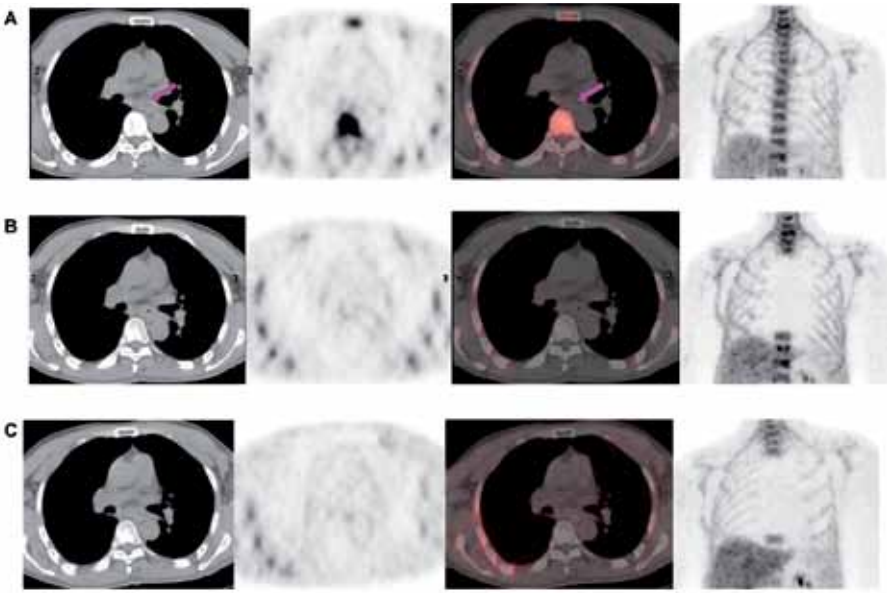
Figure 4A–C: ^{18}F-FDG PET (A), CT (B), and ^{18}F-FET PET (C) images of a 52-year-old man with a 0.7-cm squamous cell carcinoma in a 4.3-cm ulcer with inflammatory tissue (arrows). ^{18}F-FDG PET scan shows an approximately 4-cm lesion with increased ^{18}F-FDG uptake (SUV, 5.2) that allows no discrimination between carcinoma and inflammation. CT scan demonstrates an air-filled ulcer, and ^{18}F-FET PET scan reveals no abnormal ^{18}F-FET uptake (SUV, 1.5), missing the small carcinoma.

There are several other promising PET imaging agents that rely on amino acid analogues or related intracellular transport mechanisms. It is likely that amino acid analogues will be increasingly included as radiotracers when inflammation is of concern or as primary imaging agents to study pathology in tissues where glucose metabolism is not markedly increased or excretion of radiotracer is problematic. Prostate cancer is a classic example of a pathology that can be challenging to characterise with conventional imaging and biomarkers. The need for imaging of this disease is growing because its incidence is rising and promising new therapies are becoming available. The radiotracer ^{18}F-fluorocyclobutyl-1-carboxylic acid (ACBC) has shown effectiveness in imaging prostate cancer. It is believed that ^{18}F-ACBC is transported intracellularly via a Na^+ amino acid transporter that is over-expressed in prostate cancer tissue [4]. Studies have shown higher accumulation and target to background ratios of ^{18}F-ACBC within prostate tumour tissue when compared with ^{18}F-FDG [5].

Cellular proliferation

Self-sufficiency of growth signals and resistance to anti-growth signals are among the hallmarks of cancer. An integral link between cancer and proliferation therefore exists. For this reason it is desirable, when imaging tumours and evaluating the efficacy of a given therapy, to determine cellular proliferative rates prior to and following administration of treatment. The building blocks required to facilitate cellular division include the two classes of nucleotides: purines and pyrimidines. Adenine and guanine consist of two

fused rings whereas the pyrimidines, cytosine and thymine, consist of single ring structures. Studies have identified that tissues exhibiting increased cellular proliferative rates can be imaged with a radiolabelled analogue of thymine. ^{18}F-Fluorothymidine (FLT) is a substrate for thymidine kinase-1 (TK1), an enzyme in the cytosol that metabolises the molecule to ^{18}F-monophosphate, which becomes trapped intracellularly and increases in concentration over time. This thymidine salvage pathway is primarily responsible for the recovery and recycling of nucleotides from DNA and RNA that have been degraded. Human cell culture studies and presurgical FLT imaging studies of resected lung lesions have confirmed the relationships among FLT accumulation, TK1 activity and cellular division rates. Because TK1 activity is proportional to cellular proliferative rates, FLT metabolism and accumulation on PET can serve as a marker of proliferative activity.



Reproduced from Yue et al. [6]

Figure 5A–C: This patient received induction chemotherapy before radiotherapy. From left to right are shown CT, PET, fused PET/CT, and maximum-intensity-projection images. Arrows indicate oesophageal tumour. Figure 5A: Before radiotherapy, SUV_{max} was 1.2 and proliferation target volume was 0. Figure 5B: After 30 Gy/15 fractions, SUV_{max} was 1.1 and proliferation target volume was 0. Figure 5C: After 50 Gy/25 fractions, SUV_{max} was 1.2 and proliferation target volume was 0.

Recent studies have demonstrated the potential of FLT imaging in conjunction with radiotherapy in the evaluation of therapy, in addition to the detection and evaluation of tumours. Because FLT accumulates in proliferating cells it has been used to detect radiation-induced repopulation of cancer cells. This phenomenon would be difficult to evaluate with FDG because radiation-induced changes and inflammation which result in FDG accumulation may persist for weeks. It is possible that FLT PET could permit early evaluation of therapy, during the course of radiotherapy, and thereby allow for alterations and optimisation of treatments and protocols [7]. This is demonstrated in Fig. 5.

Hypoxia imaging

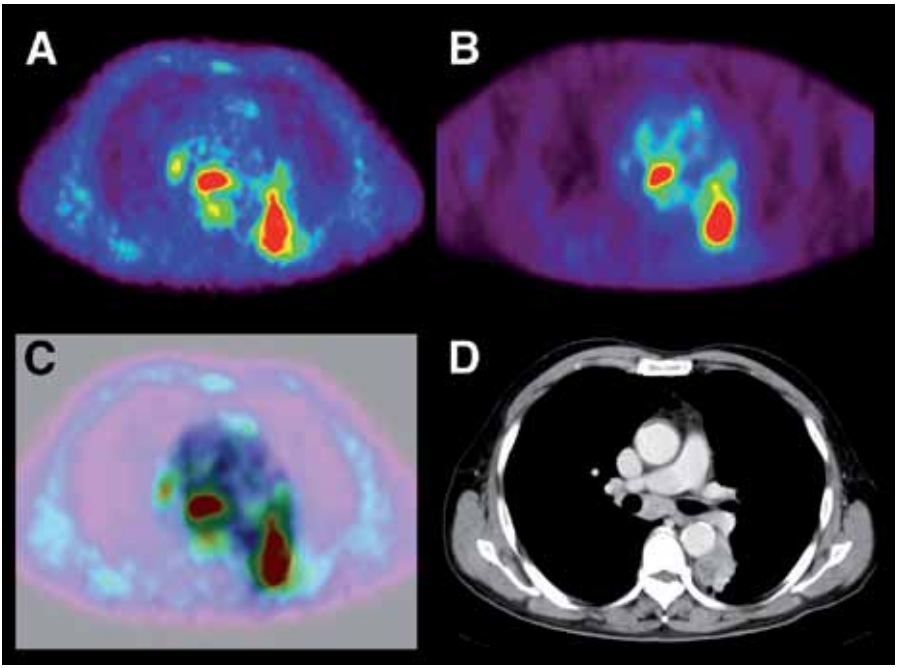
All tumours that grow beyond a volume of a few cubic millimetres require establishment of new blood vessels, also known as neo-angiogenesis, to meet the tumour cells' requirement for oxygen, nutrients and removal of waste products. Solid tumours are therefore dependent on a positive balance between pro-angiogenic and anti-angiogenic factors to stimulate the formation of functional vasculature. The most important pro-angiogenic factor is vascular endothelial growth factor (VEGF), and prevention of angiogenesis through the targeting of VEGF receptors on cancer cells has therefore been a leading area of cancer treatment research. The process of expansion of the tumour cell mass and angiogenesis is not always well balanced, and hypoxic or even necrotic regions may develop within tumours if their proliferative growth rate exceeds the angiogenic capacity. Hypoxia that results from the imbalance between tumour growth and formation of new blood vessels is known as diffusion-limited chronic hypoxia. However, tumour blood vessels are often very poorly organised, and vessel shunts and blind ends may exist. Because of this poor organisation, tumour blood vessels may experience sudden collapses, which make tumour cells acutely hypoxic in regions supplied by the non-perfused vessels. Two types of tumour hypoxia may therefore exist, although they probably cannot be viewed as independent events.

Tumour hypoxia is a negative prognostic factor and hypoxic tumour cells are more resistant to radiotherapy and certain chemotherapeutic agents than identical normoxic tumour cells. In addition to increased therapeutic resistance, tumour hypoxia has been shown to increase the risk of both local recurrence and metastasis [8]. The ability to identify tumour hypoxia may allow for adjustment of the provided treatment, including modification of radiotherapy to increase doses to hypoxic regions, using radiosensitisers and adjusting chemotherapy to potentially improve therapeutic outcomes.

Several tracers have been developed for PET imaging of tumour hypoxia. Most are based on 2-nitroimidazoles, and various fluorine-labelled 2-nitroimidazoles have been intensively evaluated as hypoxia markers. The 2-nitroimidazoles are reduced by inversely oxygen

level-dependent nitroreductases and become selectively bound to macromolecules within hypoxic cells. ^{18}F-Fluoromisonidazole (F-MISO) is the prototype of 2-nitroimidazoles for hypoxia imaging. The initial distribution of this freely diffusible, relatively lipophilic tracer is flow dependent, but after approximately 2 h intracellular oxygen tension determines its retention in hypoxic cells. The slow wash-out from normal background tissues and uptake kinetics often result in poor imaging/count statistics and low-contrast images. F-MISO accumulates from pO2 levels below 10 mmHg. F-MISO is currently the most extensively investigated and widely used PET marker of hypoxia. Uptake of F-MISO has been correlated with a poor response to therapy and a negative outcome in several studies of different human malignancies, including brain and head and neck tumours [8]. ^{18}F-Fluoroazomycin arabinoside (FAZA), a second-generation 2-nitroimidazole, is more hydrophilic than the prototype tracer F-MISO. In preclinical studies, FAZA has shown superiority to F-MISO by displaying a faster body clearance and more favourable tumour-to-blood and tumour-to-organ ratios. Early clinical studies of FAZA in cervical cancer, head and neck cancer, small cell lung cancer, non-small cell lung cancer, malignant lymphoma and high-grade gliomas reported that clinical FAZA PET imaging is feasible and that acceptable tumour to background images are obtained. Several additional 2-nitroimidazole PET tracers are currently being investigated as potential markers of tumour hypoxia.

While fluorine-labelled 2-nitroimidazoles have been the most studied tracers for hypoxia imaging, there is also a large body of research dedicated to copper-labelled diacetyl-bis(N^4-methylthiosemicarbazone) (Cu-ATSM). Figure 6 demonstrates the biodistribution characteristics of Cu-ATSM and FDG in adenocarcinoma of the lung. Cu-ATSM is among the most promising tracers for non-invasive hypoxia imaging. Cu-ATSM PET studies have reported high intratumoral contrast, high membrane permeability and rapid blood clearance. Several positron-emitting copper isotopes are available for PET imaging, with half-lives ranging from 9.7 min (^{60}Cu, 97.4% positron emission) to 12.7 h (^{64}Cu, 17.9% positron emission). Different mechanisms have been proposed for the retention of Cu-ATSM in hypoxic cells. Cu-ATSM was initially suggested to be reduced and retained as Cu(I)-ATSM only in hypoxic cells. The reduction of Cu(II)-ATSM was, however, later found also to occur under normoxic conditions. Based on these findings, Cu-ATSM has been proposed to rapidly accumulate because of a reduction-oxidation (redox) trapping mechanism. Following entry into a hypoxic cell, the Cu(II) of the ATSM molecule is reduced to Cu(I) and subsequently Cu(I) can dissociate irreversibly from the Cu-ATSM complex, trapping the Cu(I) ion intracellularly. Normoxic conditions should, however, re-oxidise the reduced Cu(I)-ATSM to the neutral lipophilic Cu(II)-ATSM, which again can freely diffuse out of the cell [9].



Reproduced from Lohith et al. [10]

Figure 6A–D. Transaxial PET images of ^{62}Cu-ATSM (A), ^{18}F-FDG (B), and their fusion (C) and corresponding CT image (D) of a 76-year-old man with adenocarcinoma in the left lower lung. Fusion image is depicted for ^{62}Cu-ATSM PET in color and for ^{18}F-FDG PET in grey scale. Both original tumour and lymph node metastasis showed similar uptake patterns between ^{18}F-FDG and ^{62}Cu-ATSM.

Applications of hypoxia imaging in oncology

The hypoxia radiotracers described above have been applied in a number of clinical settings and studies, which have identified a negative correlation between tracer accumulation and prognosis. One potential way to overcome resistance to radiation treatment would be to increase radiation dose to the hypoxic tumour regions identified by PET imaging. Intensity-modulated radiation therapy (IMRT) allows selective targeting of tumour and improved sparing of normal surrounding tissues. It has been suggested that hypoxia-guided IMRT based on PET images using hypoxia radiotracers can serve as a basis for dose escalation of radiation to the hypoxic tumour subvolumes [11]. Identification

of hypoxic tumours may additionally stratify patients who will benefit from different treatment strategies, including hypoxia radiosensitisers, chemotherapeutic regimens that are effective in hypoxic tumours and hypoxia-selective cytotoxins.

In a study involving 40 patients with advanced head and neck or non-small cell lung cancer, Eschmann et al. [8] investigated the predictive value of F-FMISO prior to radiotherapy with curative intent. All patients with a FMISO tumour to muscle ratio greater than 2 in non-small cell lung cancer and greater than 1.6 in head and neck cancer presented with tumour recurrence, further supporting the negative predictive value of significant hypoxia prior to radiation treatment.

Tumour uptake of Cu-ATSM in cervical cancers was found to be inversely related to progression-free survival and overall survival. Low pre-treatment tumour uptake of Cu-ATSM was predictive for response to therapy, while FDG PET results were not correlated with outcome measures [12]. In comparison to FMISO, Cu-ATSM exhibits higher uptake ratios between hypoxic and normoxic tissues. A particular advantage is the rapid kinetics of Cu-ATSM, which allows the identification of hypoxic tissues within 10-15 min post injection. It has been suggested that hypoxia-guided IMRT using Cu-ATSM allows the delivery of a higher dose of radiation to the hypoxic tumour subvolume.

Hypoxia imaging should be further investigated regarding the capability of guiding targeted chemotherapy using hypoxia-selective cytotoxins. Evaluation of the true benefit of these treatment strategies will also require that patients can be reliably stratified to optimise therapeutic efficacy.

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4.2 Respiratory Motion Management in CT and PET/CT for Radiation Therapy Planning

Ditte E. Nygaard and Marianne C. Aznar

The challenges of respiratory motion in radiotherapy

Thoracic and abdominal lesions, such as tumours in the lungs, liver, pancreas and kidneys, as well as tumours located in the breasts, are under the influence of respiratory motion. The magnitude of motion can vary widely between tumours, even within the same organ. The magnitude of respiratory motion of, for example, a lung tumour is typically in the range of a few millimetres to 2 cm during normal respiration, but lung tumour displacements exceeding 3 cm have been observed [1,2]. For tumours located in the liver, the typical magnitude of respiratory motion ranges from a few millimetres to 2-3 cm during normal respiration [3,4]. A tumour motion pattern can be very complex and is not necessarily regular in time. Furthermore, tumour motion can vary in magnitude, frequency and baseline (i.e. there is a shift in the whole motion pattern) within minutes as well as from day to day [2,5].

Tumours subject to respiratory motion represent a major challenge in radiotherapy (RT). A computed tomography (CT) scan is normally used for RT planning, sometimes in combination with positron emission tomography (PET) or magnetic resonance (MR) imaging, and it is crucial that the images represent the shape and position of the tumour within the patient as exactly as possible. However, if respiratory motion is not accounted for, as is the case for all conventional image modalities, the images can be affected by motion artefacts, i.e. systematic errors associated with the images [6-10]. Motion artefacts can introduce uncertainties in the treatment planning process, which will have an impact throughout the course of RT and may result in the tumour being underdosed while the surrounding healthy tissue receives an unwanted radiation dose.

Respiratory tumour motion is a challenge not only during conventional imaging for RT planning but also in conventional RT delivery. If respiratory correlated image guidance is not applied when positioning the patient at the beginning of each RT session, a shift in the tumour motion baseline can lead to a risk that the tumour will be outside the treated volume throughout the session. Furthermore, respiratory motion during conventional RT can blur the dose gradients, and the tumour may move out of the treated volume, consequently receiving a lower dose than intended. In conventional RT, respiratory motion is often accounted for by adding large margins to the treatment volume, to ensure that the tumour will always move inside a high dose volume. However, this will inevitably result in the irradiation of a large volume of healthy tissue.

To reduce the uncertainties in the treatment of tumours affected by respiration, their motion must be taken into account – during imaging as well as during RT delivery. In this chapter, we shall review different approaches to motion management in CT, PET and hybrid PET/CT from an RT planning point of view and discuss how they can be incorporated into the treatment planning strategy.

Motion management techniques in CT acquisition for radiotherapy planning

The presence of respiratory motion during conventional CT acquisition can result in motion artefacts such as a smeared or heavily distorted image of the tumour or acquisition of the tumour image during an extreme breathing phase such as end-inspiration or end-expiration [6,7]. Figure 1 shows an example of motion artefacts in a coronal reconstruction of a conventional CT scan in a patient with non-small cell lung cancer compared with an image acquired in deep inspiration breath hold. As discussed later in this chapter, breath-hold CT images are typically not affected by respiratory motion and can therefore be used as a reference for actual tumour size and shape (but not for tumour position throughout the respiration cycle). Apparent tumour volume for the conventional CT scan in Fig. 1 is 65 cm^3 compared with 35 cm^3 for the breath-hold CT scan.

Several techniques have been developed to manage respiratory motion during CT acquisition for RT planning. Knowledge of the real-time respiratory tumour motion during CT acquisition is important for managing the motion, but this knowledge is usually not directly available. Therefore, most of the techniques rely on the accuracy of either an external or an internal surrogate to generate a signal describing the tumour motion, in the following referred to as a respiration signal. External surrogate techniques may include, for example, monitoring the motion of a marker placed on the chest wall of the patient to generate a respiration signal, while internal surrogate techniques may include, for instance, tracking the motion of a fiducial marker implanted in the tumour to generate a respiration signal.

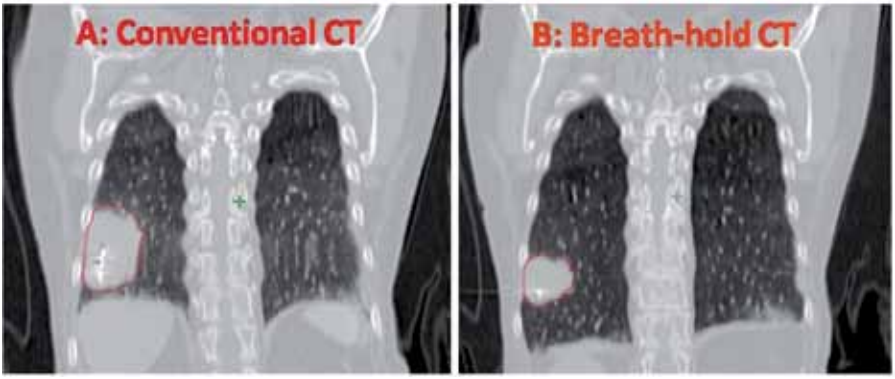


Figure 1 A, B: Coronal reconstructions of (A) conventional CT scan and (B) deep inspiration breath-hold CT scan for the same non-small cell lung cancer patient. Notice the distortion of the tumour in A due to motion artefacts

Most motion management techniques for CT acquisition also rely on the patient to control his or her respiration in a special way, e.g. by breathing very regularly or by maintaining a stable breath-hold level of certain depth. The patient can be helped to control their respiration by applying audio or visual respiratory guidance, whereby the patient is guided either by receiving feedback/guidance from the technicians/a recorded voice or by watching the monitored respiration signal during the CT acquisition. The effectiveness of respiratory guidance depends heavily on patient compliance. Therefore, proper patient selection and instruction before the scan are recommended.

This section will review three motion management techniques often used for CT imaging of respiratory moving tumours: breath-hold CT, respiratory gated CT and four-dimensional CT. The section also discusses limitations of the techniques as well as how they can be incorporated into the RT planning strategy.

Breath-hold CT

A breath-hold CT scan visualises the tumour in a pre-specified phase of the respiration cycle, by immobilising the tumour during acquisition. During breath-hold CT acquisition, a respiration signal is obtained, and the scan beam is only turned on when the respiration signal is stable during a breath hold. Breath-hold CT scan is typically acquired in either the end-expiration or the end-inspiration phase. Figure 2 shows the respiration signal for a patient during deep inspiration breath-hold CT acquisition monitored using a marker placed on the chest wall. No respiratory guidance was applied.

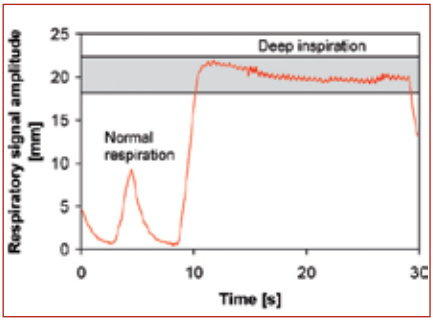


Figure 2: Respiration signal for a patient during deep inspiration breath-hold CT acquisition, obtained by monitoring the motion of a marker placed on the chest wall

Acquisition time and delivered dose for a breath-hold CT are equivalent to those for a conventional CT scan. The acquisition time is about 10 s, and the dose delivered is about 5-10 mSv depending on, for instance, the pitch, mAs and the extent of the scan.

A breath-hold CT scan will typically not be affected by motion artefacts. However, motion artefacts may arise if the patient is unable to maintain a stable breath-hold level or if the correlation between the respiration signal and the tumour motion is not stable [5].

A breath-hold CT scan is typically used for planning of breath-hold RT. During breath-hold RT, a respiration signal is monitored in the same way as during image acquisition, and the treatment beam is only turned on when the respiration signal indicates a stable breath-hold level with the same depth as during CT acquisition.

Breath-hold RT has the potential to reduce treatment-related toxicities. In the case of breast cancer, breath-hold RT may reduce both cardiac and lung toxicities compared with conventional RT, if the dose is delivered during deep inspiration breath hold [11]. The reduction is due to the spatial separation between the breast and the heart, which is increased by the inflation of the lungs during deep inspiration. Figure 3 shows transverse reconstructions at mid-breast position of a deep inspiration breath-hold CT scan and a conventional CT scan, illustrating the increased spatial separation during deep inspiration. The colour wash in Figs. 3A and 3B shows the areas covered by the RT fields when treatment is performed with deep inspiration breath-hold RT or conventional RT, respectively. The dose deposited in the heart is evidently lower for deep inspiration breath-hold RT.

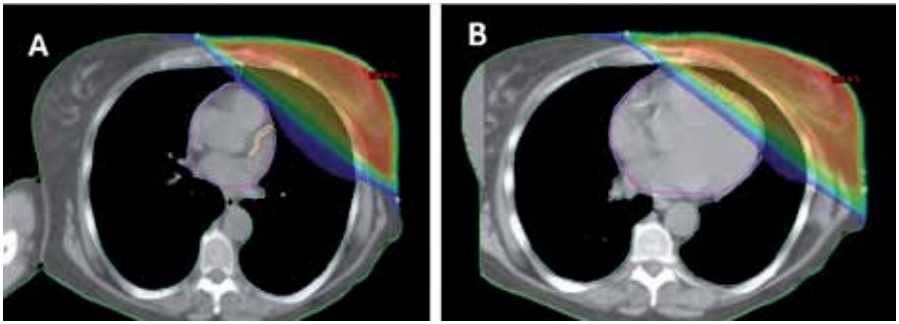


Figure 3 A, B: Transverse reconstructions at mid-breast position of (A) deep inspiration breath-hold CT and (B) conventional CT for the same breast cancer patient. The cardiac structures are pushed in the caudally direction and away from the chest wall by the inflation of the lungs. The colour wash illustrates the areas covered by the RT fields

Respiratory gated CT

A respiratory gated CT scan visualises the tumour in a pre-specified portion of the respiration cycle, commonly referred to as the gating window. During respiratory gated CT acquisition, a respiration signal is obtained, and the scan beam is only turned on when the respiration signal is within the gating window. Typically, the gating window extends over the end-inspiration phase or the end-expiration phase. Figure 4 shows the respiration signal for a patient during respiratory gated CT acquisition with a gating window covering the end-inspiration phase. The respiration signal was monitored using the motion of a marker placed on the chest wall, and audio respiratory guidance was applied.

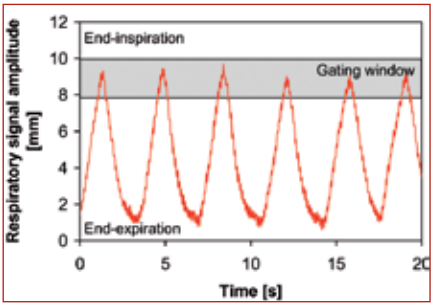


Figure 4: Respiration signal for a patient during respiratory gated CT acquisition in the end-inspiration phase. The scan beam is only turned on when the respiration signal is within the gating window, illustrated by the grey bar

A respiratory gated scan procedure takes longer than a non-gated one, since the scan beam is not on continuously. The duration of respiratory gated CT acquisition is about 250 s depending on the frequency of respiration. The dose delivered during imaging is about 5-10 mSv depending on, for example, the pitch, mAs and the extent of the scan, i.e. equivalent to a conventional CT acquisition.

The quality of respiratory gated CT is highly dependent on a regular respiration [5]. Figure 5A visualises a sagittal reconstruction of a respiratory gated CT scan highly affected by motion artefacts. Figure 5B shows the co-registered respiration signal, monitored using a marker placed on the chest wall. Audio respiratory guidance was applied during image acquisition. The respiration signal illustrates that the patient was unable to maintain a regular respiration signal amplitude even with audio respiratory guidance, leading to motion artefacts in the respiratory gated CT scan.

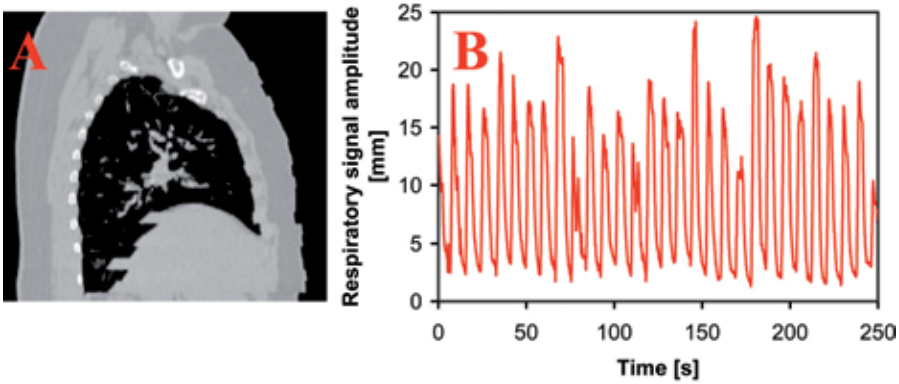


Figure 5A: Sagittal reconstruction of a respiratory gated CT scan highly affected by motion artefacts. Figure 5B: Respiration signal during image acquisition, showing an irregular breathing pattern

The quality of respiratory gated CT images can also be degraded by large residual tumour motion, i.e. tumour motion within the gating window (see Fig. 4). The quality can furthermore be degraded if the correlation between the respiration signal and the tumour motion is not stable [5].

A respiratory gated CT scan can be used for respiratory gated RT planning. During respiratory gated RT, a respiration signal is obtained in the same way as during CT acquisition, and the treatment beam is only turned on when the respiration signal is within the same pre-specified gating window as during CT acquisition.

As is the case for breath-hold RT, respiratory gated RT can potentially reduce treatment-related toxicities. As for breath-hold RT of breast cancer, respiratory gated RT may reduce both the cardiac and the lung toxicity compared with conventional RT, if the gating window covers the end-inspiration phase [12]. For respiratory gated RT of thoracic and abdominal tumours, gating in the end-expiration phase can be preferable, since tumour position during the end-expiration phase is more stable and reproducible than that during the end-inspiration phase [2,13].

Four-dimensional CT

Four-dimensional (4D) CT is an imaging technique that combines CT information in the three spatial dimensions with time as the fourth dimension, visualising the tumour as a function of time during a respiration cycle. During 4DCT acquisition the respiration of the patient is monitored, as for breath hold and respiratory gated CT. In a 4DCT scan the CT images are over-sampled and retrospectively sorted into a pre-defined number of bins (typically 8-10) based on the respiration signal.

Each bin of a 4DCT scan is related to a different phase of the respiration cycle. Figure 6 illustrates the principles of the sorting procedure for a simple reconstruction with four bins. Figure 7 illustrates the coronal reconstructions of ten bins of a 4DCT scan for the same non-small cell lung cancer as in Fig. 1. Bin 1 represents the end-inspiration phase and bin 8 represents the end-expiration phase. The tumour moves 2.4 cm in the cranio-caudal direction during one respiration cycle.

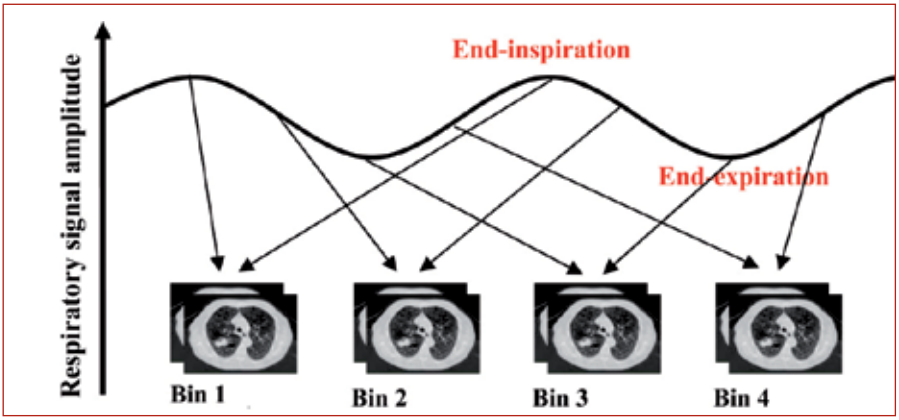


Figure 6: Principle of the 4DCT sorting procedure for a simple reconstruction with four bins. Bin 1 represents the end-inspiration phase and bin 3, the end-expiration phase

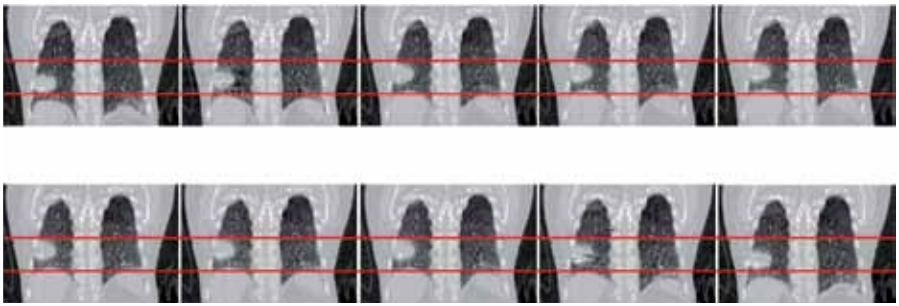


Figure 7: Coronal reconstructions of ten bins of a 4DCT scan for the same non-small cell lung cancer patient as in Fig. 1. Bins 1 and 8 represent the end-inspiration and the end-expiration phase, respectively. The red lines illustrate the end-points of tumour motion in the cranio-caudal direction

The duration of a typical 4DCT acquisition is about 100 s. The dose delivered during 4DCT acquisition is considerably higher than that for conventional, breath-hold and respiratory gated CT: about 30-50 mSv depending on, for example, the pitch, mAs and the extent of the scan.

The image quality of a 4DCT scan is highly dependent on regular respiration. The image quality can also be affected by large residual tumour motion within the bins as well as a phase shift between the respiration signal and the respiratory tumour motion [5]. Figure 8 shows a coronal reconstruction of a 4DCT bin for the same non-small cell lung cancer patient as in Figs. 1 and 7. The 4DCT bin is highly affected by motion artefacts, resulting in a tumour divided into two parts. The co-registered respiration signal during image acquisition of the tumour region, also shown in Fig. 8, indicates that the artefacts are a result of changes in the respiration depth during image acquisition.

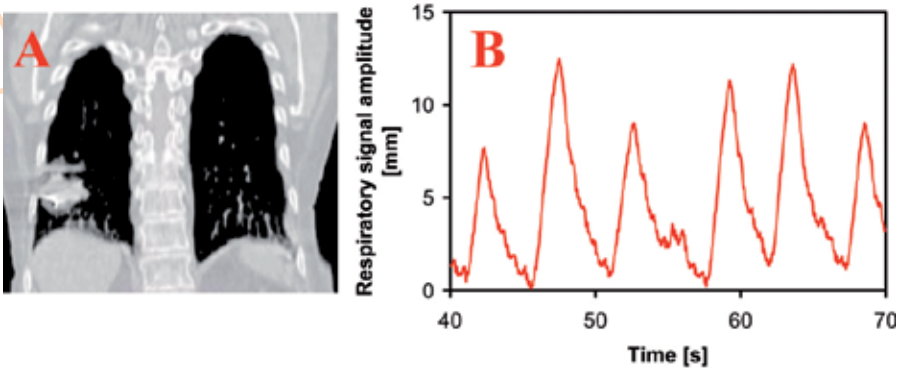


Figure 8 A: Coronal reconstruction of a 4DCT bin for the same non-small cell lung cancer patient as in Figs. 1 and 7. Figure 8B: Respiration signal during image acquisition of the tumour region. Because of the irregular respiratory pattern, the 4DCT bin is highly affected by motion artefacts: the tumour appears to be divided into two parts

4DCT can be used as a tool for evaluation of the respiratory-induced motion of the tumour and its surroundings. Knowledge of the magnitude of tumour motion can be used in the assessment of a patient-specific motion management technique during RT delivery [14] and in the calculation of patient-specific treatment field margins [15].

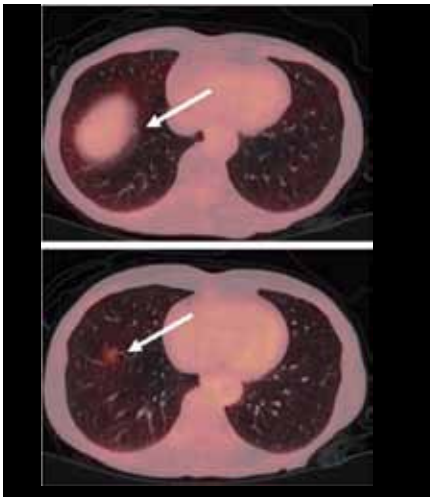
The midventilation bin of a 4DCT scan is the bin where the tumour is closest to its time-weighted mean position in the motion pattern. If only considering motion in the craniocaudal direction for the tumour in Fig. 7, bin 9 represents the midventilation bin based on visual evaluation. By using the midventilation bin for RT planning, the risk of introducing systematic errors can be reduced compared with planning on a conventional CT [16].

A bin of a 4DCT scan can also be selected with the purpose of respiratory gated RT planning. An advantage of using 4DCT for respiratory gated RT planning is that the tumour motion pattern visualised by the 4DCT scan can be used to select the most optimal gating phase. However, since dose deposited in the patient during 4DCT acquisition is much higher than for a respiratory gated CT scan, 4DCT is typically not preferable for patient groups where the optimal gating phase is predictable.

Furthermore, an internal target volume (ITV, see Sec. 4) can be created by encompassing the clinical target volume (CTV, see Sec. 4) from all the 4DCT bins. The ITV concept aims to provide 100% dose coverage to the CTV during a respiration cycle, but results in the irradiation of a large volume of healthy tissue [5].

Motion management in PET and PET/CT imaging

The introduction of PET imaging in RT potentially improves treatment planning both by helping to define the metabolically active tumour volume and by minimising the risk of geographical misses. For example, in the treatment of lung cancer and of Hodgkin lymphoma, PET information has enabled a significant reduction of the radiation target fields, thereby sparing normal tissue and reducing the side-effects of the treatment [17,18]. However, PET images will also be affected by motion artefacts, such as blurring effects: quantitative parameters such as the maximum standardised uptake value (SUV_{max}) are underestimated while the apparent tumour volume will tend to be overestimated [9,19]. Another issue arises if the patient has an irregular respiration pattern and the lesion appears in slightly different positions between PET and CT images (Fig. 9): for small lung lesions, a positional "mismatch" could result in such an incorrect attenuation correction that the lesion will mistakenly appear PET negative [20,21]. As a result there has been a drive to develop novel approaches to obtain fewer artefacts in the PET images.



Courtesy of Charlotte Birk Christensen, Rigshospitalet

Figure 9: Mismatch between CT and PET images during a hybrid PET/CT examination. The CT lesion can be seen close to the liver (top image), while the PET-positive focus appears to have moved in the cranial direction (bottom image).

Respiratory motion management in PET and PET/CT imaging is commercially available but is not yet widely used in a clinical setting. Two general philosophies of breathing adaptation will be reviewed in this section:

- approaches which (mostly) eliminate motion by acquiring images in one single breathing phase (e.g. end-inspiration or end-expiration): in this chapter, we shall focus on "breath-hold PET scanning";

- approaches which capture the tumour in all phases of the breathing cycle (similar to the 4DCT techniques presented above and here called "4DPET").

As with CT scanning, the PET imaging procedure relies on a monitoring system to translate the patient's breathing pattern into a trigger signal for image acquisition.

Breath-hold PET scanning

One simple way to eliminate motion artefacts from the images is to ask patients to hold their breath during the examination. A whole-body PET scan is not feasible in breath hold, as the scanning time will become too long: the breath-hold approach is then often limited to a single field of view (e.g. over the thorax), while the rest of the patient's anatomy is imaged in normal respiration. Patients perform several consecutive breath holds of up to 20 s, often at deep inspiration [22,23] but also at end-expiration [24]. Respiratory guidance (such as visual and/or audio coaching) may be used to ensure that patients hold their breath at a consistent level during the examination. Breath-hold scanning results in images that are free (or almost free) of motion artefacts and minimises the probability of a mismatch between PET and CT. Quantitative parameters (such as SUV_{max}) will tend to increase compared with blurred 3D images and the apparent lesion volume will likely be smaller (Fig. 10). For RT purposes, if the patient is likely to be treated at deep inspiration breath hold in order to reduce the probability of cardiac and pulmonary side-effects, it can also be an advantage to acquire PET/CT planning images in breath hold. However, as mentioned previously, not all patients will be able to comply with breath-hold instructions depending on their performance status and lung function.

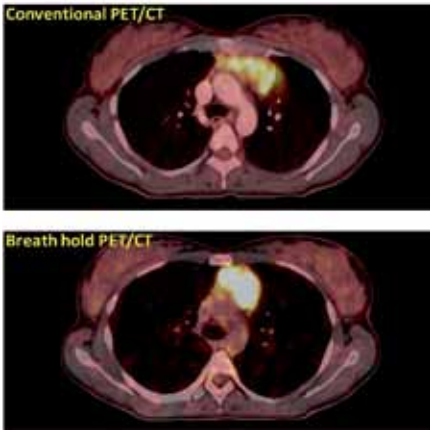
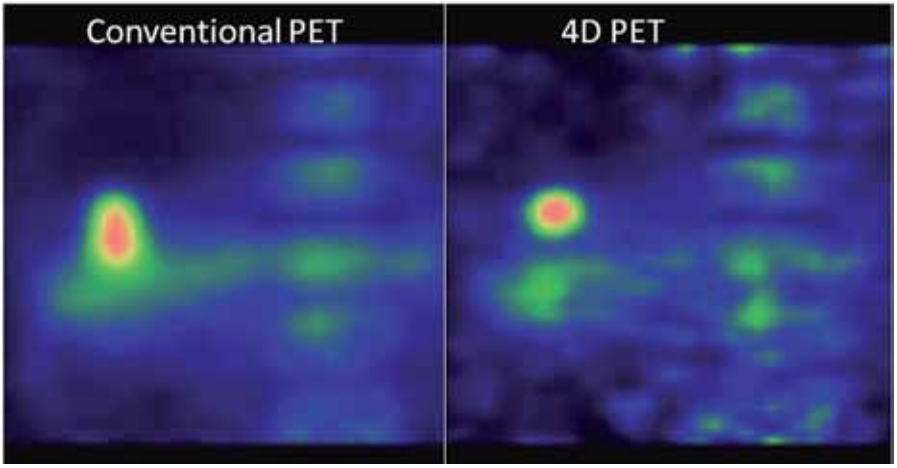


Figure 10: Transverse reconstructions of conventional (normal breathing) PET/CT followed by a single field of view, deep inspiration breath-hold PET/CT in a Hodgkin lymphoma patient. Note the changes in tumour appearance (more defined, homogeneous uptake in the breath-hold image). Both images were acquired after a single injection of 400 MBq of ^{18}F-FDG; scanning time was 2.5 min per bed for the conventional PET/CT, versus three consecutive acquisitions of 20 s for the single-bed breath-hold PET/CT.

4DPET scanning

The first clinical attempts at 4DPET were performed using an adapted version of the cardiac gating mode available on PET/CT scanners [25,26]. 4DPET consists in binning the imaging data according to pre-defined phases of the respiratory cycle (usually eight to ten bins are used), in a similar fashion to the 4DCT binning presented in Fig. 6. In this context, parameters such as SUV_{max}, SUV_{mean} and tumour volume can be recovered in spite of considerable tumour motion (over 2 cm) [9]: an example is provided in Fig. 11. 4DPET has been shown to recover the true SUV of the tumour even in the presence of breathing motion but suffers from a few caveats: the examination time is prolonged (about 20 min for a single bed position) and as the signal is distributed over several bins, the signal to noise ratio is usually poor [27,28]. Another disadvantage is that it can be necessary to increase the activity injected (for example, by 30% [29]). Moreover, similarly to 4DCT, 4DPET will depend on a regular breathing pattern or artefacts will still be present in the images.



Courtesy of Jan-Jakob Sonke, The Netherlands Cancer Institute

Figure 11: The same lung tumour imaged with conventional PET and 4D PET. Notice how the uptake area appears blurred owing to breathing artefacts in the conventional image.

In the literature, the term 4DPET/CT can refer to a 4DPET coupled to a conventional CT acquisition [30,31] as the increased dose burden from the 4DCT will be undesirable in diagnostic examinations. For lung cancer patients referred for RT, however, a full 4DPET/4DCT procedure would be ideal, as the information gained from the 4DCT is important. A mismatch between the 4DCT bins and the 4DPET bins is also possible and careful post-processing of the images may be required [29,32].

An alternative approach is to use the information from a 4DCT to reconstruct conventional PET images. For example, the mid-ventilation bin of a 4DCT scan can be used for attenuation correction of conventional PET images: in this situation, one ensures that the tumour is represented closest to its mean position on the CT-based attenuation map, and the risk of positional mismatch between PET and CT images is minimised [33].

Perspectives for RT planning and treatment

An additional potential benefit of breathing-adapted PET/CT imaging for RT is better target definition. Inter-observer delineation variation (i.e. how much variation would be observed if several radiation oncologists were asked to contour the same tumour) is an important concern in RT. Indeed, a margin is often added to the target volume to account for this uncertainty, resulting in larger radiation fields and a potential increase in treatment-related toxicity. It has been shown that PET/CT can reduce delineation variation, for example by differentiating between malignant lesions and atelectasis [34]. It is probable that breathing-adapted PET/CT will further increase delineation accuracy and thereby reduce the uncertainty margin applied to the treatment fields.

A new paradigm, called "dose painting" is now gaining interest in RT [35]: using the metabolic information provided by the PET images, the tumour can be "painted" so that volumes showing a high tracer uptake (and containing aggressive cancerous cells) receive a higher dose of radiation. It has long been recognised that increasing the dose to the tumour considerably improves local control (and therefore, potentially, survival) in some patient groups. However, such a dose escalation is not always possible as it would result in an increased exposure of normal tissue, possibly leading to an unacceptable rate of serious side-effects. In dose painting, since only aggressive sub-volumes of the tumour receive an increased dose as opposed to the whole tumour volume, the impact on the surrounding normal tissue can be minimised. A comparison of standard versus dose-painting dose distributions is presented in Fig. 12 for a lung cancer treatment.

However, for this approach to be clinically viable, blur-free images are essential to define precisely which sub-volumes of the PET-positive tumour will benefit from a higher dose. Hence, respiratory motion management during the acquisition of PET/CT images is highly desirable.

Present RT technology is capable of delivering highly modulated dose-painting treatments to static tumours. However, for tumours affected by respiration, motion management will also be required during the treatment delivery, and the technological implications have not yet been solved. "Tumour tracking" is a promising method enabling the radiation beam to follow the tumour throughout the breathing cycle [36]: in the case of dose painting, it would require that the multileaf collimator shaping the beam opening be adapted in real time to the position of the tumour (and of the high-dose target volumes) throughout the treatment delivery. Such an approach, when it becomes widely available, will close the loop by providing a truly 4D treatment based on 4D imaging.

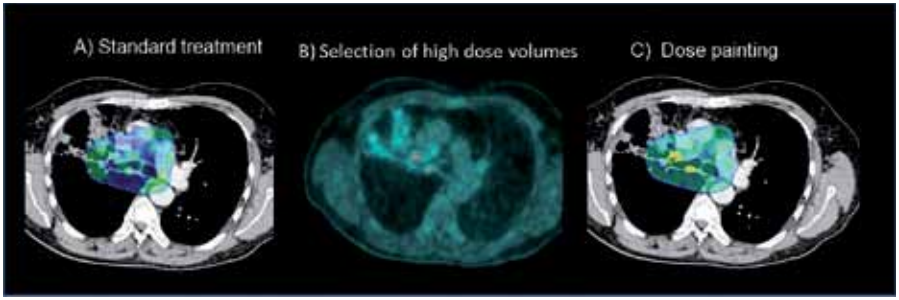


Figure 12A-C: Illustration of a simple dose painting strategy. Figure 12A represents a standard treatment, where the target volume receives a uniform dose (the dose distribution is represented by the blue-green colour wash). In Figure 12C, sub-volumes of the tumour, selected because of their high tracer uptake, receive an extra dose of radiation (yellow-red colour wash).

Conclusion

Imaging strategies able to correct or account for respiratory motion are becoming more widespread and have shown considerable potential for RT applications: for example, respiratory motion management can improve the accuracy of tumour volume definition in both CT and PET, or of quantification in PET images. Though 4D approaches provide information about the tumour over the whole breathing cycle, single-phase (gated or breath-hold) approaches may still be preferred depending on the treatment strategy for the individual patient. Additionally, more research is needed to address some technical issues, such as remaining artefacts or how to handle an irregular breathing pattern. Respiratory motion management of PET/CT will likely play a key role in the adoption of new treatment paradigms, such as dose painting and tumour tracking.

References Section 4.2

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