

## High-precision Radiotherapy

a report by

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### The Role of Radiotherapy in Cancer Management

Radiotherapy plays an increasingly dominant role in the comprehensive multidisciplinary management of cancer today. About half of all cancer patients will receive radiotherapy either as a part of the initial treatment with curative intent or as palliative treatment. The need for radiotherapy has been increasing over the last few years as a result of the expanding indications in many of the frequent cancer sites.

In Denmark (population 5.3 million) the number of treatments will almost double within a 10-year period, from 110,000 fractions in 1997 to an estimated 208,000 in 2007, according to the 2005 Danish Cancer Control Plan update. Primary radical radiotherapy is used for diseases with predominantly loco-regional spread, such as cancers of the head and neck cancer, prostate, cervix, lung or bladder. Adjuvant radiotherapy is used in combination with surgery or chemotherapy for a wide range of cancers, of which breast, lung and rectum, in that order, are the most important. Curative radiotherapy is given in many small fractions over five to eight weeks, and generally it is not possible to give this type of irradiation again in the same area. Palliative radiotherapy is indicated for bone metastases, superior vena cava syndrome, spinal cord compression, tumour ulcerations or bleedings. One or more fractions are often sufficient to relieve the symptoms, and in some cases this results in life-prolongation. The treatment can be repeated. Although half of all cancer patients are treated with radiation therapy, the cost of radiotherapy constitutes only 5% of the total expenses in oncology according to one Swedish report.<sup>1</sup>

### High-precision Conformal Radiotherapy

A number of technological developments within the last decade have opened up a huge and rapidly expanding interest from clinicians, scientists and

industry specialists in making radiation therapy more conformal and precise. By reducing the technical and clinical uncertainties in tumour targeting, it is possible to deliver the radiation dose more precisely to a specified target. It has therefore become possible to increase the radiation dose to the relevant target and/or decrease the volume of irradiated normal tissue. This should result in an improved therapeutic ratio, meaning that more patients will be cured with fewer side effects. The best examples of high-precision radiotherapy are intensity-modulated radiotherapy (IMRT) and stereotactic radiotherapy. Both techniques require very firm immobilisation of the patient, incorporation of radiological examination in the treatment planning for precise definition of the target and highly precise and technical advanced radiation equipment.

### IMRT

In IMRT, the dose intensity varies within each of the many conformal fields, allowing highly individualised dose gradients throughout the treated volume. This can be utilised to spare critical normal tissue in the vicinity – or even surrounded by areas – of tumour or regional lymph nodes. Different doses can be assigned to macroscopic and microscopic tumour volumes, allowing a so-called integrated boost in a single dose plan (see *Figure 1*). In head and neck cancer, IMRT results in less severe xerostomia and dysphagia compared with conformal radiotherapy. Sparing of the eye, optical pathways and spinal cord are other important features of head and neck IMRT. In prostate cancer, IMRT has allowed dose distribution because the technique can be used to reduce the dose to bladder and rectum.

### Stereotactic Radiotherapy of Intracranial Lesions

In stereotactic radiotherapy, multiple small conformal fields from different angles are directed against a precisely defined volume. This results in a

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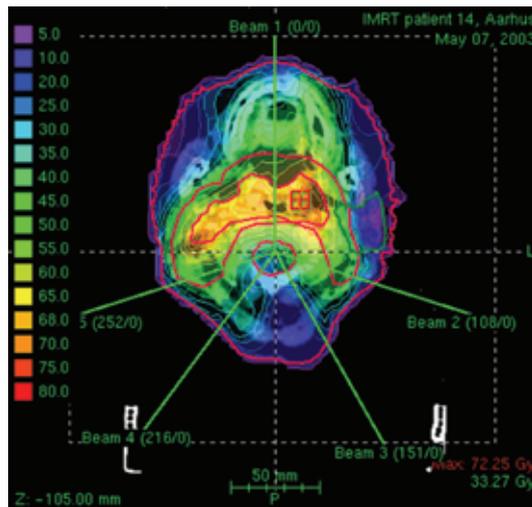
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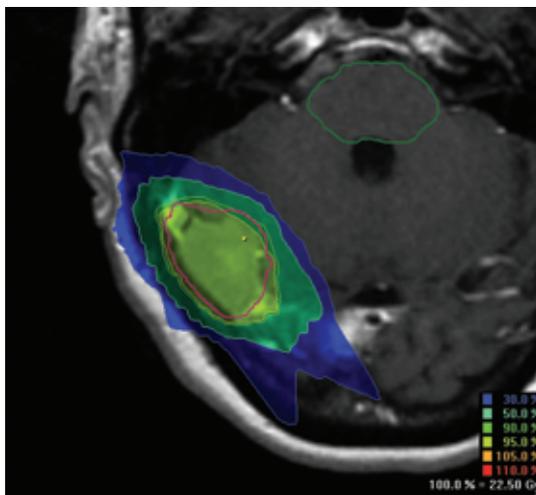
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**Figure 1: Typical Dose Distribution for IMRT of a Pharyngeal Cancer**



Note the relative sparing of spinal cord and contralateral parotid gland.

**Figure 2: Dose Distribution in Stereotactic Radiotherapy of a Brain Tumour**



The prescribed dose was 22.5Gy as a single dose.

high central dose with minimal doses to the surrounding normal tissue. Stereotactic radiotherapy or radiosurgery (SRS) was primarily developed in the treatment of benign brain tumours as a non-invasive alternative to neurosurgery. In intracranial stereotactic radiotherapy, the head of the patient is immobilised with a frame attached to the skull of the patient with screws. A computed tomography (CT) scan is performed with the frame in place as an external co-ordinate system. The CT images are fused with previous magnetic resonance imaging

(MRI) in the dose-planning system for better target definition (see *Figure 2*). The treatment is given as a single fraction and in some cases as fractionated treatment. Typical indications are inoperable meningiomas, pituitary adenomas, acoustic neurinomas, arterio-venous malformations or solitary brain metastases.

### Stereotactic Body Radiotherapy

Stereotactic body radiotherapy (SBRT) for tumours outside the brain has been used increasingly over the last 10 years. In Aarhus, more than 300 patients have been treated since 1999.<sup>2-4</sup> By stereotactic radiotherapy, a small volume is irradiated with a single or few radiation fractions by high-precision, firm immobilisation of the patient in a body frame and by use of multiple field arrangements. In this way it is possible to apply a high dose to a small tumour volume and to spare the surrounding normal tissue, potentially reducing the incidence and severity of acute and late side effects.

In contrast to conventional radiotherapy, stereotactic radiotherapy uses an external co-ordinate system for target localisation. In SBRT, a very firm immobilisation can be obtained by the stereotactic body frame, which also carries a radio-oblique fiducial system for targeting of the radiation beams to the tumour (see *Figure 3*).

In the management of lung cancer, SBRT can result in more patients being treated with curative intent. Limited-stage non-small-cell lung cancer is generally treated surgically. However, a large proportion of patients with lung cancer have a poor lung function due to tobacco smoking and they may be medically inoperable; such patients are candidates for radiotherapy (see *Figure 4*). Retrospective studies show that the five-year survival after conventional primary radiotherapy for non-small-cell lung cancer is in the range of 15% to 20%. With SBRT, the preliminary results from prospective phase 1-2 studies show a local control rate of up to 83% in limited stage disease. In the phase 2 study from Aarhus University Hospital, 48% of the patients were without evidence of disease after two years. Toxicity has generally been judged to be limited, mainly as deterioration of pulmonary function and performance status.

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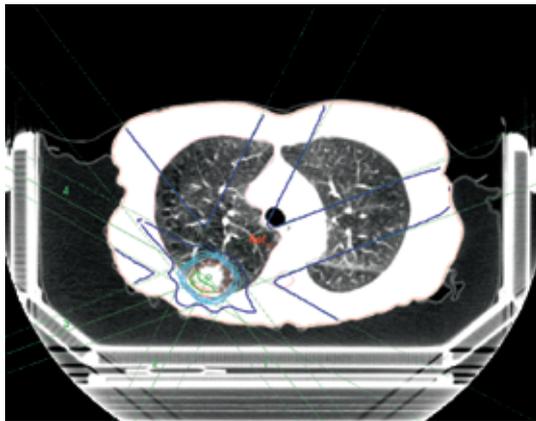
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**Figure 3: Immobilisation in Stereotactic Body Radiotherapy Using the Stereotactic Body Frame**



**Figure 4: Dose Distribution in Stereotactic Body Radiotherapy of a Limited Stage Non-small Cell Lung Cancer**



The prescribed dose was 45 Gy in three fractions in one week.

**Figure 5: In image-guided radiotherapy, high-resolution X-ray equipment mounted on the accelerators can be used to image the patient or tumour in the treatment position**



For liver tumours, SBRT is best established in the treatment of patients with liver metastases from colorectal cancer, while studies are under way regarding hepatocellular carcinoma, cholangiocarcinoma, carcinoid tumour and selected patients with liver metastasis from other cancer types. The background for local treatment of colorectal liver

metastases is based on experience from surgical resection of liver metastases, where up to 25% to 30% of patients survive five years after treatment.

SBRT so far has been offered as the 'last resort' when surgery or radiofrequency ablation has not been possible. Aarhus University Hospital has used SBRT for liver tumours since 1999 in a prospective phase 2 study. For colorectal metastases, the preliminary results showed a two-year local tumour control rate of 82%, a progression-free survival of 15% and a two-year overall survival rate of 28%. The toxicity has been acceptable with grade 0–1 in 53% of the patients within six months after treatment. More detailed experimental and clinical studies are still needed to describe the outcome of SBRT of tumours of the liver.

### Future Aspects

Although the clinical data so far on high precision radiotherapy are encouraging, experimental and clinical studies are needed to describe the volume/time/dose/fractionation relationships on control of the tumours and on damage of the normal tissue. Also, studies on the proper use of adjuvant chemotherapy and novel biological targeting in conjunction with IMRT or SBRT are warranted.

The technical challenges are still enormous. Incorporation of positron emission tomography (PET)-CT may allow a more precise definition of the target, including areas of tumour that cannot be visualised by CT alone and to exclude areas of normal tissue from the irradiated volume. Image-guided radiotherapy with X-ray equipment mounted on the accelerators or in the treatment room may be used to image the patient or tumour in the treatment position (see Figure 5). The obtained film or cone-beam CT is compared with pre-treatment planning information, and it is then possible to correct online for set-up uncertainties on a daily or weekly basis. The result is a potential for reduced technical margins, and thus less irradiated volume. The respiratory motion of tumours in the liver and lung can be substantial, and is most often compensated by routine addition of an internal margin in the target outline.

Frameless SBRT based on implanted gold markers and/or cone-beam CT may prove to be an attractive alternative, and novel adaptive imaging and delivery techniques with respiratory gating should make it possible to reduce treatment margins. With image-guided adaptive radiotherapy it may be possible to dose-escalate against smaller tumours, and/or to treat larger tumours than are currently being treated. ■