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Potential of biological images for radiation therapy of cancer

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Recent technical advances in 3D conformal and intensity modulated radiotherapy (3DCRT and IMRT) based on patient-specific CT and MRI images, have the potential of delivering exquisitely conformal dose distributions to the target volume while avoiding critical structures. Emerging clinical results in terms of reducing treatment-related morbidity and increasing local control appear promising. Recent developments in imaging have suggested that biological images may further positively impact cancer diagnosis, characterization and therapy. While in the past radiological images are largely anatomical, the new types of images can provide metabolic, biochemical, physiological, functional and molecular (genotypic and phenotypic) information. For radiation therapy, images that give information about factors (e.g. tumor hypoxia, Tpot) that influence radiosensitivity and treatment outcome can be regarded as radiobiological images.

The ability of IMRT to "paint" (in 2D) or "sculpt" (in 3D) the dose, and produce exquisitely conformal dose distributions begs the '64 million dollar question' as to how to paint or sculpt, and whether biological imaging may provide the pertinent information. Can this new approach provide 'radiobiological phenotypes'non-invasively, and incrementally improve upon the predictive assays of radiobiological characteristics such as proliferative activity (Tpot ' the potential doubling time), radiosensitivity (SF2' the surviving fraction at a dose of 2 Gy), energy status (relative to sublethal damage repair), pH (a possible surrogate of hypoxia), tumor hypoxia, etc. as prognosticator(s) of radiation treatment outcome. Important for IMRT, the spatial (geometrical) distribution of the radiobiological phenotypes provide the basis for dose distribution design to conform to both the physical (geometrical) and the biological attributes.

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Impact of imaging on the treatment choice in head and neck cancers

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The routine use of anatomic imaging modalities (CT, MR, US) and more recently functional imaging (PET and fMRI) has profoundly changed the management of patient with solid tumors in general, and with head and neck malignancies in particular. Imaging has impact on the staging, the treatment procedure especially with radiotherapy, the response evaluation and the follow-up.

For tumor staging, CT and MR and to a lesser extend US, have increased both the specificity and the sensitivity of the diagnostic procedure enabling a more thorough examination of the disease extension and consequently leading to an optimal use of the main therapeutic modalities, e.g. surgery and radiotherapy. Although promising data have been reported, the added value of functional imaging with PET ([18F]-FDG or [11C]-methionine) for tumor staging and its impact on patient management remains to be further investigated. On the other hand, PET imaging with markers probing specific cellular pathways (e.g. proliferation, hypoxia) might turn to be a strong player for prognostic significance. Validation of such markers is in progress. Treatment by radiotherapy requires an accurate delineation of the macroscopic tumor volume and its microscopic extension. For various reasons, CT scan has always been the main modality used for treatment planning purposes. Image guided therapy with MR and PET is however under evaluation. The former should bring more detailed anatomic definition especially for tumors close to the nervous structures of the base of skull, or for tumors having weak contrast with adjacent structures, e.g. base of tongue tumors. The later, combined with specific markers might enable a better tailoring of the radiation dose distribution in tumor areas expressing bad prognostic factors, such as a high metabolism, hypoxic fraction or proliferative index. Response evaluation and follow-up after complex treatment procedures where both the anatomy and the texture of the tissues might have been profoundly altered represent a challenge to oncologists. In this regard, PET has shown its potential superiority over anatomic modalities, expressing a high negative predictive value thus limiting the use of more aggressive procedures. Also, quantitative PET analysis might represent an alternative tool for the evaluation of tumor response especially after biological therapies where a real mass reduction is rarely observed.

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Impact of imaging on the treatment choice in lung cancers (with emphasis on PET scanning)

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Surgery offers the best chance for cure in lung cancer patients, but is only performed when the primary lung tumour is resectable and when there are no mediastinal and/or extrathoracic metastases. Therefore, imaging is crucial for selecting appropriate treatment. CT and MR provide excellent visualisation of anatomic structures, however, they have their limitations. In determining the mediastinal nodal status, CT relies solely on the nodal size as a discriminator of metastatic involvement. It is well known that normal-sized nodes may harbour metastases and enlarged nodes may be reactive. The finding of enlarged adrenal glands or liver lesions on CT, MR or abdominal ultrasonography is relatively common in lung cancer patients. Given the limited accuracy of the conventional imaging methods, invasive staging will be necessary in order to avoid unnecessary surgery in case of metastasised disease or denial of potentially curative surgery. Newer imaging technologies such as endoscopic ultrasound (EUS) and positron emission tomography (PET), a metabolic imaging tool, are being evaluated for their efficacy in lung cancer. EUS guided fine-needle aspiration may replace mediastinoscopy to assess mediastinal lymphadenopathy (especially left-sided lymph nodes) and is of additional value in areas where lymph nodes are inaccessible for mediastinoscopy. As compared with conventional staging methods, PET results in a more accurate classification of disease stage. Especially the high negative predictive value of mediastinal PET and its ability to detect unsuspected distant metastases in a significant number of lung cancer patients may have a profound effect on treatment choice. In non-resectable patients, PET may also contribute to the size of radiotherapy portals. Concurrent chemoradiotherapy is becoming a standard treatment for stage III non-small cell lung cancer, but toxicity is still a problem. Therefore, smaller and effective radiation fields are a necessary research target. This also applies for patients with tumour-associated atelectasis. PET may also become important in measuring post-treatment tumour response. Finally, PET may prove to be useful in selecting patients for surgery after induction chemotherapy.

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Is missing the same as failing? Required dose-distributions in radiotherapy alone or combined with other modalities

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Advances in bioimaging and in radiotherapy planning and delivery technology have led to renewed interest in optimal dose-distributions in radiation oncology. As is often the case, these new technologies have so far mainly been used as tools for (a more convenient) planning of "standard" dose distributions. It seems likely, however, that highly modulated dose-distributions could be associated with a therapeutic advantage in some patients. There are three main sources of data that are relevant to this problem: bioimaging, molecular pathology on biopsy material and analysis of failure-pattern data after radiotherapy. In the lecture, I will briefly review some of this emerging evidence. The optimum dose-distribution depends not only on the anatomical spread of malignant cells but also on the precision by which the radiation therapy can be delivered. This includes day-to-day variability in patient set-up and the internal variation in target volume position. Mathematical modelling suggests that in the presence of patient-to-patient variability in clinical radiosensitivity, a limited cold-spot in the tumour dose affects tumour control less than what could intuitively be expected. Optimal dose distributions will also change if radiotherapy is combined with cytotoxic drug therapies and this will also be discussed based on simple mathematical models of tumour control probability. Finally, I will try to identify some areas of research which could lead to a more optimal prescription of radiotherapy within the next five years.

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Opportunities and challenges for PET imaging

Abstract not received.