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EDITORIAL

The emerging evidence for Stereotactic Body Radiotherapy

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The present issue of Acta Oncologica contains publications from the Third Acta Oncological Symposium on stereotactic body radiotherapy (SBRT) which was held in Copenhagen, June 15–17, 2006.

The concept of an Acta Oncological Symposium was developed seven years ago. The aim was to focus on an issue of emergent importance for oncology, preferably within a multidisciplinary approach and with a special Nordic interest or focus. The first symposium in 2000 was inspired by the development of axillary sentinel lymph node biopsy in breast cancer patients [1]. A second symposium on prostate cancer was held in 2004 [2–12]. The current third symposium focussed on stereotactic body radiotherapy. This issue has a special Nordic flavour with the early engagement of especially Swedish research groups dealing with both cranial and extracranial stereotactic radiotherapy [13–15]. Being anecdotal in its early clinical experience, stereotactic body radiotherapy gradually has turned into a more scientific activity which through proper early clinical trials has started to develop the necessary scientific knowledge base by which the benefits and problems of such treatment can be evaluated [16–19]. That is exactly what the purpose of the symposium was, namely to evaluate the current knowledge and technology in order to get an impression of what the use and current status of such treatments may have within oncology.

The publications presented in the present issue of Acta Oncologica are very much a reflection of the current international standard within the field. The organizers of the symposium invited a broad international faculty and got positive replies from all. In addition, many abstracts were submitted for the proffered paper sessions. The contributions therefore represent the current international activity within the field both when it comes to the clinical outcome studies and the papers related to dose planning and delivery of the radiotherapy. Stereotactic body radiotherapy has so far mostly been documented for small tumors in lung and liver, when surgery and other local treatments were not possible. Obviously, the area is still in its early development and no proper randomized trials exist to identify the indications for stereotactic body radiotherapy. Unfortunately, this is the same situation as seen with other technical developments in radiotherapy where both photons and particle treatments are based on phase I and II studies, and very few large-scale randomized trials available to demonstrate the benefit [20–32]. Although some studies are emerging within the field of IMRT, we are still in the situation where technological developments in radiotherapy – in contrast to similar developments with drugs – are not evaluated in proper large-scale clinical trials. The introduction of new treatment modalities into routine practice is therefore very much based on claims of obvious benefits, in terms of better dose distribution or reduced volumes, which is said to be difficult to evaluate in randomized controlled trials. However, constraints on resources within health care systems increasingly require that also new technologies are tested in an Evidence Based Medicine setting. It is the hope that the present collection of articles can be helpful in that aspect because they describe to a large extent the current standings from which such clinical trials should take their starting point.

The steep dose gradients around the small targets leave little room for errors in both target localization and dose delivery. Although imaging techniques like

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MR, PET and PET/CT should theoretically result in better definition of tumour and normal tissues than conventional planning CT, data on the correlation between novel imaging and histological findings are still lacking [33–35]. The sensitivity and specificity of new techniques compared to conventional CT should be further investigated also for patients undergoing SBRT. Target localization in lung and liver is also complicated by both intra and inter-fraction target respiratory motion, which adds to the uncertainty in treatment planning and delivery and increase the likelihood of geographic miss [36–38]. A margin is generally added to ensure adequate target dose coverage. Several emerging studies presented in the current issue address how respiratory gating can be used to minimize such motion artefacts and in turn reduce the margins. Although the preliminary results with respiratory gating are encouraging, there is still room for clinical studies to demonstrate that such advanced and time-consuming procedures are of true benefit for the patients.

Uncertainty margins can also be reduced by using Image-Guided Radiotherapy (IGRT). IGRT involves generation of images in the treatment room prior to (each) treatment, either full 3-D volumes or orthogonal x-rays aided by fiducial markers in, or near, the tumour [39]. SBRT is an ideal test scenario for IGRT due to the few treatment sessions involved, and since the margin reduction is potentially very important. Technical solutions for IGRT are commercially available, and include e.g. cone-beam CT, tomotherapy, orthogonal kV x-ray and in-room CT. A number of studies in the current issue of Acta Oncologica show the initial feasibility of such exciting 'IG-SBRT', while we still await larger clinical studies.

Stereotactic body radiotherapy involves three biological issues. Firstly, the small treatment volumes which minimize the dose of radiation to normal tissue, but on the other hand put stronger requirements on a well-defined definition of the target. Secondly, the problems related to dose and fractionation. Since stereotactic body radiotherapy grew out of the tradition of cranial stereotactic radiosurgery, hypofractionation using only one or a few fractions has been an integrated part of the concept. Despite the benefit of smaller set-up margins, hypofractionation is probably far from optimal in all situations. In fact, there are very few clinical situations, in e.g. malignant melanoma [40–42] and to lesser degree adenocarcinomas [43–47], where large doses per fraction are justified on the basis of radiobiological data. So, the sparing of late reacting normal tissues by using smaller doses per fraction should be considered also in stereotactic body radiotherapy to further optimise the therapeutic ratio. The third biological issue is related to the fact that most solid tumours contain the risk of being hypoxic [48–52]. The hypoxia is a problem strongly enhanced when the treatment is delivered in a few large fractions. From a biological point of view it seems obvious that until the opposite has been clearly demonstrated, the delivery of stereotactic body radiotherapy should be performed together with hypoxic modification in order to diminish the risk of hypoxic radioresistance [53–56]. Avoiding such modifications carries a large inherent risk of sub-optimal biological damage to the tumour which in turn will require a substantially larger total dose to achieve the same outcome.

This limited understanding and focus on importance of securing optimal (tumour) radiobiological delivery of the dose represent the major Achilles' heel in our attempt to successfully bring stereotactic body radiotherapy into a leading therapeutic role. Past experience has shown that it is naive to neglect biological properties by assuming that everything can be dealt with by proper delivery of a dose with superior technical ability. Only by taking the greatest advantage of all our knowledge and possibilities we can achieve the desired goals.

It is our hope that by gathering the key persons in this development at the 3rd Acta Symposium and presenting their papers in the current issue, we have been instrumental in adding new fuel toward creating the emerging evidence for stereotactic body radiotherapy.

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