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The ESTRO Breur Lecture 2009. From population to voxel-based radiotherapy: Exploiting intra-tumour and intra-organ heterogeneity for advanced treatment of non-small cell lung cancer ☆

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ABSTRACT

Evidence is accumulating that radiotherapy of non-small cell lung cancer patients can be optimized by escalating the tumour dose until the normal tissue tolerances are met. To further improve the therapeutic ratio between tumour control probability and the risk of normal tissue complications, we firstly need to exploit *inter* patient variation. This variation arises, e.g. from differences in tumour shape and size, lung function and genetic factors. Secondly improvement is achieved by taking into account *intra*-tumour and *intra*-organ heterogeneity derived from molecular and functional imaging. Additional radiation dose must be delivered to those parts of the tumour that need it the most, e.g. because of increased radio-resistance or reduced therapeutic drug uptake, and away from regions inside the lung that are most prone to complication. As the delivery of these treatments plans is very sensitive for geometrical uncertainties, probabilistic treatment planning is needed to generate robust treatment plans. The administration of these complicated dose distributions requires a quality assurance procedure that can evaluate the treatment delivery and, if necessary, adapt the treatment plan during radiotherapy.

Over the past decades we have witnessed an unprecedented increase in our basic understanding of cancer at the molecular level, experienced a huge improvement in medical technology and have gained access to an ever increasing amount of data on cancer. As a consequence, modern medical diagnostic systems confront doctors with a flood of clinical, anatomical, molecular en genetic data and an increasing number of therapeutic strategies. It is a huge challenge to integrate all available information and select the best, individualized treatment for each patient that best fits his/her needs. This is relevant because amongst patients with the same tumour stage there is a large variation with respect to response to systemic treatment and radiotherapy for both the tumour as well as the healthy organs. Although biologically effective dose levels of at least 100 Gy are required to achieve local tumour control rates of 90% or more [1,2], in most radiotherapy departments it is a common practice to prescribe the same dose to all patients, e.g. 66 Gy delivered in 33 fractions over about 7 weeks, which is equivalent to a biological dose of less than 51 Gy [3]. Higher local control rates may be achieved if the dose would be escalated to the highest dose that can be delivered to the tumour at an acceptable normal tissue complication level for each patient. This idea was exploited recently in a prospective single-arm dose-escalation study where stages I–III, non-operable NSCLC patients were treated iso-toxically with sequential chemo-radiation [4]. The radiation dose to the tumour was escalated from 54 Gy to a maximum of 79.2 Gy, delivered in twice-daily fractions of 1.8 Gy to achieve an overall treatment time of less than 5 weeks, until a fixed mean lung dose (MLD) was reached that depended on the lung function of the patient. Since patients with a reduced lung function are more likely to have complications, the allowed MLD for these patients (12 or 15 Gy) was lower than for patients with a good lung function (19 Gy). The 2-years survival of the patients included in this trial was 45%, which is comparable to patients treated with concurrent chemo-radiotherapy. This indicates how the balance between toxicity and tumour control could be used in the clinic to improve the treatment and it underlines the importance of individualized

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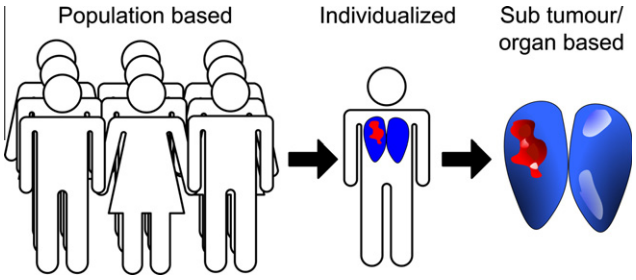

Fig. 1. Schematic scheme illustrating how the treatment of lung cancer with radiotherapy evolves from population based to individualized, to strategies that take into account differences in radio-sensitivity within the tumour and lungs. With individualized radiotherapy the tumour and lungs are considered as homogeneous organs. The next step is to consider intra-tumour and lung heterogeneity. Red and blue indicate tumour and lung, respectively. See power point version of the figure in the Supplementary data.

radiotherapy. "One size fits all" will no longer be an option for the treatment of lung cancer in the upcoming era.

To further refine the selection of the best treatment based on the balance between probability of cure and complications, accurate models must be used to predict the therapeutic ratio of a treatment for individual patients, i.e. the ratio between the probability of tumour control and the risk on normal tissue complications. Validated models can then be incorporated into a decision support system (DSS) that presents the different treatment options with the expected therapeutic ratios to the physician. The simplest and most intuitive example of a decision support tool is a nomogram. Nomograms are graphical representations of prediction models that are used to add up different risk factors and calculate the probability of a certain outcome [5–8]. More advanced DSSs can make predictions about more than one outcome measure, e.g. normal tissue toxicity, local tumour control, distance metastasis and quality of adjusted life year (QALY) expectancy [9]. Developing an accurate DSS is very challenging because it requires a huge amount of data from sufficient patients that have been treated with different treatment regimes.

DSSs can be used to exploit *inter* patient heterogeneity by selecting for each patient individually the treatment with the best therapeutic ratio. However, even if a DSS would be available that could perfectly exploit *inter* patient heterogeneity, for a large number of patients the tumour dose simply cannot be elevated enough to obtain a high tumour control probability without accepting severe complications [10,11]. Further improvement of the therapeutic ratio between tumour control probability (TCP) and normal tissue complication probability (NTCP) could be achieved by exploiting *intra*-tumour and *intra*-organ heterogeneity. Both tumours and organs are known to be heterogeneous structures with regions of different radio-sensitivity, functionality and drug uptake. In contrast to other treatment modalities, radiotherapy can be used to exploit this spatial heterogeneity. Guiding dose towards the most radio-resistant part of the tumour or to regions with a low therapeutic drug uptake and simultaneously away from the sensitive, functional or complication prone parts of the lungs can lead to higher control probability without increasing the complication probability. The therapeutic ratio can thus be improved by exploiting tumour and organ heterogeneity. Fig. 1 illustrates how radiotherapy evolves from population to voxel based.

Tumour heterogeneity

A malignant tumour is not a homogeneous mass, but is composed of regions that differ in tumour cell density, normal tissue involvement, vasculature, hypoxia, proliferation, gene expression and drug uptake [12]. This heterogeneity within the tumour results in large spatial differences in response to radiotherapy, chemotherapy, or new targeted agents. The discovery of intra-tumour heterogeneity opens new therapeutic possibilities for individualized patient treatment. Today, radiation is given to the tumour at a more or less homogeneous dose (international guidelines from the ICRU 50 report state that the whole tumour should receive 95–107% of the prescribed dose). Cells with an increased resistance to radiation thus receive the same dose as the more sensitive cells, resulting in a "waste" of dose to the sensitive areas and to a non-effective dose to the resistant parts of a tumour. If the total radiation dose cannot further be escalated because it is restricted by normal tissue tolerance, dose redistribution with a higher dose to resistant and a lower dose to sensitive areas within the tumour has a theoretical advantage. If this tumour heterogeneity can be assessed with volumetric (3D) or even time-resolved (4D) imaging methods [13–15] it is possible to design a therapy that targets the most resistant regions of the tumour, by redistributing or boosting the radiation dose to these regions. A number of theoretical concepts exploring the therapeutic possibilities of intra-tumour heterogeneity have been published [12,16–23]. Many research groups considered giving a higher dose to some parts of the tumour based on some expectation of radio-resistance in that region, i.e. "dose-painting". Others investigated dose-painting-by-numbers were each tumour voxel or subvolume has an individual target dose depending on images of tracer uptake. The major challenge remains how to determine to which tumour regions how much dose should be administered and by which techniques this can be achieved.

Three different but complementary approaches are outlined below to select tumour regions that may benefit from an additional boost dose.

Dose-painting based on biological characteristics

The first approach is to determine the radio-sensitivity of the areas with different biological characteristics such as hypoxia, proliferation and clonogen cell density. Hypoxia, as a result of rapid

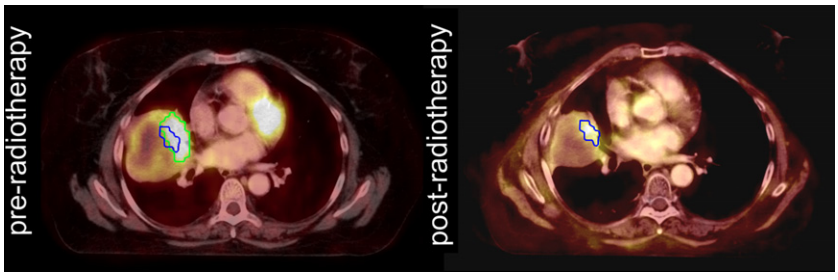

Fig. 2. FDG-PET-CT scans before and 3 months after radiotherapy of a single patient. The green contour is the 50% SUV_{max} contour and the blue contour represents the location of the residual metabolic active areas after radiotherapy. The overlap of the contours was on average 70% for 22 patients [15]. Parts of this figure have been published previously in reference [15]. See power point version of the figure in the Supplementary data.

cellular expansion and/or insufficient tumour angiogenesis [24], is an important biological property in solid tumours that can accelerate malignant progression and metastatic potential of primary carcinomas and also lead to increased resistance to cancer therapies [25–28]. There is therefore a clear rationale to administer an additional radiation dose to hypoxic regions of the tumour. Non-invasive imaging techniques have been proposed to measure oxygenation levels in solid tumours. One such technique involves PET using radiolabelled 2-nitroimidazoles, like [^{18}F]fluoromisonidazole ([^{18}F]FMISO) [29–33].

Dose-painting based on topography of relapse

The second strategy is based on images of metabolic activity. Tumour regions with high metabolic activity have been shown to correlate with the site of tumour relapse after radiotherapy. Laprie et al. [34] demonstrated this in Glioblastoma by measuring the choline (Cho)/*N*-acetyl-aspartate (NAA) ratio before radiotherapy. Other groups found similar results looking at the metabolic residual areas after radiotherapy using 18-fluorodeoxyglucose (FDG)PET-CT scans. In NSCLC patients it was shown that the residual metabolic active areas after treatment could be identified with the high FDG-uptake areas before treatment [15,35]. Fig. 2 shows an example of the pre- and post-treatment FDG-PET-CT scan of a patient that had residual metabolic activity after therapy [15]. These 28 patients had a significantly worse overall survival (hazard ratio of 2.9) than the 27 patients without residual metabolic activity after therapy (95% confidence interval: 1.4–6.0; $p = 0.002$). In a separate paper it has been shown that the location of metabolically active areas remains stable during therapy [36]. These observations suggest that high FDG-uptake areas within the tumour may be a potential target for dose-painting. This rationale has also been supported by animal experiments [37]. Studies are now needed to correlate the heterogeneity in FDG uptake with pathological features [38]. Currently the hypothesis that high FDG-uptake regions are more radio-resistant than low FDG-uptake regions is tested in a two-arm randomized phase II trial in the Netherlands. (NCT01024829: Dose-escalation by boosting radiation dose in stage II and III non-small cell lung cancer (NSCLC): a phase II trial (BTV Boost), (http://clinicaltrials.gov/ct2/show/NCT01024829).) Patients in arm A will receive radiotherapy (66 Gy) in 24 fractions of 2.75 Gy with an integrated boost to the primary tumour as a whole. Patients in arm B receive radiotherapy (66 Gy) in 24 fractions of 2.75 Gy with an integrated boost to the 50% SUV_{max} area of the primary tumour. The size of the boost dose is determined by the normal tissue constraints and therefore the mean PTV dose will be approximately equal in both the arms.

An alternative strategy to escalate dose based on FDG uptake is by reassessing the tumour volume after the first weeks of radiotherapy using FDG-PET-CT scans and replan if the tumour decreased in size. However this allows only a modest improvement in the context of dose-escalation [39], which confirms the need to consider intra-tumour heterogeneity for dose-escalation.

Dose-painting based on receptor imaging

A third method to determine which tumour regions must receive an additional dose is by non-invasively imaging the volumetric uptake of labelled drugs, in particular monoclonal antibodies (mAb), inside the tumour. Systemic treatment, chemotherapy or targeted drugs, in combination with radiotherapy play a pivotal role in the treatment of various solid cancers. Systemic treatments are still administered based on the principle of "administered dose", the equivalent of skin dose in radiotherapy. Introduction of immuno-PET, the combination of PET with mAbs combines the high sensitivity and resolution of a PET camera with the specificity of a mAb for

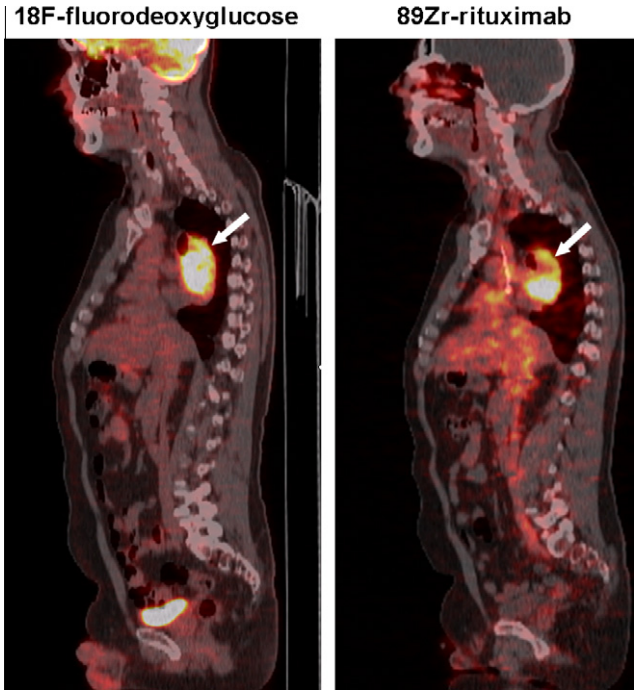

Fig. 3. Comparison of an FDG-PET-CT scan (left) and an ^{89}Zr-rituximab PET-CT scan (right) in a patient with relapsed follicular non-Hodgkin's lymphoma. The bottom part of the tumour shows significant higher rituximab uptake than the upper part. See power point version of the figure in the Supplementary data.

tumour specific antigens. The ability to measure the expression of these receptors is promising for selecting patients for targeted therapy. We know from various preclinical studies that not only the receptor expression, but also the absorption of therapeutic drugs is often not homogeneous. Also a disparity between receptor levels and drug uptake has been reported, i.e. a tumour with high receptor levels can report lower uptake than tumours with lower receptor levels. This indicates that also reachability of tumour tissue by large mAbs is an important factor [40]. Preliminary unpublished data suggest that immuno-PET with ^{89}Zirconium labelled rituximab is more accurate than ^{18}FDG-PET to depict viable lymphoma in patients with relapsed CD20+ B-cell non-Hodgkin's lymphoma and that the uptake of rituximab can be very heterogeneous throughout the tumour (Fig. 3) [41]. Besides the inherent heterogeneity of antigen-expression in the tumour, tumour regions with low therapeutic drug uptake can also reflect the loss of receptor-expression in clonogens during the course of disease, saturation of receptors due to previous administrations of the drug or the presence of intra-tumoural necrotic or inflammatory tissue. Although still hypothetical, receptor imaging and drug uptake imaging with PET could be an interesting new approach for identifying tumour regions that might benefit from an additional boost.

How much dose should be redistributed?

It is challenging to define which tumour subregions are suitable candidates for an additional dose. An even more difficult question is how much dose should be redistributed. Different strategies are possible. If biological images can be calibrated to, e.g. partial oxygen pressure, cell density or proliferation, the linear quadratic model of cell survival, or another radiobiological alternative, can be used to determine how much dose should be redistributed [17,20,28,42,43]. It should be noted that such a calibration from image intensity to a biological property is a huge challenge and previous studies that applied this approach have relied on qualitative correlations instead of on quantitative relations. An alternative

strategy is to start treating patients with a fixed, additional boost to a subregion of the tumour and analyze the patterns of relapse after treatment. If the relapse occurs in the boost region, more dose should have been redistributed. If it occurs outside the boost regions, too much dose was redistributed. After the first cohort has been treated and evaluated the boost dose to a new cohort of patients can be refined using the data of the first cohort. By repeating this procedure the optimal boost dose can be determined. This is a very pragmatic approach but it requires data from a large number of patients that have been treated with a boost dose and 3D dosimetry (see Section 'Dose delivery verification') to determine the delivered dose distribution in every subvolume of the tumour for evaluating the patterns of relapse. This procedure has been proposed in a recent publication where it was applied to patients treated with a flat tumour dose ranging between 45 and 79 Gy [23]. Within the coming years data will become available from patients who have been treated with a boost dose to subregions of the tumour.

Organ heterogeneity: the example of lung

Not only tumours but also healthy organs can be heterogeneous in function and sensitivity for complications. However, at present models presume that all parts of an organ have the same functional capacity, i.e. every subvolume has the same function and contributes equally to the global organ function. This is certainly not correct for lungs [44]. Gas diffusion only occurs in the alveoli and there is a large heterogeneity in the functional areas of the lungs because of differences in ventilation and perfusion. In the lungs of patients with lung diseases, such as COPD and lung emphysema, this heterogeneity is even larger. Lung cancer patients often have large non-functional air pockets in the lung (bullae) and sites of inflammation that might be more susceptible to radiation damage. It is expected that a radiation dose to the bullae is less harmful for the patient than dose to regions that contribute most to the lung function.

Different imaging techniques can be used to acquire information about functional and non-functional lung tissue and inflammation. Magnetic resonance imaging (MRI) is a powerful tool for the static and dynamic imaging of many organs including the lungs [45]. Many attempts have been made to visualize local ventilation using the inhalation of hyperpolarized gases or gadolinium aerosol responding to MRI. Groups have shown that mathematical processing of data derived from serial MRI scans during the respiratory cycle produces good quality images of local ventilation without any contrast agent. In patient investigations good correlations were seen between pulmonary function tests and MR ventilation measurements [46]. The ventilation images can be used for intensity modulated radiotherapy (IMRT) planning strategies to spare the well ventilated lung regions [47].

CT is another technique that has been used in a research setting to obtain ventilation images of the lungs. According to Simon the Hounsfield unit of a voxel in the lung depends linearly on the fractional volume of air in that voxel [48]. The difference in the amount of air in a voxel between inspiration and expiration is a measure of the ventilation [49]. Large variations in ventilation have been observed between different regions of the lung [50]. Since the ventilation measurements are done with the CT scan used for treatment planning the ventilation maps can easily be imported into the treatment planning system and used for treatment planning to limit the radiation dose to functional regions [51].

Together with ventilation, adequate perfusion is needed for sufficient gas exchange in the lungs. Patients with NSCLC often have inhomogeneous perfusion in the lung that can be caused by bullous disease, atelectase and infiltration by the tumour. Radiation can have two separate effects on lung perfusion. On one hand radiation damage to well-perfused lung regions can decrease the perfusion. On the other hand tumour regression caused by radiation may cause an increase in perfusion in poorly-perfused lung regions close to the tumour [52]. Also the stiff scar tissue surrounding the bullae can be damaged or decreased by radiation, leading to more perfusion and a local increase in elasticity of the lung tissue yielding more ventilation. There is thus a clear rationale for guiding dose towards poorly-perfused and away from well-perfused lung regions. Perfusion can be measured in 3D using single photon emission computed tomography (SPECT) scanners with an ^{99m}Tc-labelled macro-aggregated albumin [53,54]. Different groups have shown the technical feasibility of incorporating these 3D perfusion maps for treatment planning to decrease the dose to functional lung regions [54–56].

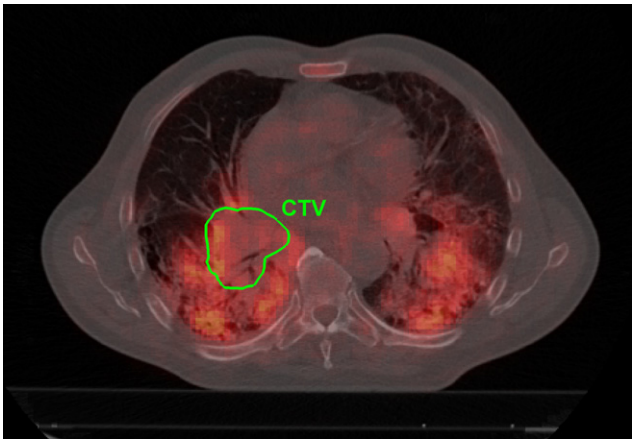

Fig. 4. Illustration of a patient with high FDG uptake in the lungs before radiotherapy. The clinical target volume (CTV) is shown in green. A recent study showed that a large overlap between voxels in the lung with a high FDG uptake and the dose distribution was a risk factor for radiation induced lung toxicity. This finding let us hypothesize that by shielding these high FDG-uptake regions the risk may be decreased [60]. See power point version of the figure in the Supplementary data.

Apart from assessing the contribution of different lung regions to the lung function, imaging techniques can also be used to identify parts of the lung that may be more susceptible for radiation damage. An increased uptake of FDG has already been associated with a number of inflammatory, non-malignant disorders [57]. Also a high FDG uptake in the lungs before treatment and an increase of FDG in the lungs during treatment have been associated with an increased risk on radiation induced lung toxicity (RILT) [58–60]. Only a dose of a few gray to the high FDG-uptake regions increased the risk of RILT [60] (Fig. 4). These results suggest that the lung toxicity can be avoided by shielding regions with high FDG uptake from the radiation fields.

Treatment planning incorporating tumour and organ heterogeneity and geometrical uncertainties

The technical feasibility of treatment planning with multiple dose prescription levels to the tumour based on biological images has been demonstrated by different groups [17,19–22,43,61–64]. Dose prescriptions ranged from 2 dose levels to a dose distribution that varied continuously based on tracer uptake. Also different groups showed how 3D lung perfusion and/or ventilation maps can be used as input for conformal and IMRT treatment planning to limit the dose to well ventilated/perfused tissue [47,51,53–56,65,66]. Das et al. combined information on both tumour (measured with FDG) and lung heterogeneity (perfusion measured with SPECT) in one dose optimization algorithm [67].

These studies did not address how to take into account the uncertainty in delivered dose that arises from positioning errors, organ motion and deformations affiliated with fractionated radiotherapy, when administering a dose distribution with multiple dose levels to the tumour. In current radiotherapy practice, with a homogeneous prescription dose to the tumour, these uncertainties are taken into account by the safety margin applied to the delineated gross tumour volume. The reason that the margin approach works, is that tumours are assumed to be homogeneous and that thus a uniform dose distribution is the best way to treat a tumour. As uncertainties in dose delivery occur mostly around dose gradients, the dose uncertainty in a uniform dose distribution is located at the edges of the tumour/uniform dose area. With the margin approach this is exactly the area where the safety margin is applied. However, in the case of a heterogeneous tumour treated with multiple dose levels (e.g. dose-painting), the geometric uncertainties during fractionated treatment and gradients between dose levels result in dose delivery uncertainties, occurring within the tumour. To account for these uncertainties with a margin would require applying a margin for each of the heterogeneous zones or even for each voxel within the tumour. Also the size of the margin would depend on the dose gradient (i.e. a large dose gradient requires a large margin) between the zones and would thus be a result of the planned dose rather than an input for the planning process. The margins approach thus becomes problematic when multiple dose levels need to be prescribed to different regions of a single tumour.

The solution is to incorporate the uncertainties that give rise to the margin directly into the treatment planning system and use them in the treatment plan optimization process. Different groups have shown how probabilistic distributions of systematic and random positioning error and breathing motion can be incorporated directly into the treatment optimization [68,69]. These methods are usually demonstrated with a homogeneous dose prescription. If little information is available about the probability distributions of the uncertain variables, which is in general the case, the difference between a conventional margin based dose distribution and a probabilistic planning dose distribution is small in case of a homogeneous prescribed tumour dose. However, when multiple dose levels within the tumour are prescribed, this probabilistic planning is the method of choice to generate a dose distribution that is more robust to geometrical uncertainties.

Dose delivery verification

The delivery of complicated, heterogeneous dose distributions with very high dose levels to small target volumes requires steep dose gradients and small multi-leaf collimator (MLC) shaped segments. As a consequence, small changes in patient anatomy or MLC configuration can result in large deviations from the planned dose distribution. Therefore precise geometric and dosimetric verification is of utmost importance to ensure correct planning and delivery for these advanced and complex types of treatment. The state of the art for dose verification are quality assurance procedures using electronic portal imaging devices (EPID) [70]. EPID dosimetry can be used as a QA procedure prior to treatment by comparing the predicted and measured dose of the non-attenuated beam at the EPID plane in 2D. EPID dosimetry can also be used to verify the delivered dose during treatment by comparing the predicted and measured dose of the attenuated beams that exit the patient. 2D EPID dosimetry is already routinely used in a number

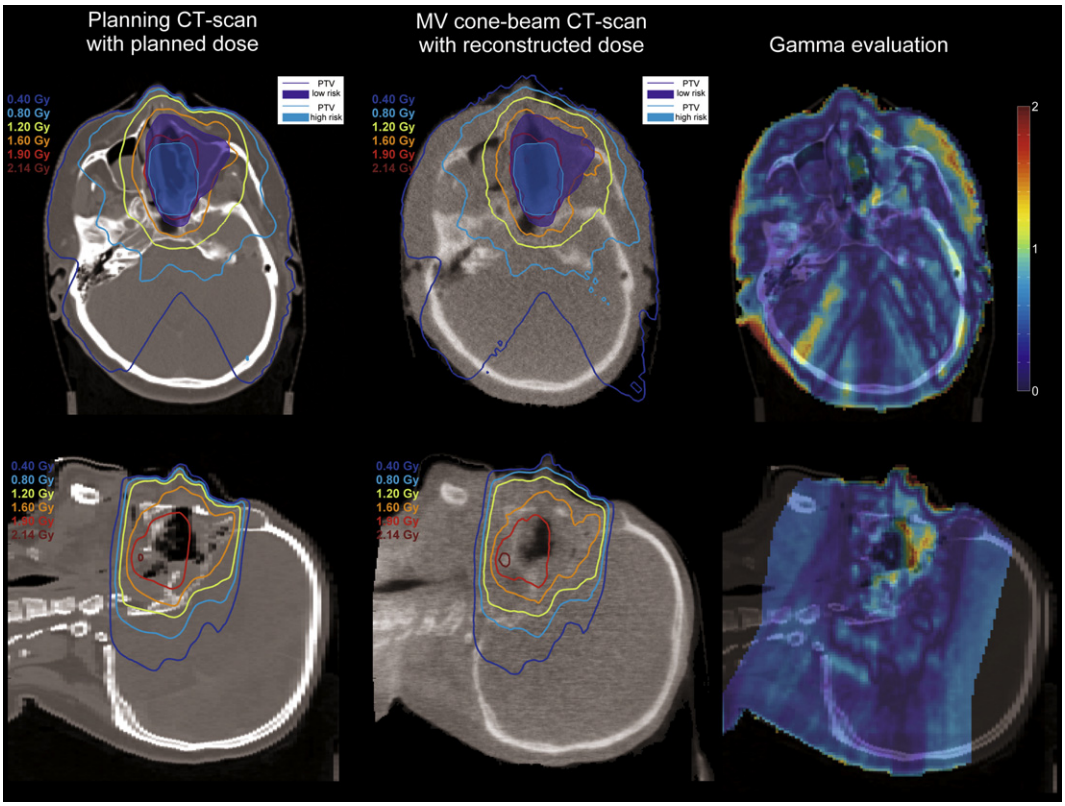

Fig. 5. The planned dose distribution projected on the planning CT scan together with the delivered dose distribution calculated on the megavoltage-cone-beam CT scan acquired at the seventh treatment fraction. The exit dose of each treatment beam is measured with the EPID and back-projected through the patient to calculate the input fluence, which is used by an independent Monte Carlo dose calculation engine to calculate the delivered dose distribution in the cone-beam CT. The right column shows gamma images (3%/3 mm distance to agreement). This method allows the calculation of the actual delivered dose distribution in 3D. This figure was published previously in reference [82]. See power point version of the figure in the Supplementary data.

of clinics and the first commercial solutions are becoming available [71–74]. Although 2D EPID dosimetry is a perfect tool to asses if differences have occurred between the planned and delivered dose distribution, it is not always straightforward to interpret the effect of differences in terms of the dose to the organs and target [71]. This becomes even more complicated when a boost dose is delivered to a subregion of the tumour. A method better suited for the QA of these advanced treatments is 3D EPID *in vivo* dosimetry [75–82]. The treatment beams delivered are captured behind the patient with an EPID and back-projected through a 3D image of the patient acquired moments before or after each treatment session. The volumetric images can be obtained with cone-beam CT, helical CT or using an in-room diagnostic CT-scanner. The absorbed dose can then be estimated in every voxel of the 3D image. 3D EPID *in vivo* dosimetry is currently the only method capable of providing the full delivered dose distribution in 3D. It can be fully automated and does not require additional machine time. Fig. 5 shows an example of the planned and delivered dose in a head-and-neck patient. In our opinion this is the method of choice for the verification and QA of treatment plans with different target dose levels to a single tumour.

Another strength of 3D EPID *in vivo* dosimetry is the ability to provide the feedback needed for plan adaptation, as discussed in the next section, and to evaluate the treatment. As mentioned in Section 'Tumour heterogeneity', data of patients enrolled in studies where different parts of the tumour are irradiated with different dose levels, are needed to further refine dose response relations. For these provide unique information of the response of parts of the tumour with different biological characteristics to different dose levels. For this purpose it is crucial to know very precisely the delivered dose in each part of the tumour and therefore 3D EPID *in vivo* dosimetry is a prerequisite.

Plan adaptation

Quality assurance using 3D dose delivery verification is not only needed to guarantee that the treatment is delivered as planned. If during therapy it becomes clear that the treatment plan needs to be adapted, the total delivered dose distribution up to that point in time needs to be known and used in the treatment adaptation strategy to ensure that the new plan compensates for the deviations between the desired and delivered dose distribution. Reasons for treatment plan adaptation can be either anatomical or functional (biology) related.

Changes in anatomy can be caused by weight loss or gain, tumour shrinkage or growth and a shift in tumour or organ position [83–86]. These changes can be detected with the in-room imaging techniques used for patient positioning such as cone-beam CT imaging, without additional burden to the patient and limited workload for the medical team. The appropriate strategy for treatment plan adaptation depends on the type and the timing of observed anatomical changes [87]. Ideally, if unacceptable dosimetric deviations are observed, a new treatment plan must be generated before the next treatment fraction with an updated dose delivery compensating for the non-optimal delivered dose distribution. Also online strategies may be considered, where the treatment plan is adapted on a daily basis while the patient is on the treatment couch [88,89], but due to computational power and logistic limitations, the clinical introduction of these methods is challenging.

Functional or biological changes not only include alteration in normal tissues, e.g. perfusion, ventilation and atelectases in the lungs, but also for the target volumes, e.g. changes in size, shape and location of the radio-resistant tumour regions. These changes usually cannot be detected with in-room imaging, but additional CT, PET, SPECT or MRI scans are needed. In a prospective study with 23 NSCLC patients, it was shown that the metabolically active regions remained at the same location throughout the course of therapy [36]. For hypoxia, however, which can be chronic or acute, larger differences might occur between scans at different time-points. In contrast to anatomical changes, it is less obvious how to adapt the treatment plan if the distribution of the biological parameter of interest has changed.

The treatment plan can also be adapted as a result of changes in the normal tissue. Patients with a high increase in FDG uptake during or after therapy have an increased risk of radiation induced lung toxicity [58,59]. If in the first 2 weeks of treatment a strong increase in uptake in the lungs is shown, it might be necessary to reduce the overall dose to the lungs and tumour, to avoid severe complications. On the other hand, no increase of FDG uptake in the lungs could suggest that the total radiation dose to the tumour can be increased without an elevated risk of complications.

Conclusions

We hypothesize that in the near future decision support systems will be used to select for each patient individually the treatment with the best balance between probability of cure and complications based on *inter* patient heterogeneity. Apart from *inter* patient heterogeneity, *intra* patient heterogeneity could be exploited to further optimize the therapeutic ratio. The dose to complication prone regions of the lungs can be reduced and additional dose can be delivered towards the parts of the tumour that need it the most, for instance because of limited therapeutic drug uptake. The planning of these dose distributions requires that geometrical uncertainties, that are normally included in a treatment planning margin, are directly incorporated into a treatment planning system and used for treatment plan optimization to obtain robust treatment plans. For the quality assurance of these complicated dose distributions 3D EPID *in vivo* dosimetry is needed to calculate the delivered dose distributions, evaluate them, and if needed, use them for treatment plan adaptation. In short, both inter and intra patient heterogeneity may be exploited to improve the treatment of NSCLC patients with radiotherapy.

Conflict of interest

We are not aware of any actual or potential conflicts of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.radonc.2010.07.001.

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