Radiotherapy and Oncology xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original article

Multi-modality functional image guided dose escalation in the presence of uncertainties

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ARTICLE INFO

Article history:
Received 20 January 2014
Received in revised form 22 March 2014
Accepted 27 April 2014
Available online xxxx

Keywords:
Functional imaging
MRI
PET
Dose painting
Prostate cancer
IMRT

ABSTRACT

Background and purpose: In order to increase local tumour control by radiotherapy without increasing toxicity, it appears promising to harness functional imaging (FI) to guide dose to sub-volumes of the target with a high tumour load and perhaps de-escalate dose to low risk volumes, in order to maximise the efficiency of the deposited radiation dose.

Methods and materials: A number of problems have to be solved to make focal dose escalation (FDE) efficient and safe: (1) how to combine ambiguous information from multiple imaging modalities; (2) how to take into account uncertainties of FI based tissue classification; (3) how to account for geometric uncertainties in treatment delivery; (4) how to add complementary FI modalities to an existing scheme. A generic optimisation concept addresses these points and is explicitly designed for clinical efficacy and for lowering the implementation threshold to FI-guided FDE. It combines classic tumour control probability modelling with a multi-variate logistic regression model of FI accuracy and an uncomplicated robust optimisation method.

Results: Its key elements are (1) that dose is deposited optimally when it achieves equivalent expected effect everywhere in the target volume and (2) that one needs to cap the certainty about the absence of tumour anywhere in the target region. For illustration, an example of a PET/MR-guided FDE in prostate cancer is given.

Conclusions: FDE can be safeguarded against FI uncertainties, at the price of a limit on the sensible dose escalation.

Functional imaging modalities (FI), e.g. various magnetic resonance imaging techniques (MRI) or positron emission tomography (PET) with various tracers, are increasingly being linked to tumour physiology or shown to have predictive or prognostic value [1]. Prevalent local failure in some tumour entities forms the rationale for a focal escalation of radiation dose (FDE) which is under investigation in pioneering clinical trials [2–5]. When it comes to quantitative use of FI, image interpretation and – quality quickly become an issue. Reported values of sensitivity and specificity of the most promising FI are usually in the range of 0.7–0.8, despite a multitude of technical challenges that have been mastered to establish reproducibility [6–8]. Apart from the large influence of inter-patient heterogeneity, volumetric pathologic ground truth for quantitative validation is cumbersome to obtain, limited in sample size and fraught with uncertainties of its own [9]. The combination of multiple FIs can increase sensitivity and specificity to up to 0.9 [10,11], but leaves the question how multiple FI can be harnessed for FDE.

FI-guided FDE can be achieved via a binary prescription dose map [12]. For example, Korporaal et al. [13] derived a logistic regression model from expert image classification of dynamic contrast enhanced (DCE) computed tomography and established tumour classification in prostate by thresholding. Langer et al. [14] and Groenendaal et al. [9,10] combined multiple MRI modalities via a logistic regression model and obtained binary tumour maps for prostate cancer via thresholding. Both models were derived from expert readings, and only the latter was validated against pathology. In this rapidly growing field, new FI are developed so quickly that a quantitative, volumetric pathologic validation may not commonly be available for any combination of modalities, thus raising the question how individually validated modalities can be combined with benefit.

As an alternative to binary volumes, Oberhammer et al. [15] interpreted the result of a support vector regression model as a pointwise probability of tumour presence. Subsequently, the dose prescription was directly based on this 3D probability map,

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http://dx.doi.org/10.1016/j.radonc.2014.04.016
0167-8140/

Please cite this article in press as: Alber M, Thorwarth D. Multi-modality functional image guided dose escalation in the presence of uncertainties. Radiother Oncol (2014), http://dx.doi.org/10.1016/j.radonc.2014.04.016

thereby obviating thresholds. This was also mentioned in [13]. Here, we combine the advantages of both concepts to suggest a solution to four practical problems in FI-guided FDE: (1) how to amalgamate the information from multiple imaging modalities; (2) how to take into account uncertainties of FI-based tissue classification; (3) how to account for geometric uncertainties in treatment delivery; (4) how to incorporate additional FI to an existing scheme without having to establish volumetric pathologic ground truth for every new modality in combination with the others.

The concept is exemplified by a prostate case, comprising Diffusion-Weighted Imaging (DWI), resulting in an Apparent Diffusion Coefficient Map (ADC), dynamic contrast enhanced (DCE) MRI, yielding the parameter K^{trans} and [^{18}F]-Choline PET, simultaneously acquired on a PET/MR scanner.

Methods and materials

Probability of tumour presence

Assume a set of n properly registered FIs with intensities $I_{1\ldots n}(x)$ in N image points x is given. We choose a multivariate logistic regression model. Let the probability of finding tumour in the location x

$$p(x) = \frac{1}{1+\exp(-\gamma_0 - \sum_{i=1}^{n}\gamma_i I_i(x))}. \tag{1}$$

The regression coefficients $\gamma_i,\ i = 0\ldots n$ need to be determined ideally from pathology, expert readings, a pattern of failure analysis, or using alternative strategies (see example case). Notice that the logistic regression model assumes that the FI are independent, which needs verification especially for some MRI methods. The detrimental effect of correlations can be dealt with as presented in 'Derivation of odds from image intensity'.

For the following, it is helpful to review the alternative formulation of the logistic regression function in terms of the odds R_i:

$$p(x) = \frac{1}{1+\prod_{i=1}^{n} R_i(I_i(x))}. \tag{2}$$

In other words, if the image intensity $I(x)$ is found in point x, it is $R(I)$ times more likely to find *no* tumour there than to find any. Perfect certainty of tumour presence equals $R = 0$, while certainty about tumour absence is asymptotically approached if $R \to \infty$. In the case of volumes where p is small, a good approximation to Eq. (2) can be found

$$\log(p) = -\log\left(1+\prod_{i=1}^{n} R_i\right) \lesssim -\sum_{i=1}^{n}\log R_i \tag{3}$$

that illustrates how and with which weighting individual imaging modalities contribute independently to the local probability of tumour presence.

Maximizing tumour control in the presence of imaging uncertainties

The most commonly used measure for success in radiotherapy is the tumour control *probability* Q, i.e. treatment quality is measured in terms of a *high likelihood* of achieving the desired result. We extend this concept by the classification probability p, assuming that the tumour control probability $q(D(x))$ at dose $D(x)$ in point x is independent of its neighbours [16]. We find

$$Q = \prod_x([1-p(x)] + [p(x)q(x)]), \tag{4}$$

where the first term is the tumour control when the point is indeed free of tumour and the second term the tumour control by the treatment else. For the purposes of dose optimisation, it is beneficial to choose $-\log(Q)$ as a cost function [17]. We find

$$-\log(Q) = -\sum_x \log\left(1-p(x)(1-q(x))\right) \tag{5}$$

$$\approx \sum_x p(x)(1-q(x)) \tag{6}$$

by a Taylor expansion of $\log(1-\epsilon) \approx -\epsilon$. Notice that in the context of dose optimisation, we can restrict ourselves to the situation of doses yielding reasonable tumour control, in other words the probability of failed cell kill $1-q(x)$ is typically in the order of 10^{-2} cm^{-3}. It is frequently expressed as $1-q = C\exp(-\alpha D-\beta D^2)$ with some cell-density-dependent constant C. Thus, the tumour presence probability $p(x)$ acts like a local cost function density weight, which is in keeping with its interpretation as a probability of a systematic classification error (see discussion). With the right calibration of C, the cost function becomes the expected number of surviving tumour cells given the uncertainty about their presence.

Accounting for systematic and random treatment uncertainties

The probability of tumour presence $p(x)$ is defined in the *patient* coordinate system. For treatment planning, the patient coordinate system has to be aligned with the *treatment* coordinate system. Naturally, the treatment plan and therefore also the optimum dose are defined relative to the treatment coordinate system. Random errors (with probability distribution $T(x,x')$) and systematic errors (with probability distribution $S(x,x')$) displace the points of the patient coordinate system relative to the treatment coordinate system. The effect of random errors, especially in a treatment with many fractions and a deep-seated target, is an averaging of the dose delivered to point x, which can be dealt with at several levels of approximation, depending on the target location. For the example below, we choose the dose convolution approach [18,19] which is appropriate if a random error does not affect the dose in the treatment coordinate system.

Systematic errors lead to an uncertainty about the classification of a point x at a location x' in the treatment coordinate system. For cost functions of the type of Eq. (5), a coverage probability $s(x')$ can be computed [20–23]:

$$s(x') = \int S(x,x')dx. \tag{7}$$

The cost function for the target in treatment coordinate system then reads

$$F = -\log(Q) = C\sum_{x'}\left(\int p(x)S(x,x')dx\right)\exp(-\alpha D(x')), \tag{8}$$

where the constant C could be dropped for convenience. For simplicity of the following argument, the fraction size dependence of the linear-quadratic-formalism has also been omitted. The integral $\tilde{p} = \int p(x)S(x,x')dx$ is the composite classification probability originating from FI interpretation uncertainty and systematic patient geometry errors in dose planning. Coverage probability can be applied to other cost functions such as equivalent uniform dose (EUD) or DVH penalties analogously.

Derivation of odds from image intensity

For clarity of argument, we start with

$$F = C\sum_x p(x)\exp(-\alpha D(x))$$

$$= C\sum_x \exp\left(-\alpha\left(D(x) - \frac{1}{\alpha}\log(p(x))\right)\right). \tag{9}$$

The optimum dose distribution $D^*(x)$ is required to employ the deposited energy with maximum efficiency for cell kill. This amounts to the requirement that the derivative with respect to D of all terms of the sum is equal in all points x, i.e. an additional dose

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