Dose painting

Can radiotherapy be improved with image driven dose-responses derived from retrospective radiotherapy data?

ERIC GRÖNLUND
Abstract

The main aim of curative radiotherapy for cancer is to prescribe and deliver doses that eradicate the tumor and spare the normal healthy tissues. Radiotherapy is commonly performed by delivering a homogeneous radiation dose to the tumor. However, concern have been raised that functional imaging methods such as magnetic resonance imaging (MRI) and positron emission tomography (PET) can provide a basis for prescribing heterogeneous doses - higher doses in malignant regions of the tumor and less dose where the tumor is less malignant. This form of radiotherapy is called “dose painting” and has the aim of utilizing the radiant energy as efficiently as possible to increase the tumor control probability (TCP) and to reduce the risk for unwanted side effects of the neighboring normal tissues.

In this project we have studied how dose painting prescriptions could be derived through retrospectively analyzing pre-RT image data and post-RT outcomes for two different patient groups: one diagnosed with head and neck cancer with pre-RT fluorodeoxyglucose (18F-FDG) PET image data; and one patient group diagnosed with prostate cancer with pre-RT Gleason score data that were constructed to be mapped from apparent diffusion coefficient (ADC) data acquired from MRI. The resulting dose painting prescriptions for each of these diagnoses indicated that the TCP could be increased without increasing the average dose to the tumor volumes as compared to homogeneous dose treatments. These TCP increases were more noticeable when the tumors were larger and more heterogeneous than for smaller and more homogeneous tumors.

We have also studied the potential to realize TCP increases with dose painting in comparison to homogeneous dose treatments by optimizing clinically deliverable dose painting plans for both diagnoses, i.e. head and neck cancer and prostate cancer. These plans were optimized with minimax optimization that aimed to maximize a robust TCP increase by considering uncertainties of the patient geometry. These plan optimizations indicated that the TCP compared to homogeneous dose treatments was increasing and robust regarding uncertainties of the patient geometry.

Keywords: Radiotherapy, functional imaging, dose painting, dose painting by numbers, robust optimization

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Happiness is good health and a bad memory

Quote by Ingrid Bergman
List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.


IV. **Grönlund E**, Almhagen E, Johansson S, Traneus E, Nyholm T, Thellenberg C, Ahnesjö A. Robust treatment planning of dose painting for prostate cancer based on ADC-to-Gleason score mapping – what is the potential to increase the tumor control probability?, *Manuscript*.

All papers were designed in collaboration by me and the respective co-authors. I produced all results and took part in evaluating and selecting which results to be displayed. The main writing of the papers was done by me. Reprints were made with permission from the respective publishers.
### Abbreviations

<table>
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<th>Abbreviation</th>
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<tr>
<td>ADC</td>
<td>Apparent Diffusion Coefficient</td>
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<td>CT</td>
<td>Computed Tomography</td>
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<td>CTV</td>
<td>Clinical Target Volume</td>
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<td>DPBC</td>
<td>Dose Painting By Contours</td>
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<td>DPBN</td>
<td>Dose Painting By Numbers</td>
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<td>DSB</td>
<td>Double Strand Break</td>
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<td>EQD2</td>
<td>Equivalent Dose in 2 Gray fractions</td>
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<td>GTV</td>
<td>Gross Tumor Volume</td>
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<td>IMRT</td>
<td>Intensity-Modulated Radiation Therapy</td>
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<td>ITV</td>
<td>Internal Target Volume</td>
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<td>LCR</td>
<td>Local Control Ratio</td>
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<td>LS</td>
<td>Learning Set</td>
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<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
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<td>NTCP</td>
<td>Normal Tissue Complication Probability</td>
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<td>OAR</td>
<td>Organ At Risk</td>
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<td>PC</td>
<td>Patient Cohort</td>
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<td>PDF</td>
<td>Probability Density Function</td>
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<td>PET</td>
<td>Positron Emission Tomography</td>
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<td>PTV</td>
<td>Planning Target Volume</td>
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<tr>
<td>ROI</td>
<td>Region Of Interest</td>
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<td>RT</td>
<td>Radiotherapy</td>
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<td>RV</td>
<td>Recurrence Volume</td>
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<td>SF</td>
<td>Surviving Fraction</td>
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<td>SSB</td>
<td>Single Strand Break</td>
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<td>SUV</td>
<td>Standardized Uptake Value</td>
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<td>TCP</td>
<td>Tumor Control Probability</td>
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<td>TPS</td>
<td>Treatment Planning System</td>
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<td>VMAT</td>
<td>Volumetric-Modulated Arc Therapy</td>
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1 Introduction

Cancer is a group of diseases characterized by uncontrolled cell division with the risk of such cells to spread and invade healthy parts of the body. It has been estimated that 8.2 million cancer deaths occurred in 2012 worldwide and that this number is expected to grow because of the growth and aging of the human population (Torre et al. 2015). Since cancer constitutes an enormous burden of the public health worldwide, even small therapy improvements of can be of value because the fate for many patients can be improved.

Radiotherapy has a long history originating from the latter part of the 19th century when X-rays first was discovered by Wilhelm Röntgen that earned him the first Nobel Prize in Physics 1901. It was soon discovered that these X-rays could be used as a treatment for cancer, albeit the underlying mechanisms of why it seemed to work was not known.

Explanations came with the discovery of the DNA molecule and that ionizing radiation causes DNA strand breaks within the cell nuclei. The DNA strand breaks are either caused by ionization events directly occurring on DNA molecules, or by free radicals generated from other ionizing events that indirectly induces DNA strand breaks. Furthermore, if both DNA strands are closely broken a double strand break (DSB) has occurred, whereas a single strand break (SSB) implies a breaking on one side of the DNA strand only. Most of the DNA strand breaks are repaired by inherent repairing mechanisms within the cell, but the repairing of a DSB is more likely to fail than for a SSB because a SSB has structural support from the unbroken strand. When the DNA strands are not repairable the cell is likely to become sterile. Radiotherapy works hence as a cancer treatment because of its ability to limit the reproduction of new cells.

However, normal healthy cells are also affected by ionizing radiation which can yield unwanted side effects. Nevertheless, the DNA repair is more likely to be corrupted for fast proliferating cells, which is a typical characteristic for cancer cells, than for the more slowly proliferating normal healthy cells. There is hence a therapeutic window between the radiation doses that yield a desirable sterilizing effect on the cancer cells without yielding unacceptable effects on the normal healthy cells.

Most concepts proposed for improving radiotherapy have the aim of widening the therapeutic window, i.e. to increase the chance for cure and/or decrease the risk for unacceptable side effects. Such concepts include: flash
therapy, based on observations that very high dose rates are gentle to normal tissues without compromising tumor control (Durante et al. 2018); response modifiers, where for example gold nano-particles placed within a tumor yield an increased radiation effectiveness by inducing dense clusters of secondary electrons (Pagáčová et al. 2019); Grid therapy, based on observations that the use of small beams for irradiation seems to yield an increased radiation tolerance for body tissues because the irradiation then is more heterogeneous and hence allows for an improved reparation of the tissues that were subjected to a lower dose (Laissue et al. 2012, Girst et al. 2016). Another proposal that also may improve radiotherapy is dose painting, which is the prescription of a heterogeneous dose distribution to a tumor based on functional image data that map the spatially varying risk for a tumor relapse. The purpose of this thesis is to further explore dose painting and its potential to improve radiotherapy.

1.1 The radiotherapy process

Depending on the source of radiation different forms of radiotherapy has evolved. Most common is to use a particle accelerator that accelerates electrons towards a high atomic number target. When the electrons are impinged on the target, bremsstrahlung photons are emitted that by means of a rotating gantry and collimators can be precisely aimed at the tumor location within a patient’s body. This form of radiotherapy is called external beam radiation therapy simply because the source of radiation is outside of the body. There are other forms of radiotherapy such as brachytherapy where encapsulated radioactive sources are placed in the direct vicinity of the tumor, and targeted therapy where one injects a radioactive isotope bound to ligand molecules that attach to tumor cells. However, the focus in this thesis is on external beam radiation therapy and henceforth the abbreviation RT will refer to this form of radiotherapy only.

When preparing a patient for RT the following issues are critical:

1. where to irradiate, i.e. where is the tumor localized?
2. what radiation dose shall be given to sterilize the tumor without too high risks for normal tissue complications?

To address the first issue, the RT process begins with imaging the anatomy of the patient in order to determine the position and extent of the tumor and surrounding normal tissues. The most common image modality is computed tomography (CT) that maps how tissues absorb X-rays but gives no functional information about the imaged tissues. Other image modalities such as magnetic resonance imaging (MRI) and positron emission tomography (PET) are increasingly used to aid in tumor localization and tumor character-
ization, which will be described more thoroughly in the next chapter. Furthermore, the information hub in RT is a treatment planning system (TPS) in which the tumor (i.e. the target volume) and surrounding normal tissues of interest are segmented and labelled. For this segmentation process a set of standard volumes have been defined (ICRU 1993, 1999, 2010). The target definition starts with the gross tumor volume (GTV) defined as the tumor visible from the image data. Furthermore, to include likely adjacent microscopic spread the GTV is expanded by a margin to form a clinical target volume (CTV) which is defined as the volume to be treated. To handle uncertainties from body movements, the CTV is expanded which results in the internal target volume (ITV). The ITV is further expanded with a margin to form the planning target volume (PTV) which is used as the target volume for clinical dose planning. The purpose of the PTV is to ensure a dose coverage of the CTV despite potential uncertainties of the CTV location.

Regarding the second issue, it is generally accepted that for a fixed integral dose and under the assumption that the CTV is uniformly populated with equally responding cancer cells, it is a homogeneous dose distribution that yields the highest probability to sterilize the tumor (Brahme 1984, Webb et al. 1994). Hence, the current paradigm of performing RT is based on irradiating the tumor volume (i.e. the PTV) with a homogeneous dose. The dose is commonly delivered for several fractions to allow for normal tissue repairing between the fractions, where different diagnoses are treated with different fractionation schedules. Furthermore, clinically used homogeneous dose prescriptions are based on earlier clinical experience of which dose is most likely needed to sterilize the tumor without too high risks for unacceptable side effects.

When both issues have been resolved, a treatment plan can be produced by means of the TPS. Finally, when such a plan has been produced and approved by the clinical staff, the treatment of the patient can start.

1.2 Optimal use of radiation - dose painting

The concept “dose painting” (coined by Ling et al. (2000)) is based upon the idea that that functional image data can differentiate spatially varying radiation sensitivities of tumors as a basis to “paint” heterogeneous dose prescriptions. More dose where more is needed and less dose where less is needed. The aim is to use the radiant energy as efficient as possible which, if the tumor is radio-biologically heterogeneous, implies that a heterogeneous dose prescription can increase the tumor control probability (TCP) without increasing dose burdens to normal tissues, or alternatively, decrease the normal tissue complication probability (NTCP) without affecting the TCP.

The dose painting concept does thus merge the two issues stated in section 1.1 into one - can the image data that in conventional RT only aid for
tumor localization also be used to determine heterogeneous dose prescriptions? Ultimately, this leads to the question, can dose painting increase the prospects for patients compared to conventional homogeneous dose treatments?

1.3 Acquiring dose painting prescriptions

To acquire dose painting prescriptions, detailed relationships between pre-treatment image data and the risk for post-treatment relapse locations are needed. In theory, two approaches may be used to solve this problem. Appealing would be a “bottom-up” approach that from the acquired image data give a complete deterministic outcome prediction based on underlying biomechanistic processes. This is however unrealistic, because it would require complete knowledge of the enormous biological complexity of clinical cases. Nevertheless, several studies have modeled partial processes, such as Thorwarth et al. (2007) who derived different dose escalation factors that depended on varying oxygen levels of tumors, where the varying oxygen levels were imaged with a technique called $^{15}$FMISO-PET (see chapter 2 for more details).

More practical is a “top-down” approach that simply uses observed post-treatment relapse occurrences and correlate these with image quantities acquired before treatment. Furthermore, Bentzen and Grégoire have in a review (2011) conclusively stated that dose painting prescriptions ideally should be based on empirical correlations between pre-treatment image data and post-treatment outcomes. One such example of a top-down approach is the study from Vogelius et al. (2013) who determined dose painting prescriptions for different tumor volumes by observing the varying post-treatment recurrence frequencies for these volumes. This PhD thesis is to a large degree inspired by the top-down approach given by Vogelius et al. (2013).

1.4 Geometrically robust dose painting

As described in section 1.1, the standard practice for conventional RT with homogeneous doses is to use a PTV by applying margins to the CTV. The intent of the PTV is to ensure that the CTV will receive the prescribed dose despite uncertainties of the CTV location during dose delivery. However, since dose painting utilizes heterogeneous dose prescriptions, simple margins cannot be used. Other methods are therefore needed for the planning of dose painting plans. One such method is minimax optimization (Fredriksson et al. 2011, Unkelbach et al. 2018). Minimax optimization use a set of simulated scenarios (e.g. different translations of the patient position) that can
occur during treatment. By using these scenarios with a certain planning objective, such as to achieve a certain dose distribution within the CTV or to maximize the TCP, one can optimize towards a treatment plan that fulfill the planning objective as good as possible for the worst-case scenario. We have in this thesis used and tested minimax optimization for the design of dose painting plans.

1.5 Aims of the thesis

The general aim of this thesis is to explore potential gains with dose painting in comparison to homogeneous dose treatments. This has been explored by utilizing a top-down analysis of retrospective patient data, consisting of pre-RT image data and post-RT outcomes, with the intents to:

- derive dose painting prescriptions for patients with head and neck cancer (paper I) and prostate cancer (paper II).
- analyze how effective dose painting can be implemented in clinical reality by considering clinical delivery constraints and robustness requirements for treatment of head and neck cancer (paper III) and prostate cancer (paper IV).
2 Functional imaging for radiation oncology

Allan M. Cormack and Godfrey N. Hounsfield was 1979 awarded the Nobel Prize for Physiology or Medicine for the development of computed tomography (CT). The work from Allan M. Cormack was to a large degree driven with the aim to develop RT towards the modern-day RT that uses three-dimensional (3D) CT images of patients. CT is an X-ray imaging technique that uses a set of X-ray projections acquired from multiple angles around the patient from which a 3D map of the patient can be reconstructed. A CT image is hence a 3D map of different tissues ability to attenuate X-ray photons, where the 3D map consists of voxels (analogous to pixels for 2D images). Moreover, the linear attenuation coefficient for each voxel ($\mu$) is normalized relative to water ($\mu_{\text{water}}$) and air ($\mu_{\text{air}}$), that yield the Hounsfield unit (HU)

$$\text{HU} = 1000 \times \frac{\mu - \mu_{\text{water}}}{\mu_{\text{water}} - \mu_{\text{air}}}$$

which is the commonly used voxel quantity for CT images.

However, CT imaging provides only with anatomical information which is insufficient for a comprehensive medical assessment of a patient’s disease status. A way to reach a more comprehensive medical assessment, is by together with anatomical imaging also monitor tissue function - functional imaging. Functional imaging refers to the use of at least one the following approaches: first, monitor physiological processes such as blood flow within healthy or diseased tissues; second, monitor metabolic and biochemical activities within the body such as sugar consumption or lipid consumption; third, the use of established pharmacologic methods for drug development or to assess disease processes (Alavi et al. 2004). Furthermore, if functional imaging can provide with image data that map a spatially varying risk for tumor relapses, it may form a basis for deriving dose painting prescriptions. We have in this project used two modalities of functional imaging to derive dose painting prescriptions; positron emission tomography (PET) for head and neck cancers in papers I and III; magnetic resonance imaging (MRI) for prostate cancers in papers II and IV. The following sections 2.1 and 2.2 describe these two imaging modalities in more detail.
2.1 Positron emission tomography

Positron emission tomography (PET) is a method to image the location of positron emissions by detecting pairs of opposite directed gamma rays produced by the annihilation of the emitted positrons with electrons. Through binding the positron emitting nuclide to a suitable pharmaceutical (commonly called a tracer), functional information can be concluded from the detected distribution of positron emissions. Because PET imaging only provides with functional information, it is used together with CT imaging or MR imaging to be able to analyze the functional information with the corresponding anatomical locations.

A characteristic of relevance for oncology that can be imaged with PET is the lack of oxygenation within a tumor, i.e. hypoxia, that increase the radiation resistance for tumors (Nordsmark et al. 1996, Brizel et al. 1997, Nordsmark and Overgaard 2000). Hypoxia can e.g. be imaged with the tracer fluoromisonidazole ($^{18}$FMISO). $^{18}$FMISO works by passively diffusing into cells where it is reduced into metabolites that are reoxidized to FMISO under oxygenated conditions, but not in hypoxic, and hence the metabolites are accumulated in hypoxic cells (Lee and Scott 2007).

Another PET tracer of interest is to bind $^{68}$Ga to the prostate-specific membrane antigen ($^{68}$Ga-PSMA) which is an enzyme overexpressed on the cell membrane of almost all prostate cancer cells and relate to tumor aggressiveness and the probability of recurrences (Weineisen et al. 2015, Piert et al. 2016). PSMA is hence a promising tracer to image and stage prostate cancer.

However, the most common tracer for PET is fluorodeoxyglucose ($^{18}$FDG). This tracer yield images that map glucose metabolism, and because an increased cell proliferation is an energy consuming activity and a typical marker for cancerous tissue, it means that such tumors often can be localized with $^{18}$FDG-PET. For papers I and III we correlated pre-RT $^{18}$FDG-PET image data with post-RT recurrence locations to derive dose painting prescriptions and to optimize dose painting plans for head and neck cancers. See Figure 1 for an illustration of an $^{18}$FDG-PET image of a patient with head and neck cancer.

PET images are commonly presented as distributions of the standardized uptake value (SUV) defined as

$$\text{SUV} = \frac{n_u/V_{\text{vox}}}{n_i/m_{\text{pat}}} \quad [\text{g/cm}^3]$$

where $n_u/V_{\text{vox}}$ is the measured uptake $n_u$ per voxel volume $V_{\text{vox}}$ in Bq/cm$^3$, and $n_i/m_{\text{pat}}$ is the injected activity $n_i$ divided by the mass of the patient $m_{\text{pat}}$ in Bq/g. However, it is common to approximate that soft tissues within the body has a density of 1 g/cm$^3$ which implies that SUV can be considered as a dimensionless number. From eq. (2) it follows that if the injected activity is
distributed homogeneously in the body, SUV would equal unity for all image voxels.

Figure 1. An $^{18}$FDG-PET image overlaid on a CT image for a patient with head and neck cancer. The FDG uptake is visualized by the orange colors. The red contour is the GTV delineated according to the increased uptake of FDG, i.e. increasing SUV. The blue contour is the delineated CTV.
2.2 MR imaging

Magnetic resonance imaging (MRI) is based upon the physical phenomenon of nuclear magnetic resonance observed by Bloch (1946) and Purcell et al. (1946) which earned them the Nobel Prize in Physics 1952. This phenomenon is the energy absorption of photons in the radio spectrum by certain atomic nuclei subjected to a strong magnetic field. One such nucleus is hydrogen that is abundant in human tissues. When hydrogen nuclei are subjected to an external magnetic field the magnetic moment of the nuclei reach a precession frequency in direct proportion to the magnetic field strength, i.e. the nuclei have been polarized. These polarized nuclei can absorb the energy from photons that have a frequency in resonance with the precession frequency of the nuclei, and further on re-emit photons after the energy absorption has occurred. By applying a gradient (i.e. a slope of the magnetic field strength) on the external magnetic field, one can hence measure different radio frequencies due to different precession frequencies of hydrogen nuclei, which yield that tomographic images of human tissues can be resolved.

MRI is superior for resolving soft tissues and provides a large degree of freedom of what one wants to image. Besides anatomical imaging, MRI can capture blood flow, brain activation and chemical compositions in different tissues. Another MRI technique of interest for oncology is to map tumor vasculature, which can be done by tracing an injected contrast agent passage through a tumor, which is known as dynamic contrast enhanced (DCE) imaging.

Tumor activity can also be characterized due to that an increased cell proliferation yields increased cell density that hampers the diffusion of water. This can be imaged with MRI through diffusion weighted imaging (DWI). DWI utilizes strong gradients on the external magnetic field that yields a significant decrease in signal when hydrogen nuclei of water molecules diffuse freely, but not when the water molecules are more stationary. The signal decrease can be expressed as

\[ S(b) = S_0 \cdot e^{-b \cdot \text{ADC}} \]  

(3)

where \( b \) in s/m² is a factor dependent on the strength and timing of the diffusion weighted gradients, and \( S_0 \) is the baseline signal when \( b=0 \). Hence, by imaging both with \( b=0 \) and \( b>0 \) the apparent diffusion coefficient (ADC) can be calculated from eq. (3) as

\[ \text{ADC} = \frac{\ln[S_0/S(b)]}{b} \quad [\text{m}^2/\text{s}]. \]  

(4)

See Figure 2 for an image with ADC data for a patient with prostate cancer. ADC data has been shown to relate with Gleason scores (deSouza et al. 2008, Tamada et al. 2008, Mazaheri et al. 2009, Turkbey et al. 2011, Bittencourt et al. 2012, Shigemura et al. 2013) which is an important prognostic factor for prostate cancer and also shown to correlate with an increased re-
currence risk after RT (Epstein, Zelefsky, et al. 2016). For papers II and IV we used such a correlation between ADC data and Gleason scores from Turkbey et al. (2011) to form dose painting prescriptions and optimize dose painting plans for prostate cancer.

Figure 2. An ADC image visualized by yellow colors overlaid on a CT image for a patient with prostate cancer. The red contour is the GTV delineated according to decreasing values of ADC, i.e. decreasing water diffusion. The blue contour outlines the whole prostate volume that for RT normally is assigned as the CTV.
3 Dose-response functions for radiotherapy

Dose-response modelling is the concept of relating the response of a living cell, organ, function or organism, to a quantified exposure of an agent such as drugs, pollutants or radiation doses. For RT, dose-response models are used to estimate the probability for a certain type of response, or endpoint, as a function of the absorbed dose. Endpoints of interest for RT are tumor sterilization formalized as tumor control probability (TCP), and side effects formalized as normal tissue complication probability (NTCP). Furthermore, it is possible that different compartments of a tumor may have different and independent TCP predictions for an equal absorbed dose. Our work is based upon this idea, i.e. that functional image data can map spatially varying dose-responses of tumor volumes in order to derive heterogeneous dose painting prescriptions.

For both TCP and NTCP the endpoint probability follows an S-shaped sigmoid function, with low probabilities at low doses that steeply increases for higher doses to asymptotically go to unity at even higher doses. There are many mathematical functions with such properties, however, for RT the most common functions are the Poisson, the logistic, and the probit dose-response functions (Bentzen and Tucker 1997), which are further described in the next section.

3.1 Poisson dose-response function

Experimental data based upon the irradiation of cell populations with different doses show that the surviving fraction (SF) of the cell population decrease linear-quadratically on a logarithmic scale as

\[ SF(D) = e^{-\left(\alpha D + \beta D^2\right)} \]  \hspace{1cm} (5)

where \( D \) is the dose and \( \alpha \) and \( \beta \) are empirical proportionality factors that can be interpreted as descriptors of the radiation sensitivity of the cell population. This model is commonly called the linear-quadratic (LQ) model. Moreover, the dose where the contribution to cell sterilization from \( \alpha D \) equals the contribution from \( \beta D^2 \) is given by the ratio \( \alpha/\beta \). This ratio can be used as a descriptor of different cells or tissues radiation sensitivity regarding different fractionation schedules. It can also be used to calculate an isoeffective dose,
i.e. a total dose for a reference fraction dose that yields an equal endpoint as for another used fraction dose. Such an isoeffective dose measure is the equivalent dose for 2 Gray fractions (EQD 2), that is commonly used for clinical practice. See Figure 3 for an illustration of the surviving fraction for different hypothetical cell populations with different ratios of $\alpha/\beta$.

**Figure 3.** Illustration of the decrease of the surviving fraction (SF) for different hypothetical cell populations (shown by the different colors) as a function of an increased dose. All curves share the value of $\alpha=0.2$ Gy$^{-1}$ but with different values of $\beta$, where a decreased value of the $\alpha/\beta$ ratio yields a more pronounced shoulder with a faster decrease of the SF for higher doses. Also shown (in yellow) is the log-linear decrease of the SF when $\beta=0$ Gy$^{-2}$.

A semi-mechanistic derivation of the LQ-model given by eq. (5) can be done by means of the statistical Poisson distribution. The Poisson distribution can also be used to derive a dose-response model for TCP that is formulated as

$$\text{TCP}(D) = e^{-N_0^\text{SF}(D)},$$

where $N_0$ is the number of cells irradiated with a homogeneous dose $D$, and SF is given by eq. (5). The Poisson dose-response function as described by eq. (6) is useful and provides with semi-mechanistic interpretations. It can also be reformulated with extra parameters that that relate to the radiation sensitivity of tumor cells. An example of such a phenomenon is hypoxia, which in several studies have been included in the LQ-model (Thorwarth et al. 2007, Toma-Dasu and Dasu 2013, Lindblom et al. 2014). However, by using eq. (6) with single values for the input parameters, the dose-response derivatives becomes too steep compared to empirical observations from pa-
tient data (Dasu et al. 2003). This does thus motivate the use of other parameterizations for dose-responses, which will be described in the next section.

3.2 Dose-response parameterization with $D_{50}$ and $\gamma_{50}$

For practical applications mechanistic dose-response functions are not necessary if other empirically determined dose-response functions can provide with sufficiently accurate endpoint predictions. Such empirical dose-response functions used for RT are commonly parameterized with two parameters: $D_{50}$ which is the dose level for an endpoint probability of 50%; and $\gamma_{50}$ (introduced by Brahme (1984)) formalized as

$$\gamma_{50} = D_{50} \cdot \frac{dTCP(D)}{dD} \bigg|_{D=D_{50}}$$

which is the normalized dose-response derivative at $D_{50}$. The $\gamma_{50}$ parameter is because of this normalization (eq. (7)) a dimensionless number that describes how much the endpoint probability changes for a relative change of the dose (Brahme 1984).

The Poisson dose-response function for TCP, as described by eq. (6), can be expressed in terms of $D_{50}$ and $\gamma_{50}$. Based on eq. (6), we get for $\beta=0$ the substitutions $x=2\gamma_{50}/(\ln[2]D_{50})$ and $N_0 = \ln[2] \cdot e^{2\gamma_{50}/\ln[2]}$ that yields

$$TCP_{\text{Poisson}}(D) = 2 \cdot e^{\frac{2\gamma_{50}}{\ln[2]} - \frac{D}{D_{50}}}$$.  (8)

Other examples of sigmoidal TCP functions parameterized with the $D_{50}$ and $\gamma_{50}$ parameters are the logistic

$$TCP_{\text{logistic}}(D) = \frac{1}{1 + \exp \left\{ 4\gamma_{50} \cdot \left( 1 - \frac{D}{D_{50}} \right) \right\}}$$,  (9)

and probit

$$TCP_{\text{probit}}(D) = \frac{1}{2} \left( 1 - \text{Erf} \left[ \gamma_{50} \cdot \sqrt{\pi} \cdot \left( 1 - \frac{D}{D_{50}} \right) \right] \right)$$,  (10)

dose-response functions, see Bentzen and Tucker (1997). Furthermore, it has been proposed that as opposed to using the dose as covariate, to instead use the logarithm of dose as covariate for dose-response functions (Bentzen and Tucker 1997). This has the advantage that the dose-response function always goes to zero as the dose goes to zero (Herring,
The dose-response functions given by eqs. (8)-(10) are with the logarithm of dose as covariate described as

\[
\text{TCP}_{\text{Poisson, ln}(D)}(D) = 2 \left( \frac{D}{D_{50}} \right)^{\frac{\gamma_{50}}{\ln(2)}},
\]

\[
\text{TCP}_{\text{logistic, ln}(D)}(D) = \frac{1}{1 + \left( \frac{D}{D_{50}} \right)^{4\gamma_{50}}},
\]

and

\[
\text{TCP}_{\text{probit, ln}(D)}(D) = \frac{1}{2} \left( 1 + \text{Erf} \left( \gamma_{50} \cdot \sqrt{\pi} \cdot \ln \left( \frac{D}{D_{50}} \right) \right) \right),
\]

which are illustrated in Figure 4.

By using empirical outcome data for a certain patient group that have been treated with a homogeneous dose, one can hence fit the given data to one of the dose-response functions from eqs. (8)-(13) and extract the parameters of \(D_{50}\) and \(\gamma_{50}\). Such an empirically determined dose-response function can hence be used to give a prediction of either the TCP or the NTCP for a single patient treated with a specific homogeneous dose.

**Figure 4. Left:** Visualization of the three different dose-response functions from eqs. (11)-(13) with the logarithm of dose a covariate and with equal values of \(\gamma_{50}\) and \(D_{50}\). This yields similarity at \(D_{50}\) but with some deviations for other dose regions. **Right:** The same dose-response functions from eqs. (11)-(13) where the values of \(\gamma_{50}\) and \(D_{50}\) are adjusted to yield similarity at the working dose region of 70 Gy.
3.3 Optimization of dose painting prescriptions with dose-response functions

Dose painting rests upon the assumption that tumor volumes are comprised of sub-compartments with varying radiation sensitivities that can be mapped by means of functional imaging. The sub-compartments can be differentiated by delineating or thresholding these into different contours, and furthermore assign a dose prescription to each contour, i.e. dose painting by contours (DPBC). More general is however to prescribe doses on a voxel-level, i.e. dose painting by numbers (DPBN) (Bentzen 2005). In this thesis the focus is on the latter approach.

By assuming that the presence of tumor cells in different voxels can be controlled independently, the probability to control the tumor (i.e. the CTV) with voxel specific doses $D(r)$ is

$$TCP_vox(D) = \prod_{vox \in CTV} TCP_vox(D)$$

where $TCP_vox(D)$ represent the dose-response function for each voxel within the CTV. The position argument $r$ will for simplicity not be further used, as $TCP_vox$ is assumed to depend on dose and image value only, not on its position within the tumor. Hence, if functional imaging can map the $TCP_vox$ functions, one can assign a specific dose to each voxel to acquire a TCP prediction for a patient. One can even use the $TCP_vox$ functions to optimize towards a certain dose distribution. However, by using eq. (14) it is clear that a very high TCP simply can be reached by assigning very high dose values to each voxel. This would nevertheless result in unacceptable normal tissue complications. Since the major aim of dose painting is to use the radiant energy as efficiently as possible, the planning objective that strives to fulfill this aim can be expressed as

$$\begin{align*}
\text{maximize} & \quad \prod_{vox \in CTV} TCP_vox(D) \\
\text{subject to} & \quad \bar{D} = D_h
\end{align*}$$

where $\bar{D}$ is the mean absorbed dose to the CTV. Effectively, eq. (15) acts as a surrogate for equal risk of side-effect as for conventional homogeneous dose treatments, because the average dose is kept equal as for a homogeneous dose treatment. Nevertheless, if all voxels have the same dose-response relation, then a homogeneous dose yields the greatest TCP for a fixed mean dose to the tumor volume (Webb et al. 1994). A general solution to eq. (15) can be acquired through the use of Lagrange multiplicative (Ebert and Hoban 1996, Yang and Xing 2005). The solution is found where the gradients of the objective to be maximized and the mean dose constraint is aligned, see Figure 5.
**Figure 5. Left:** Visualization of dose-response functions for a simple tumor consisting of two compartments; vox1 and vox2 with different dose-responses (orange and red). The TCP product for the two compartments yields the total TCP as a function of equal (homogeneous) voxel doses (blue). Also shown as a function of the voxels mean dose $\bar{D}$ is the maximum possible $TCP_{\text{max}}$ (green) resulting from solving eq. (15). Hence, at the mean dose of 42 Gy the total TCP can increase from 50% to 64% for the optimal voxel doses 36 and 48 Gy (shown with ‘+’). **Right:** TCP lines of 64% (green) and 50% (blue) shown as a function of different doses given to vox1 (horizontal axis) and vox2 (vertical axis). The optimal dose combination for the compartments is shown with ‘+’ and is located where the gradient of the green TCP function is aligned with the gradient of the mean dose function (dashed black). Also shown is that equal voxel doses of 42 Gy yields a TCP of 50% (black dot). Note that the gradients are shown in their negative direction, denoted by “(-)”. 
4 Dose painting prescriptions

As stated by Bentzen and Gregoire (2011), dose painting prescriptions should preferably be based on empirical observations between pre-treatment image data and post-treatment dose-responses. However, detailed knowledge between image data and dose-responses is to a large degree missing. To circumvent this problem, several studies have proposed that a linear prescription function can be used to map image data directly into a dose prescription (Das et al. 2004, Vanderstraeten et al. 2006, Rickhey et al. 2008, Duprez et al. 2011, Witte et al. 2011, Berwouts et al. 2013, Arnesen et al. 2015, Barragán et al. 2015, Differding et al. 2015, Fontanarosa et al. 2015). This linear prescription function can be formulated as

\[ D(I) = D_{CTV} + \frac{I - I_{\text{min}}}{I_{\text{max}} - I_{\text{min}}} \cdot (D_{\text{max}} - D_{\text{min}}), \quad (16) \]

where \( D_{CTV} \) corresponds to a lower baseline dose for the CTV, \( D_{\text{max}} \) corresponds to a maximum allowed boost dose, \( I \) is the image data for a voxel, and \( I_{\text{min}} \) and \( I_{\text{max}} \) corresponds to the minimum and maximum image values for voxels of the CTV. Another similar proposal to acquire dose painting prescriptions has been formulated by Flynn et al. (2007) as

\[ D(I) = D_{CTV} + \frac{I}{I_{\text{mean}}} \cdot D_{\text{boost}}, \quad (17) \]

where \( D_{CTV} \) is a baseline dose for the CTV, \( D_{\text{boost}} \) is a boost dose, \( I \) is the image data for a voxel, and \( I_{\text{mean}} \) is the mean image data value for the CTV. The difference between these two prescription functions is that Flynn’s formulation, eq. (17), conserves the total integral dose to the CTV (i.e. \( D_{CTV} + D_{\text{boost}} \) is conserved) as opposed to eq. (16). But both prescriptions functions share the assumption that the image data can yield a beneficial dose painting prescription without any considerations whether the image data may differentiate varying dose-responses.

Yet another approach to acquire dose painting prescriptions has been proposed by Alber and Thorwarth (2014) based on the probability of tumor presence in voxels. Their probabilistically based dose prescription function is formulated as
\[ D(I) = D_{\text{presc}} + \frac{1}{\alpha} \ln[P(I)] \] (18)

where \( D_{\text{presc}} \) is the dose needed for voxels with a certain probability of tumor presence (i.e. unit probability), \( \alpha \) is the radiation sensitivity parameter of the LQ-model (see eq. (5)), and \( P(I) \) is the probability of tumor presence for a voxel with image data \( I \) (however note that a threshold probability above zero needs to be set to not let the logarithm reach \(-\infty\)). A consequence of eq. (18) is that if a tumor has tumor cells everywhere, the resulting prescription will be a homogeneous dose.

In contrast to the previously described dose prescription functions, is the idea that different image data implies different dose-responses that in turn can be used to optimize dose painting prescriptions (as described in chapter 3.3). An example of this approach has been presented by Vogelius et al. (2013), that performed a retrospective analysis of patients treated with RT for head and neck cancer. Based on observed recurrence patterns, they derived dose-response functions for different contours defined before the treatment by means of \(^{18}\text{FDG-PET}\). These contour specific dose-response functions were used to optimize dose painting prescriptions that maximized the TCP under the constraint of maintaining the same integral dose to the treated tumor volumes as for the conventional treatment, see eq. (15). The same approach is in this thesis generalized to derive dose painting by numbers (i.e. voxel-specific) prescriptions by retrospective analysis of RT data consisting of patient groups with pre-RT image data and post-RT outcomes. These patient groups were either diagnosed with head and neck cancer (paper I) or prostate cancer (paper II). We used data from these two diagnoses to determine image driven dose-response functions, which in turn were used to optimize dose painting prescriptions. The following sections describes the derivation of the used dose-response functions.

4.1 Deriving image driven dose-response functions from retrospective treatment data

In principle can a general image driven dose-response function be derived by using a large set of cancer patients and treat these with different dose levels to map pre-treatment functional image data with post-treatment recurrence locations. Such an approach would however be highly unethical and other methods are hence needed. Our derivation is therefore based on using outcome data for patients that have been imaged with functional imaging before treatment and then treated with conventionally used dose levels. Such retrospective patient data will in the following be expressed as a learning set (denoted by ‘ls’) although the learning set in paper I had the term patient cohort (denoted by ‘pc’). To circumvent the problem of missing outcome data for
other dose levels than the conventionally used dose, two requirements are introduced (that also have been described by Vogelius et al. (2013) and Lühr et al. (2017)): first, the image driven dose-response functions must for the treatment dose of the learning set reconstruct the learning set’s observed recurrence frequency; second, the image driven dose-responses must for the treatment dose reconstruct the learning set’s dose-response slope. These requirements are formulated as

\[
\text{TCP}_{\text{hs}}(D_h) = \frac{1}{N} \sum_{\text{pat}=1}^{N} \prod_{\text{vox} \in \text{CTV}_{\text{pat}}} \text{TCP}_{\text{vox}}(D_h, I) \quad (19)
\]

and

\[
\frac{d}{dD} \text{TCP}_{\text{hs}}(D) \bigg|_{D=D_h} = \frac{1}{N} \sum_{\text{pat}=1}^{N} \frac{d}{dD} \left( \prod_{\text{vox} \in \text{CTV}_{\text{pat}}} \text{TCP}_{\text{vox}}(D, I) \right) \bigg|_{D=D_h} \quad (20)
\]

where \( \text{TCP}_{\text{hs}}(D) \) is an empirically determined dose-response function for the learning set consisting of \( N \) patients with a known recurrence frequency and a known dose-response slope for the homogeneous treatment dose \( D=D_h \). Moreover, in eq. (19) \( \text{TCP}_{\text{vox}}(D_h, I) \) is the dose-response for a voxel with dose \( D=D_h \) and image value \( I \), that based on eq. (14) yield that the TCP for a patient’s CTV treated with the dose \( D=D_h \) is

\[
\text{TCP}_{\text{pat}}(D_h) = \prod_{\text{vox} \in \text{CTV}_{\text{pat}}} \text{TCP}_{\text{vox}}(D_h, I). \quad (21)
\]

Furthermore, for the derivation of a general \( \text{TCP}_{\text{vox}}(D, I) \) function for any dose level, we have in addition used three assumptions: first, that \( \text{TCP}_{\text{vox}}(D, I) \) at the dose \( D=D_h \) is known or can be determined from the learning set data; second, that \( \text{TCP}_{\text{vox}}(D, I) \) can be parameterized with a logistic dose-response function given by eq. (12); third, that the \( \gamma_{50} \) parameter that govern the slope of the \( \text{TCP}_{\text{vox}}(D, I) \) function can be treated as a constant for all \( I \) which yield that the dose-response differentiation is a function of \( D_{50} \) only. Hence, based on the two requirements given by eqs. (19)-(20) and the three aforementioned assumptions, it is possible to determine the needed parameters for the \( \text{TCP}_{\text{vox}}(D, I) \) functions, i.e. \( D_{50} \) as a function different image data \( I \), and a constant effective value of \( \gamma_{50,\text{eff}} \). The described formalism is applied in papers I and II to optimize dose-painting prescriptions, by means of voxel specific dose-response functions driven by SUV from \(^{18}\text{FDG-PET} \) for head and neck cancer (paper I); and driven by the mapping of ADC data into Gleason scores for prostate cancer (paper II). These two works do also provide a more rigorous derivation of the respective voxel
specific dose-response functions for each diagnosis. See Figure 6 for an illustration of this formalism.

**Figure 6.** Illustration of the formalism to derive image driven dose-response functions for voxels based on the retrospective outcome data for the learning set of head and neck cancer patients included in paper I. **Upper panel:** The logistic dose-response function (see eq. (12)) for the learning set (green) with $\gamma_{50,ls}=1.8$ (taken from literature (Bentzen 1994)) and $D_{50}$ set to fulfill the learning set’s observed recurrence frequency (TCP=71%) for the treatment dose $D_h=70.1$ Gy EQD$_2$ (black dot). This function yields a certain dose-response slope at the dose $D_h=70.1$ Gy EQD$_2$ (black tangent line). **Lower panel:** The multiplication of voxel specific dose-response functions (not shown) yields patient specific dose-response functions (red color). By averaging these patient specific functions, one gets the average dose-response function (dashed dark blue) that must fulfill the learning set’s recurrence frequency and dose-response slope (i.e. the two requirements set by eqs. (19)-(20)). This does thus imply that the parameters $\gamma_{50,eff}$ and $D_{50}(I)$ have been determined consistently for the voxel specific dose-response functions, see Figure 7 for the resulting dose-response functions.
4.2 Dose painting prescriptions for head and neck cancer (I)

Radiotherapy is one of the standard options for treating head and neck cancers and the survival frequency for head and neck cancer patients in Europe has been estimated to 72% and 42% at 1 and 5 years year post-treatment, respectively (Grégoire et al. 2010). Moreover, for head and neck cancer it has been shown that increased SUV from $^{18}$FDG-PET correlate with an increased recurrence risk after RT (Kunkel et al. 2003, Soto et al. 2008, Xie et al. 2010, Vogelius et al. 2013, Due et al. 2014, Jeong et al. 2014).

The aim of paper I was to derive and illustrate $^{18}$FDG-PET driven dose painting prescriptions for this diagnosis by using a learning set with pre-RT $^{18}$FDG-PET image data and post-RT outcomes. We had data for 59 patients where the primary clinical target volume (CTVT) had been treated with an average dose of 70.1 Gy EQD$_2$. After treatment, a total of 17 of the 59 patients were locally recurring within their treated CTVT with a median time of 4.1 months (range 1.3–11.8 months) after RT. Hence, the TCP for local control of the learning was TCP$_{ls}$=1−17/59 (i.e. 71%).

To derive dose-response functions driven by SUV from the acquired $^{18}$FDG-PET image data, TCP$_{vox}(D,SUV)$ at the dose $D=D_h$ needed to be determined (i.e. the first assumption described in section 4.1, page 27). This was done by defining a local control ratio (LCR) as

$$\text{LCR}(\text{SUV}) = 1 - \frac{f_{RVs}(\text{SUV})}{f_{RVs \cup CTVTs}(\text{SUV})},$$

where $f_{RVs}(\text{SUV})$ is the SUV frequency for all 17 recurrence volumes (RVs) that had been delineated by an experienced radiation oncologist on the pre-RT CT images, and $f_{RVs \cup CTVTs}(\text{SUV})$ is the SUV frequency for the union of the 17 RVs with the 59 CTVTs. Based on the thus given LCR function we rescaled by means of an exponent $k$ such that the TCP for voxels at the treatment dose $D_h$ is given as

$$\text{TCP}_{vox}(D_h,\text{SUV}) = (\text{LCR}(\text{SUV}))^k,$$

where the exponent $k$ was set to fulfill the requirement given by eq. (19), i.e. that TCP$_{vox}(D,SUV)$ for the treatment dose $D_h$=70.1 Gy EQD$_2$ reconstructs the observed recurrence frequency TCP$_{ls}$=71%. Further details to determine the voxel-specific TCP$_{vox}(D,SUV)$ functions for arbitrary dose levels are described more thoroughly in paper I. The resulting dose-response functions are shown in Figure 7 and demonstrate an increasing radiation resistance for increasing SUV that hence implies that increasing SUV are optimized towards higher dose levels, as shown in Figure 8.
Figure 7. Left: $D_{50}$ as a function of different SUV for voxels with a volume of 3.0×3.0×2.5 mm$^3$, where an increasing SUV hence implies an increasing radiation resistance. Also shown is the value of $\gamma_{50,\text{eff}}$ for the dose-response functions to the right. Right: The resulting SUV driven dose-response functions for three different SUV that were parameterized with a logistic dose-response function (eq. (12)). The figure is adapted from the corrigendum (paper i).

To acquire a dose painting prescription for each patient, we used the derived SUV driven dose-response functions (shown in Figure 7) with the objective to maximize the TCP for the CTVT for an equal average dose as the learning set’s treatment dose, i.e. 70.1 Gy EQD2, see eq. (15). Note that the resulting dose painting prescriptions hence are given in Gy EQD2. Furthermore, the resulting prescriptions (Figure 8) were optimized without any consideration of physical radiation transport phenomena, i.e. the dose to each voxel was independent of the dose to the neighboring voxels. The optimized dose painting prescriptions gave TCP increases that for different patients varied between 0.2 percentage points (p.p.) to 15 p.p which were found to correlate with the standard deviation of SUV multiplied by the CTVT volumes (Figure 8). This finding can hence potentially be used for patient selection in prospective dose painting studies.
Figure 8. **Left:** Optimized dose painting prescriptions for the patients of the learning set vs. SUV for each CTVT. Each of the prescriptions are different, because each patient has a different CTVT volume with a different distribution of SUV. **Right:** The increase in TCP as compared to a homogeneous dose distribution with $D=D_h$. The TCP increases are plotted vs. the standard deviation of SUV ($\sigma_{SUV}$) multiplied by the volume of each CTVT, showing that the gain with DPBN increases with tumor size and tumor heterogeneity. Adapted from the corrigendum (paper i).

After paper I had been published, we found a data processing error of the SUV from the $^{18}$FDG-PET images. The error was that the SUV had not been corrected for radioactive decay between injection and imaging. This error had no impact of the conclusions, but affected the data values given in paper I. These corrected values were published in a corrigendum (denoted as “i” in the list of papers).
4.3 Dose painting prescriptions for prostate cancer (II)

Prostate cancer is the most common cancer diagnosis for men in the developed countries (Torre et al. 2015). One of the most significant prognosis predictors for prostate cancer is the Gleason grading developed by Donald F. Gleason (Gleason et al. 1974). The grading ranges from 1 to 5 and is based upon the microscopic pattern of cancer cells in biopsy samples of prostatic tissue. Each sample is assigned with a primary grading (i.e. the predominant pattern) and a secondary grading (i.e. the second most common pattern) that when added yields the Gleason score. An increasing Gleason score indicates a poorer cell differentiation and relates to a higher risk for metastatic spread (Humphrey 2004). It has also been shown that increasing Gleason scores correlates with decreasing apparent diffusion coefficient (ADC) data acquired from diffusion weighted MRI (deSouza et al. 2008, Tamada et al. 2008, Mazaheri et al. 2009, Turkbey et al. 2011, Bittencourt et al. 2012, Shigemura et al. 2013, Boesen et al. 2015).

Because an increasing Gleason score correlates with an increased recurrence risk after RT for prostate cancer (Epstein, Zelefsky, et al. 2016), we hypothesized in paper II that Gleason score driven dose-response functions could be used to optimize dose painting prescriptions. These Gleason score driven dose-response functions were derived from a learning set of patient data, consisting of pre-RT biopsy record data and post-RT outcomes. Furthermore, because increasing Gleason scores correlates with decreasing values of ADC from MRI, we constructed a formalism where ADC image data is mapped into the Gleason driven dose-response functions from which dose painting prescriptions could be optimized for a test set consisting of 18 patients with pre-RT ADC images.

The learning set consisted of 122 patients diagnosed with high risk prostate cancer (risk criteria according to Mohler et al. (2010)) with pre-RT Gleason scores and post-RT outcome data. The included patients constituted a subset of the patient group described by Johansson et al. (2019) which had been treated with a proton boost of 5 Gy for 4 fractions to the prostate volume (CTVT) only, followed by X-rays of 2 Gy for 25 fractions to both the CTVT and lymph node regions. By using RBE=1.1 for protons and $\alpha/\beta=1.93$ Gy (based on Vogelius and Bentzen (2013)) the homogeneous CTVT dose was estimated to 91.6 Gy EQD2. Moreover, the 5-year bio-chemical recurrence free frequency for the learning set was observed to be TCP$_{5\%}$=74%.

To derive Gleason score driven dose-response functions, we constructed virtual prostate volumes voxelized by each patient’s pre-RT Gleason score data. Furthermore, since our formalism uses the assumption that the voxel specific TCP variation at the homogeneous treatment dose $D=D_h$ is known (see chapter 4.1), we used the following assumption
TCP_{vox}(D_h, G) = \begin{cases} b, & G \leq 6 \\ b - m \cdot (G - 6), & G > 6 \end{cases}, \quad (24)

where \( b \) was determined to reconstruct the 5-year post-RT TCP given by (Epstein, Zelefsky, et al. 2016) for the subset of the learning set that had values of \( G \leq 6 \) only, and \( m \) were determined to reconstruct the whole learning set’s TCP_{\text{h}}=74\% \) (with the requirement given by eq. (19)). Moreover, in eq. (24), \( b \) corresponds to a constant TCP for Gleason scores \( (G) \) equal or below 6, since the new Gleason score consensus classifies such values of \( G \) into the same risk category (Epstein et al. 2005, Epstein, Egevad, et al. 2016), and \( m \) corresponds to a linear decrease of the TCP for \( G \) above 6, because higher values of values of \( G \) corresponds to an increased recurrence progression (Epstein, Zelefsky, et al. 2016, Magi-Galluzzi et al. 2016). This TCP variation is shown in Figure 9.

Figure 9. TCP variation at \( D_h=91.6 \) Gy EQD\(_2\) for voxels with different Gleason scores and a voxel volume of \( 3\times3\times3 \) mm\(^3\), where the values of \( b \) and \( m \) were determined to fulfill the requirement given by eq. (19). The TCP values are very close to a probability of unity, which when multiplying the TCP values of many voxels comprising a patient’s tumor volume (eq. (21)) yields a lower TCP for the patient.
Based on the determined TCP variation for different values of $G$ (Figure 9), we derived voxel specific $G$ driven dose-response functions, shown in Figure 10. Further details for the derivation of the $G$ driven dose-responses is given in paper II. From the derived $G$ driven dose-response functions (Figure 10), dose painting prescriptions were optimized for the 122 virtual voxelized prostate volumes (shown in Figure 12). These prescriptions were as in paper I, optimized with the objective to maximize the TCP for the constraint of equal average dose as for the conventional uniform dose treatment with $D_h=91.6$ Gy EQD2, see eq. (15).

**Figure 10.** Left: $D_{50}$ as a function of voxelized Gleason scores $G$ with the value for $\gamma_{50,\text{eff}}$ also shown. Right: The voxel specific Gleason score driven dose-response functions, where higher values of $G$ demonstrate an increased radiation resistance compared to lower values of $G$. Also shown is the learning set’s homogeneous treatment dose $D_h=91.6$ Gy EQD2. The figure is adapted from paper II.

To enable ADC driven optimization of dose painting prescriptions we needed a mapping of ADC from G, which we based upon published data from Turkbey et al. (2011). However, their data correlate G to ADC whereas we needed the mapping to be reversed, i.e. from ADC to G. Hence, we constructed PDFs based on the given data that we renormalized into a conditional probability map $P(G|\text{ADC})$, see Figure 11.
To acquire ADC driven dose painting prescriptions, we included a test set with pre-RT ADC maps from 18 patients diagnosed with high-risk prostate cancer. Based on the conditional probability map (Figure 11), and the already derived Gleason driven dose-response functions (Figure 10), ADC driven dose painting prescriptions could be optimized for the test set in the same manner as for the learning set, see eq. (15). However, by directly using the conditional probability map (Figure 11), the distribution of $G$ for the test set were biased towards higher $G$ compared to the distribution of $G$ for the learning set. To circumvent this, after the ADC data had been mapped to maps of $G$, we performed a geometrical erosion of the resulting $G$ maps of the test set. In Figure 12 is the resulting increases in TCP versus the TCP for a homogeneous dose shown both for the learning set and the test set. Furthermore, one of the test set patient’s dose painting prescription is shown in Figure 13.

Figure 11. Left: PDFs for different $G$ (each parameterized with a log-normal PDF) as a function of ADC constructed from the data given by Turkbey et al. (2011). Right: The renormalized conditional probability map used to map ADC values to a probability distribution of $G$. A specific ADC value (horizontal axis) yields a probability distribution of $G$ (along the vertical axis), where increasing probabilities are indicated by increasing whiteness. The figure is adapted from paper II.
Figure 12. **Upper left:** Dose painting prescriptions for all learning set patients plotted vs. voxelized Gleason scores within each prostate volume. The learning set patients had single valued Gleason scores given from the biopsy records which explain the distinct shapes of the lines. **Upper right:** Dose painting prescriptions for the test set patients plotted vs. the average value of Gleason scores mapped from ADC image data with the conditional probability map $P(G|\text{ADC})$ shown in Figure 11. **Lower left:** TCP increases per patient resulting from the optimized dose painting prescriptions as compared to homogeneous dose prescriptions plotted vs. the standard deviation of voxelized Gleason scores multiplied by the prostate (CTVT) volumes. **Lower right:** The TCP increases from the left panel plotted vs. each patient’s TCP for a homogeneous dose prescription of $D_h=91.6$ Gy EQD$_2$. The figure is adapted from paper II.
Figure 13. **Left:** ADC map for a central prostate slice from the test set patient that had the highest TCP increase (30p.p.) from the optimized dose painting prescription. **Right:** The resulting dose painting prescription based on the ADC map to the left. Due to the erosion operation, small regions with high probabilities for high $G$ were optimized to lower dose levels. The figure is adapted from paper II.

Conclusively, with paper II we demonstrated that Gleason score driven dose painting prescriptions could be constructed from a learning set of pre-RT Gleason scores and published ADC-to-Gleason score correlations. The resulting TCP increases per patient increased with increasing prostate volumes and Gleason score heterogeneity which may serve as an indicative factor of which patients are more likely to benefit from a dose painting treatment.
5 Robust dose painting optimization

To determine if dose painting has a clinical potential, dose painting prescriptions need to be realized into clinically deliverable dose painting plans. For this realization, robust procedures are needed to ensure a spatially correct dose deliverance despite uncertainties stemming from systematic (comprising all fractions) and random (fraction specific) geometrical errors (van Herk et al. 2000). Systematic errors originate from the treatment planning procedure and involve inaccuracies of the definition of the patient’s treatment planning setup, dose calculation, and tumor and organ segmentation etc. Moreover, random errors occur during the treatment execution of each fraction and stem from anatomical changes (e.g. organ motions, weight loss etc.) and inaccuracies of reproducing the patient’s setup versus the setup used for treatment planning.

For conventional RT with homogeneous doses, the CTV is expanded by a margin to form the PTV which is defined and used to ensure a geometrically robust dose coverage for the CTV (ICRU 1993, 1999, 2010). However, because dose painting by numbers is based upon prescriptions per voxel, it becomes cumbersome to apply margins to ensure a geometrically robust dose coverage for each voxel (Witte et al. 2011, Unkelbach et al. 2018). Nevertheless, several planning techniques have been proposed that aims to ensure geometrical robustness without the use of margins (Birkner et al. 2003, Unkelbach and Oelfke 2004, Baum et al. 2006, Chan et al. 2006, McShan et al. 2006, Witte et al. 2007, Unkelbach et al. 2009, 2018, Gordon et al. 2010, Fredriksson et al. 2011, Fredriksson and Bokrantz 2016, Tilly et al. 2019). One of these methods is minimax optimization (Fredriksson et al. 2011, Unkelbach et al. 2018), which will be described more thoroughly in the following section, and was used in paper III and IV to yield deliverable dose painting plans that aimed to maximize a robust TCP.
5.1 Minimax optimization

The minimax concept originates from John von Neumann (von Neumann 1928, von Neumann et al. 1944) and is commonly used for decision making in e.g. finance by minimizing the possible loss for a worst case (maximum loss) scenario. Minimax optimization can also be used for RT to ensure a geometrically robust dose plan without the use of CTV-to-PTV margins. Treatment planning with minimax optimization is based upon sampling a set of realistic treatment scenarios that may occur and hence influence the dose distribution to be delivered for the actual treatment. These scenarios can include setup errors of the patient positioning, body and organ motions, and range uncertainties (used for RT with protons). By using such scenarios one can hence optimize towards a treatment plan that is as good as possible for the worst-case scenario (Fredriksson et al. 2011, Unkelbach et al. 2018).

The aim of the treatment planning process is to produce a deliverable dose plan that include certain planning objectives regarding dose coverage of the tumor volume and sparing of the normal tissues. By formulating these objectives on a mathematical form, the treatment planning can be formulated as a mathematical optimization problem. An optimization problem consists of an objective function that strives to fulfill all planning objectives (often by summing all planning objectives, see eq. (25)), and a set of constraints that must be fulfilled. For RT it is common that the objective function aims to be minimized, and hence the robust minimax optimization problem can be formulated as

\[
\min_d \left( \max_j \left[ \sum_{i=1}^{n} w_i f_i(d_j) \right] \right) \tag{25}
\]

subject to \( c_q(d_j) \leq 0, \quad q = 1, \ldots, Q \)

where \( d_j \) is the physical dose distribution for each of the \( j \) number of sampled scenarios, \( w_i \) is non-negative importance weights for the \( n \) number of planning objectives \( f_i \), and \( Q \) is the number of constraints \( c_q \). Note that eq. (25) is formulated to include minimax optimization for all planning objectives, but it is feasible to use minimax optimization for constraints and/or exclude certain planning objectives from the minimax part of the optimization.
5.2 Robust dose painting optimization for head and neck cancer (III)

In paper III we implemented the formalism for $^{18}$FDG-PET driven dose painting prescriptions for head and neck cancers given in paper I as planning objective in a research version of a TPS (RayStation v.5.99). This planning objective was implemented to be feasible with robust minimax optimization, see eq. (25). This implementation did thus make it feasible to optimize DPBN plans directly driven to optimize towards a robustly maximized TCP, as opposed to other dose painting studies that have focused on optimizing towards a robust dose distribution (Witte et al. 2011, Sterpin et al. 2014, Barragán et al. 2015).

The aim of the study was to evaluate the potential and robustness to increase the TCP with DPBN plans in comparison to the TCP for conventional uniform dose plans. We also analyzed the impact on the TCP maximization by including potential uncertainties of the $^{18}$FDG-PET driven dose-response functions used for DPBN optimization.

A total of 20 patients out of the 59 patients in paper I were included for optimization of dose painting plans. These 20 patients were selected to evenly represent the range of TCP increases resulting from ideal dose redistributions for all 59 patients in paper I (see Figure 8 in chapter 4.2). For each patient we optimized four dose plans with volumetric-modulated arc therapy (VMAT) for delivery in 35 fractions. Of these plans, one reference plan was optimized with a uniform dose to the PTVT (i.e. the primary target CTVT expanded with 0.5 cm), and three plans were optimized with DPBN for different allowed dose levels to the CTVT. Because the CTVT-to-PTVT margin was 0.5 cm for the uniform dose plan, we optimized the DPBN plans with minimax optimization for a robustness distance of 0.5 cm. Furthermore, for the DPBN plans we included a hot spot constraint of $D_{1cm} \leq 84$ Gy physical dose for the CTVT, based on the observed maximum tolerated dose from Olteanu et al. (2018). See Table 1 for the different settings of the four plan optimizations per patient.

<table>
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<th>optimization setting: DPBN or Uniform</th>
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<th>robustness distance [cm]</th>
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<td>Not included</td>
<td>0.5</td>
</tr>
<tr>
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<td>75</td>
<td>0.5</td>
</tr>
<tr>
<td>DPBN</td>
<td>6</td>
<td>70</td>
<td>0.5</td>
</tr>
<tr>
<td>Uniform</td>
<td>6</td>
<td>70</td>
<td>CTVT-to-PTVT margin 0.5</td>
</tr>
</tbody>
</table>

Table 1. Different settings for the plan optimizations, yielding a total of 3 DPBN plans per patient, and 1 reference plan optimized with a uniform dose to the PTVT.
We evaluated the robustness in TCP for all DPBN plans by generating treatment scenarios with randomly sampled displacements of the patient positioning (i.e. isocenter displacements). For this process we sampled a systematic displacement $\mathbf{x}_s$ for all 35 fractions, and additionally a random displacement for each fraction $\mathbf{x}_r$. The total displacement per fraction was thus $\mathbf{x}_{\text{frac}} = \mathbf{x}_s + \mathbf{x}_r$. The sampling were done using isotropic 3D-Gaussian distributions with zero mean and standard deviations of 0.19 cm for $\mathbf{x}_s$ and 0.13 cm for $\mathbf{x}_r$. A total of 25 treatment scenarios were generated per plan, yielding for each plan a total of $25 \times 35 = 875$ fraction specific dose calculations.

Furthermore, we analyzed the impact on the potential to increase the TCP with DPBN due to potential uncertainties of the voxel-specific $\text{TCP}_\text{vox}$ functions (see Figure 7 in chapter 4.2 for the nominal $\text{TCP}_\text{vox}$ functions). For this analysis we derived a set of perturbed $\text{TCP}_\text{vox}$ functions under the assumption that the recurrence frequency of the learning set data either was increased or decreased by one standard deviation from the observed recurrence frequency for the original patient cohort (given in paper I and described in chapter 4.2). We used these perturbed $\text{TCP}_\text{vox}$ functions for optimizing a new set of DPBN plans for a subset of the included patients (i.e. 6 patients out of the 20 patients).

The average increase in TCP as compared to a homogeneous dose treatment was 3 percentage points (p.p.) (range 0-9p.p.), 12 p.p. (range 2-27p.p.), and 20p.p. (range 4-45p.p.), for the optimizations with the mean dose constrained to 70 Gy, 75 Gy, and not constrained, respectively (see Figure 14). It was also found as in paper I that the patients with large tumors and large spread of SUV gained the greatest TCP increases. Furthermore, by considering dose-response uncertainties it was found that if the TCP prediction for a homogeneous dose decrease the dose painting allows for almost all cases a larger TCP increase, and vice versa. These findings were more noticeable for the patients with a poorer prognosis and by escalating the allowed dose (see Figure 14).

Furthermore, the robustly optimized DPBN plans were found to have consistently robust TCP values with a median deviation below 1p.p. for all 25 sampled treatment scenarios per plan and patient. The maximum observed deviation in TCP increase for a single scenario was 3.5p.p., found for a patient’s plan optimized without a mean dose constraint, see Figure 15.
Figure 14. Left column: TCP increases for the DPBN plans vs. uniform dose plans with 70 Gy target dose. Data are plotted versus the standard deviation of SUV multiplied by the CTVT volumes. Also shown are linear fits with their resulting slope and intercept (with the rightmost data point excluded as an outlier). The panel rows differentiate the results for planning without a mean dose constraint (uppermost), mean dose constraint of 75 Gy (middle row), and a mean dose constraint of 70 Gy (lowermost). Right column: The TCP increases shown in the left column plotted versus the TCP for plans with a homogeneous dose of 70 Gy. In both columns error bars are included for a subset of six patients showing the resulting deviations due to TCPvox functions based on an assumed increased recurrence frequency for the learning set (orange bars), and a decreased recurrence frequency (purple bars) by one standard deviation for both cases. The figure is adapted from Paper III.
Figure 15. Box and whisker plots (box 25\textsuperscript{th} to 75\textsuperscript{th} percentile, whiskers 1.5 interquartile range, dots outliers) of the deviation in TCP from simulating treatment scenarios for 20 patients. The uppermost panel shows results for plans without a mean dose constraint, middle for mean dose constraint 75 Gy, and lowermost with mean dose constraint 70 Gy.
In conclusion, with paper III we demonstrated that it is feasible to optimize $^{18}$FDG-PET driven dose painting plans for head and neck cancers that robustly increase the TCP compared to homogeneous dose treatments. As already observed in paper I the greatest potential for TCP increases were found for patients with larger and more SUV heterogeneous tumors.

5.3 Robust dose painting optimization for prostate cancer (IV)

In paper IV we implemented the dose painting formalism for prostate cancers given in paper II to be used as a planning objective in a research version of a TPS (RayStation v.5.99). This implementation did hence make it feasible to optimize dose painting plans driven by the mapping of ADC data to Gleason score driven dose-response functions. Similar to paper III, this planning objective was implemented to be feasible with robust minimax optimization, see eq. (25).

The aim of paper IV was to evaluate the potential to actualize TCP increases with DPBN plans as compared to uniform dose treatments for prostate cancer. The actualization potential was quantified by the DPBN efficiency ($\eta_{\text{DPBN}}$) defined as

$$\eta_{\text{DPBN}} = \frac{TCP_{\text{real}} - TCP_{\text{hom}}}{TCP_{\text{ideal}} - TCP_{\text{hom}}}$$

(26)

where $TCP_{\text{real}}$ corresponds to the TCP for an optimized DPBN plan, $TCP_{\text{hom}}$ the TCP for a homogeneous dose, and $TCP_{\text{ideal}}$ the TCP for an ideal DPBN prescription (i.e. a dose distribution that does not consider radiation transport phenomena). Both the ideal DPBN prescriptions and the DPBN plans were optimized to acquire a maximum TCP for an equal average dose to the CTVT as for a uniform dose of $D_{h}=91.6$ Gy EQD$_2$, see eq. (15). However, to acquire a theoretical maximum gain in TCP for the ideal DPBN prescriptions, we assumed that the ADC data could be exactly mapped into a specific Gleason score (i.e. by using the average Gleason score of the ADC-to-Gleason map given in Figure 11). The impact on the DPBN efficiency was tested by varying 3 different conditions for the DPBN plan optimizations: first, by using different photon energies 6 and 15 MV; second, by applying different levels of precision when mapping ADC data into Gleason score driven dose-responses; third, for three different robustness distances, i.e. for different deviations of the iso-center positioning. This yielded 12 different plan optimizations per included patient, see Table 2. A total of 17 patients were included as a test set for the DPBN plan optimization. These were the same 18 patients used as a test set in paper II, where one patient was exclud-
ed because of a large anatomical difference of the rectum between the CT and ADC image sets.

**Table 2.** The different conditions for the plan optimizations, where the photon energy, precision on the mapping of ADC→Gleason scores, and the robustness distance was varied, yielding a total of 12 plans per patient.

<table>
<thead>
<tr>
<th>photon energy</th>
<th>mapping of ADC→Gleason score</th>
<th>robustness distance</th>
</tr>
</thead>
<tbody>
<tr>
<td>[MV]</td>
<td>Low precision (LP) or High precision (HP)</td>
<td>[cm]</td>
</tr>
<tr>
<td>6</td>
<td>LP</td>
<td>0.0</td>
</tr>
<tr>
<td>6</td>
<td>LP</td>
<td>0.2</td>
</tr>
<tr>
<td>6</td>
<td>LP</td>
<td>0.6</td>
</tr>
<tr>
<td>6</td>
<td>HP</td>
<td>0.0</td>
</tr>
<tr>
<td>6</td>
<td>HP</td>
<td>0.2</td>
</tr>
<tr>
<td>6</td>
<td>HP</td>
<td>0.6</td>
</tr>
<tr>
<td>15</td>
<td>LP</td>
<td>0.0</td>
</tr>
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<td>15</td>
<td>LP</td>
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<td>0.2</td>
</tr>
<tr>
<td>15</td>
<td>HP</td>
<td>0.6</td>
</tr>
</tbody>
</table>

Figure 16 shows the resulting DPBN efficiency for each plan optimization. The plans that demonstrated the greatest DPBN efficiency were those reflecting very high precision irradiation, i.e. the plans optimized without robustness distance of 0.0 cm and a high precision mapping of ADC-to-Gleason scores. However, the effect on the DPBN efficiency by optimizing with different photon energies was not as large as the other tested conditions. Some plans had a negative DPBN efficiency, meaning that these DPBN plans had a lower TCP than for a uniform dose treatment. Nevertheless, the 25th percentile of the DPBN efficiency for all planning scenarios all had a positive efficiency meaning that at least 75% of the DPBN plans yielded a greater TCP than the TCP for a uniform dose treatment. In Figure 17 is one of the DPBN plans shown as an example.
In conclusion, in paper IV we found that TCP increases are more likely when there is a high precision on the mapping of image data into dose-responses and a high certainty of the tumor position during treatment. These findings does thus highlight the relevance of finding strong correlations between image data and dose-responses and the immense importance of a high spatial certainty in tumor positioning when implementing DPBN.
Figure 17. Illustration of a CT-image slice for one of the included patients where the blue contour is the prostate target volume (CTVT) with a TCP prediction of 34% for a homogeneous dose treatment. **Uppermost:** The ADC image data within the CTVT, where the low-ADC regions are distinguished with a red coloring and the high-ADC regions with a blue coloring. **Middle row:** the ideal DPBN prescription, where the low-ADC regions are prescribed a higher dose than the high-ADC regions with a lower dose. **Lowermost:** One of the DPBN plans, optimized with 15MV photons, high precision (HP) mapping of ADC-to-Gleason scores, and a robustness distance of 0.2 cm.
6 Summary and directions for future research

This thesis has presented how retrospective treatment data can be used to optimize top-down based dose painting prescriptions driven by pre-treatment functional image data, papers I & II. These dose painting prescriptions were further on realized into deliverable dose painting plans that indicated that the potential TCP increases both could be significant and robust with regard to geometrical uncertainties of the patient anatomy, papers III & IV. Furthermore, since the presented formalism is agnostic to underlying mechanisms for dose-responses, it is hence not limited to a specific imaging modality or to a specific diagnosis. The presented formalism relies only on correlations between pre-treatment quantities that can be imaged and post-treatment outcomes, and does thus not utilize mechanistic or semi-mechanistic interpretations of the image data.

However, the presented methodology is based on several assumptions that must be considered carefully before clinical implementation. First, the assumption that tumor voxels are controlled independently of each other, is an assumption that does not consider any potential underlying intra-dependent tumor biology. This assumption of voxel independency does also imply a dose-volume effect (i.e. that larger tumor volumes need higher doses to be sterilized) that varies exponentially by the number of voxels comprising a tumor (see eq. (14)), which may need consideration. Second, we have chosen to use dose-response functions which only vary with voxel dose and with a single input quantity of SUV in paper I and III, and Gleason score in paper II and IV. It is likely that other pre-treatment factors also affect the treatment outcome of individual patients. Third, we have only used one image modality per diagnosis. By including several image modalities that each resolve different functional patterns of tumor tissues, it would likely yield image driven dose-responses that can provide with a more certain dose-response prediction. Fourth, our optimization of dose painting prescriptions assumes that keeping the mean CTV dose to that as for conventional treatments acts as a surrogate to not increase NTCP, which needs consideration. It would however be possible to utilize the presented dose-response formalism to directly optimize towards a trade off between the TCP vs. the NTCP if we had access to reliable dose-response functions for all possible toxicities per used diagnosis. Nevertheless, the presented formalism does not exlude the use of clinically used planning objectives for organs at risks, as shown in papers III and IV. Fifth, the pre-treatment
functional image data needs to be robust both spatially and temporally to ensure that the dose painting prescriptions are valid for several treatment fractions. It has however been shown that $^{18}$FDG-PET imaging can provide with image data that, at least for the startup for an $^{18}$FDG-PET driven dose painting setting, is spatially and temporally robust (Rasmussen et al. 2015).

Even though the presented formalism indicates that TCP increases can be acquired with dose painting, further research is needed to verify or reject whether the presented dose painting formalism relies on valid assumptions and hence actually can improve the outcomes for patients with head and neck cancer or prostate cancer. Such studies can be based upon the inclusion of multi-institutional data of patients with pre-RT image data and post-RT outcomes, in order to tune the dose-response functions to be as prognostically predictive as possible for each diagnosis. If such studies would prove to be veracious, a next step would be to start performing clinical trials. Furthermore, since the presented formalism already have been implemented into a TPS, it is at least from a technical point of view not far out of reach to start such studies.
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8 References


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A doctoral dissertation from the Faculty of Medicine, Uppsala University, is usually a summary of a number of papers. A few copies of the complete dissertation are kept at major Swedish research libraries, while the summary alone is distributed internationally through the series Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine. (Prior to January, 2005, the series was published under the title “Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine”.)