DEVELOPMENT OF ATLAS-BASED AUTO-SEGMENTATION AND KNOWLEDGE-BASED TREATMENT PLANNING FOR RADIOTHERAPEUTIC PALLIATION OF SPINE METASTASES

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Abstract

Purpose: Uncomplicated spine metastases are routinely treated with conventional external beam radiotherapy (cEBRT). In cEBRT, there is no delineation of target volumes or organs at risk (OAR), and no attempt to optimise the dose distribution. An automated solution for conformal radiotherapy treatment planning through the development, validation and evaluation of atlas-based auto-segmentation (ABAS) for delineation of target volumes and OAR and volumetric-modulated arc therapy (VMAT) knowledge-based planning (KBP) for conformal radiotherapy is described here.

Materials and Methods: A SmartSegmentation atlas has been developed and evaluated to provide ABAS of the thoracic and lumbar vertebral spine and OAR. A RapidPlan model has been developed and validated for VMAT KBP. The application of both for conformal radiotherapy treatment planning has been compared with the equivalent dose distributions for cEBRT.

Results: Planning target volume (PTV) coverage for VMAT KBP was superior to cEBRT. With PTV Dmean=7.86±0.16Gy, Dmin=3.46±1.79Gy, Dmax=8.56±0.05Gy for RapidPlan generated plans compared to Dmean=7.78±0.24Gy, Dmin=1.83±1.08Gy, Dmax=10.46±0.41Gy for cEBRT. Homogeneity index and conformity index were 0.236±0.215 and 1.201±0.121 respectively for RapidPlan generated plans compared to 0.508±0.137 and 1.789±0.437 for cEBRT. Dose to spinal cord and cauda equina was reduced for RapidPlan generated plans, with Dmax of 7.91±0.16Gy and 7.94±0.13Gy respectively compared to 8.67±0.13Gy and 8.90±0.16Gy for cEBRT.

Discussion: ABAS of the vertebral spine and OAR had varying degrees of success, but was sufficient for application of VMAT KBP to provide conformal treatment plans for uncomplicated spine metastases. RapidPlan generated plans were superior to cEBRT in terms of target coverage, homogeneity and conformity and was achievable in a clinically acceptable time, with improved sparing of the spinal cord and cauda equina.

Conclusion: Implementation of ABAS and VMAT KBP is feasible in the clinical environment. Further work is required to establish a truly automated conformal radiotherapy treatment planning solution for uncomplicated spine metastases.

Lay abstract

A metastasis is a tumour appearing in a different location to the primary tumour as a result of cancer spreading elsewhere. A spine metastasis occurs in the vertebral spine. Spine metastases are painful and some can cause an additional complication called metastatic spinal cord compression, where the tumour grows and compresses the spinal cord, which could lead to paralysis and loss of bladder or bowel control, for example. Radiotherapy is used to treat spine metastases. Radiotherapy can provide long-term pain relief in many patients, but some patients require many re-treatments. The radiotherapy technique routinely used is conventional radiotherapy, where one or two radiation fields are directed at the tumour. This means everything within the field or fields, and in the path of the field or fields, receives a radiation dose that varies in intensity as it passes through the patient to reach the tumour. There is not much sparing of healthy tissues in the vicinity of the tumour from the radiation. This technique for delivering radiotherapy to treat spine metastases has remained unchanged for decades despite many technological advances in radiotherapy. These advances include delivering radiation around the patient with multiple radiation fields that are continuously adjusted as the radiation travels around the patient, changing the shape and intensity of the radiation. This technique ensures the intensity of radiation is highest at the tumour, and that the intensity is reduced beyond the tumour to better spare healthy tissues from the radiation. This technique requires lots of complex planning and calculations called treatment planning. Treatment planning is a two stage process. The first stage involves the tumour and any healthy structures being identified on a CT scan by manually drawing around them on the CT images. The second stage involves working out how best to deliver the multiple radiation fields to give the best possible radiation dose distribution in terms of covering the tumour and sparing the healthy tissues. This treatment planning is difficult, requires significant expertise, and is time consuming. This work describes how computers can be used to assist in the two stages of treatment planning, which in turn may allow patients to receive more advanced radiotherapy treatment as opposed to conventional radiotherapy for spine metastases in the future.

Declaration

No portion of the work referred to in this thesis has been submitted in support of an application for another degree or qualification of this or any other university or institute of learning.

Copyright statement

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MSc Medical Radiation Physics, University of Wales, Swansea, 2001 (as Emma-Louise Pengilly). Dissertation title - An MCNP study: Influence of collimator position on electron output from small applicators.

Mannion, L. Bosco, C., Nair, R., Mullassery, V., Enting, D., Jones, E-L., Van Hemelrijck, M. and Hughes, S. (2020). 'Overall survival, disease specific survival and local recurrence outcomes in patients with muscle invasive bladder cancer treated with external beam radiotherapy and brachytherapy: A systematic review', *BJU International*, 125(6), pp.780-791.

Jones, E-L., Tonino Baldion, A., Thomas, C., Burrows, T., Byrne, N., Newton, V. and Aldridge, S.E. (2017). 'Introduction of novel 3D-printed superficial applicators for high-dose-rate skin brachytherapy', *Brachytherapy*, 16(2), pp. 409-414.

Challapalli, A., Jones, E., Harvey, C., Hellawell, G.O. and Mangar, S.A. (2012). 'High dose rate prostate brachytherapy: An overview of the rationale, experience and emerging applications in the treatment of prostate cancer', *British Journal of Radiology*, 85(1), pp.S18-S27.

Submission format

This thesis is submitted in journal format, with sections written in a format suitable for publication in peer-reviewed journals.

Three manuscripts are included along with introduction, literature review, critical appraisal and conclusion chapters. Each manuscript is self-contained, with its own reference list in the format required by the intended journal. The author of this thesis and the three manuscripts is the primary researcher of the work presented, and has written all of the text therein contained. Contributions from additional authors are presented in appendix C.

The taught, and previously assessed, components of the HSST programme are summarised in appendix A of this thesis.

The innovations proposal, an additional requirement for DClinSci submission, is provided in appendix B of this thesis.

1. Introduction

1.1. Background

Uncomplicated spine metastases are a common feature of advanced-stage malignancies (Lewandrowski *et al*, 2006) and primarily occur in the vertebral body of the spine (Coleman, 2006), with an approximate distribution of 70%, 20% and 10% in the thoracic, lumbar and cervical regions respectively (Nguyen *et al*, 2011). Cheon *et al* (2015, p.13) define uncomplicated spine metastases as the "presence of painful bone metastases unassociated with impending or existing pathologic fracture or existing spinal cord… compression". Overall survival of patients with spine metastases varies widely. Survival from the diagnosis of uncomplicated spine metastases originating from primary prostate and breast cancer is measured in years, compared to spine metastases originating from primary lung cancer being measured in months (Vassiliou *et al*, 2014).

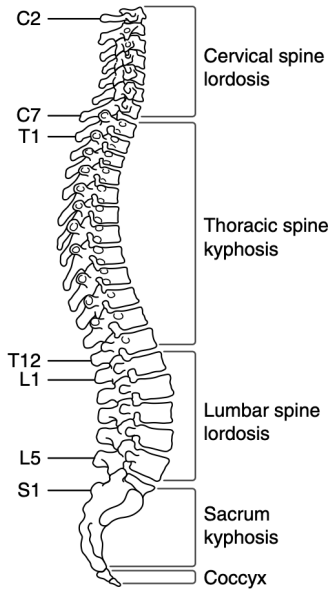

Figure 1.1: Lateral view of the vertebral spine with the vertebral regions and normal curvature of the spine indicated (Fisicaro *et al*, 2005, p.1).

All treatment for spine metastases is considered palliative. The primary aim of radiotherapy to treat uncomplicated spine metastases is to provide pain relief and preserve quality of life. Spine metastases result in considerable morbidity and can cause severe and debilitating effects, which as well as pain, include pathologic

fractures, hypercalcaemia and metastatic spinal cord compression (MSCC) (Lutz *et al*, 2011). MSCC is considered a medical emergency. MSCC occurs when a metastasis applies pressure to the spinal cord and nerves, resulting in reduced blood supply, which can result in paralysis and can impact neurological function (NICE, 2008).

Fairchild (2013) describes how a good palliative treatment should be simple to administer and have a high-probability of both timely and durable control of symptoms. The use of radiotherapy as a palliative treatment of spine metastases is well established (Wu *et al*, 2003; Gerszten *et al*, 2009; Chow *et al*, 2012a). Radiotherapy provides palliation in 50-80% of patients (Chow *et al*, 2007), and improvement in quality of life (McDonald *et al*, 2015). However, Huisman *et al* (2015) argue that 40% of patients treated with radiotherapy fail to obtain pain relief. Recurrent pain is common, with 20% of patients requiring re-irradiation of spine metastases (Lutz *et al*, 2011; van der Velden *et al*, 2016), additionally patients may require further irradiation of adjacent spine metastases. Further irradiation and re-irradiation of spine metastases presents a radiotherapy challenge. Radiation myelopathy is a risk following irradiation of the spinal cord (Kirkpatrick *et al*, 2010) and re-irradiation may not always be feasible if the spinal cord dose tolerance is likely to be exceeded (Gröger *et al*, 2013). Organs at risk (OAR) in the irradiation and re-irradiation of spine metastases are not limited to the spinal cord and may also include the oesophagus, heart, lungs, kidneys and cauda equina. Toxicity following radiotherapy for spine metastases has not been extensively studied, Spencer *et al* (2018) suggest acute toxicity following radiotherapy is usually resolved within 6 weeks of completing radiotherapy and late toxicity is uncommon. However, Lewandrowski *et al* (2006) suggest that advances in primary treatment and treatment of local recurrences result in patients surviving longer with cancer. As such, more patients may require irradiation and re-irradiation for spine metastases and surviving longer potentially places patients at greater risk of late toxicity, which can impact on quality of life (Lewandrowski *et al*, 2006). Therefore, treatment of spine metastases is of increasing clinical importance.

Non-conformal conventional external beam radiotherapy (cEBRT) is the most utilised treatment technique for radiotherapy of uncomplicated spine metastases despite conformal treatment techniques being available. While the dosimetric advantages of conformal radiotherapy treatment approaches for improving target volume coverage and sparing OAR have been demonstrated (Ewing *et al*, 2012;

Yeo, 2015). It has not yet been established if conformal radiotherapy which includes intensity-modulated radiation therapy (IMRT), volumetric-modulated arc therapy (VMAT) and stereotactic ablative radiotherapy (SABR) are clinically advantageous for palliation of spine metastases (Buergy *et al*, 2017). There is, however, some limited evidence that suggests these techniques, in particular SABR, have the potential to improve pain relief and durability of pain control (Sahgal *et al*, 2021) but this requires further research (Cellini *et al*, 2021; van der Velden and van der Linden, 2021).

1.2. Context

Rief *et al* (2014) argue that every patient with spine metastases should receive the most advanced radiotherapy available. NHS England's Commissioning Through Evaluation (CTE) programme (NHS England, 2015) has resulted in SABR being utilised for irradiation and re-irradiation of spine metastases for patients that meet the inclusion criteria. It is not unreasonable to assume that IMRT and VMAT, for those patients not suitable for inclusion, will increase in the coming years, despite the difficulties in obtaining high-quality evidence for clinical advantage for palliation of spine metastases. Conformal radiotherapy requires accurate and precise patient positioning and immobilisation with on-board imaging, which usually leads to longer treatment times. In the age of advanced radiotherapy treatment planning and delivery, the continued use of non-conformal cEBRT is unrealistic. However Westhoff *et al* (2018) argue that conformal techniques require time-consuming, complex and technically demanding treatment preparation and planning, making clinical implementation of these techniques challenging.

This research investigates whether automating stages of the treatment planning process enables implementation of conformal radiotherapy for uncomplicated spine metastases in the clinical environment. Specifically, automation of target volume and OAR delineation using atlas-based auto-segmentation (ABAS) and automation in radiotherapy treatment planning using knowledge-based planning (KBP).

This research provides new insight into the use of ABAS for the delineation of the thoracic and lumbar vertebral spine for the radiotherapeutic palliation of spine metastases, as well as additional insight into ABAS for OAR in the vicinity of the thoracic and lumbar regions of the vertebral spine. This research builds on the work of Buergy *et al* (2017), Mian *et al* (2016), Younge *et al* (2018); Foy *et al* (2017) and Dennis *et al* (2021) who have all investigated various approaches to automate

radiotherapy treatment planning for spine metastases. This research aims to determine whether ABAS and KBP provide a workable treatment planning solution over cEBRT in the clinical environment, the combined use of which has not been reported on in the literature. VMAT treatment plans generated using ABAS and KBP have not been dosimetrically compared to their equivalent cEBRT treatment plans, and therefore additionally this research provides valuable insight into what is achievable in terms of homogeneity and conformity of target volume coverage and OAR dose. However, this work does not investigate whether VMAT of uncomplicated spine metastases confers any clinical benefit over cEBRT.

1.3. Significance and Scope of Research

Management of patients with uncomplicated spine metastases is of increasing clinical importance. Patients are living longer with spine metastases and more frequently requiring irradiation and re-irradiation for pain relief, durable pain control and controlling progressive disease (Kotecha *et al*, 2020). Living longer potentially places patients at greater risk of late toxicity, which can impact on quality of life (Lewandrowski *et al*, 2006). Non-conformal cEBRT remains the most utilised radiotherapy treatment technique for irradiation and re-irradiation of spine metastases, although the use of conformal radiotherapy treatment techniques such as IMRT, VMAT and SABR is increasing. Given this, automation of treatment planning using ABAS and KBP deserves further study.

1.3.1. Clinical Audit

This work was submitted as a clinical audit and is listed in the Guy's and St Thomas' NHS Foundation Trust clinical audit and quality improvement register. The need for written consent for use of patient computed tomography (CT) images was waived. No personal data were collected beyond age and sex, and all patient data was anonymised.

1.4. Aims and Objectives

The aim of this research was to develop and evaluate a comprehensive automated workflow for VMAT treatment planning of uncomplicated spine metastases using ABAS and KBP.

The objectives included:

- Develop and evaluate ABAS of the thoracic and lumbar vertebral spine for delineation of spine metastases target volumes.
- Develop and evaluate ABAS for delineation of OAR in the vicinity of the thoracic and lumbar regions of the vertebral spine.
- Develop and validate VMAT KBP treatment planning for spine metastases target volumes.
- Evaluate VMAT KBP treatment planning for spine metastases target volumes and compare with equivalent cEBRT treatment plans.
- Determine if ABAS and KBP provide a workable treatment planning solution for palliative spine metastases radiotherapy over cEBRT in the clinical environment.

1.4.1. Commercial Interest

This work was supported by a research grant from Varian Medical Systems, Inc (Varian). An investigator initiated research agreement was reached between Guy's and St Thomas' NHS Foundation Trust and Varian on 15 November 2018. Varian were provided with an interim report outlining progress at 6 months, and a final report at 12 months, both of which were required to secure release of research grant funds. The research agreement has now expired and there are no restrictions on publication.

1.4.2. Conflict of Interest

This work was supported by a research grant from Varian Medical Systems, Inc.

2. Literature Review

2.1. Radiotherapy Techniques for Palliation of Spine Metastases

Radiotherapy techniques for palliation of uncomplicated spine metastases include non-conformal cEBRT, and conformal 3D external beam radiotherapy (3DCRT), IMRT, VMAT and SABR. cEBRT is well established (Wu *et al*, 2003; Gerszsten *et al*, 2009; Chow *et al*, 2012a) and much of the focus of the literature, although in recent years the use of conformal radiotherapy has increased, with IMRT, VMAT, and in particular SABR, increasingly being used for irradiation and re-irradiation of spine metastases (Sahgal *et al*, 2008; Myrehaug *et al*, 2017).

2.1.1. Conventional External Beam Radiotherapy of Spine Metastases

To deliver radiotherapy treatment in a timely manner the technique generally used to treat uncomplicated spine metastases is cEBRT (Rich *et al*, 2018). cEBRT can be broadly defined as the application of a single applied posterior, or two opposing anterior-posterior, open un-modulated radiation fields directed at the affected vertebral body (Gerszten *et al*, 2009).

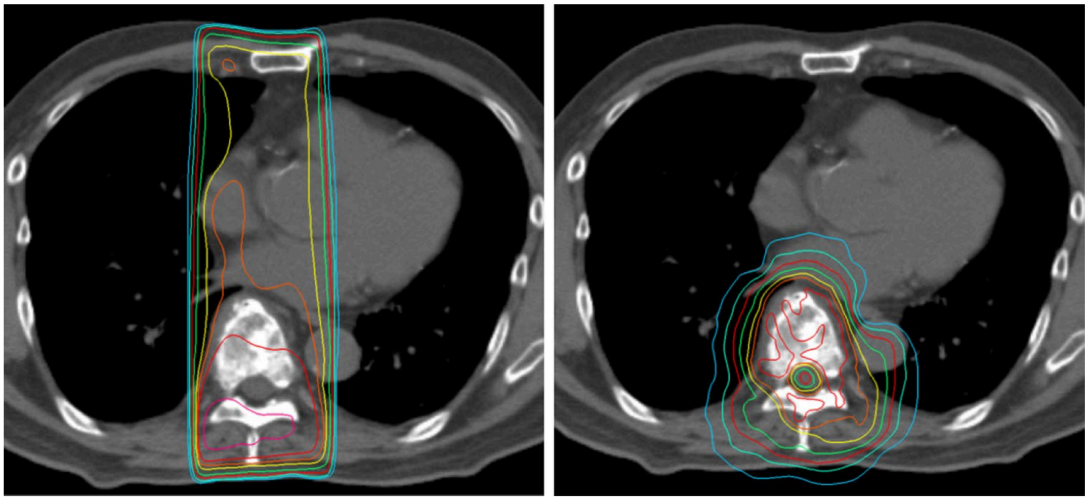

Figure 2.1: Single slice isodose distribution for cEBRT (left hand side) and corresponding IMRT isodose distribution (right hand side) for radiotherapy of spine metastases (Ejima *et al*, 2015, p.587).

Treatment planning for cEBRT consists of virtual simulation on CT images through which energy, prescription depth and field size are defined, and multi-leaf collimator

(MLC) shielding applied if appropriate. Field size is chosen to ensure coverage of the affected vertebra as well as two additional vertebrae, one above and one below the affected vertebra (Ratanatharathorn and Powers, 1991).

Figure 2.1 shows a single slice isodose distribution for cEBRT and a corresponding conformal IMRT isodose distribution (Ejima *et al*, 2015, p.587). As demonstrated in figure 1, a homogeneous and conformal isodose distribution is not possible with cEBRT and any sparing of OAR (in this example spinal cord, heart and lungs) in the vicinity of the target volume is limited. MLC shielding is often used to spare kidneys when they are situated within the radiation field, but it is not possible to spare further OAR with MLC shielding for cEBRT without compromising target volume coverage.

The dose regimen for palliation of spine metastases is a matter of considerable debate (Rief *et al*, 2014) and is the primary focus of much of the literature. Typically, cEBRT is delivered at a high dose per fraction for a small number of fractions (8Gy in 1 fraction, 20Gy in 5 fractions, or 30Gy in 10 fractions) (Johnstone and Lutz, 2014). A number of randomised controlled trials, and subsequent systematic reviews and meta-analyses, have shown that there is no significant difference in the efficacy of cEBRT for pain relief between the three fractionation regimens (Wu *et al*, 2003; Chow *et al*, 2007; Chow *et al*, 2012a; Rich *et al,* 2018), but re-irradiation is more frequently required following 8Gy in 1 fraction (Lutz *et al*, 2011). Lutz *et al* (2011) suggest a re-irradiation rate for recurrent pain of 20% following a single fraction regimen compared to 8% for a multi-fraction regimen. However 8Gy in 1 fraction remains the most widely used regimen for providing patients with durable pain control at less inconvenience to the patient compared to multi-fraction radiotherapy.

Barton *et al* (2002) argue that despite considerable research being carried out on the dose and fractionation of cEBRT for palliation of spine metastases, few studies have considered the prescription depth and heterogeneity of dose distribution across the target volume. Furthermore, Andic *et al* (2009) argue that the relationship between re-irradiation rate of cEBRT and dose coverage has not been investigated. Re-irradiation of spine metastases presents a challenge, with the tolerance dose of the spinal cord potentially limiting the dose required for pain relief (Gröger *et al*, 2013). With the exception of altering prescription depth, there is no attempt to spare spinal cord with cEBRT and as such re-irradiation without exceeding the tolerance to the spinal cord with further cEBRT may be challenging, particularly following radiotherapy of primary cancer in the vicinity of the spinal cord. In this instance

conformal radiotherapy may have potential to spare the spinal cord and allow safe re-irradiation (*Ibid.*).

In the clinical environment cEBRT remains the most utilised radiotherapy treatment technique for irradiation and re-irradiation of uncomplicated spine metastases despite conformal radiotherapy being widely accessible. Rief *et al* (2014) argue that every patient with spine metastases should receive the most advanced radiotherapy available. Westhoff *et al* (2018) argue that conformal radiotherapy requires time-consuming, complex and technically demanding treatment preparation and planning. Furthermore, cEBRT and conformal radiotherapy both require a level of accurate and precise patient positioning and on-board imaging, but conformal radiotherapy often requires patient immobilisation and additional steps in the patient setup process to ensure a higher degree of accuracy and precision before treatment delivery, making clinical implementation challenging.

2.1.2. Conformal Radiotherapy of Spine Metastases

Conformal radiotherapy can be broadly defined as shaped, intensity-modulated radiation delivered with multiple fields (IMRT) or in an arc around the patient (VMAT) to produce homogeneous dose distributions to irregularly shaped target volumes, with sparing of adjacent OAR. SABR can be delivered using IMRT or VMAT, but SABR specifically exploits specialist positioning and immobilisation of patients to ensure a high degree of precision and accuracy in treatment delivery. This allows for steep dose gradient isodose shaping with enhanced sparing of adjacent OAR and hypo-fractionated dose regimens. SABR has emerged as a treatment option in recent years (Gerszten *et al*, 2009). Figure 2.2 shows IMRT single isodose distributions for the cervical, thoracic and lumbar regions of the vertebral spine (Rief *et al*, 2015, p.191).

Conformal radiotherapy is increasingly being used for irradiation and re-irradiation of spine metastases, however, the clinical benefit compared to cEBRT remains to be demonstrated (Westhoff *et al*, 2018). Although studies have examined the role of IMRT, VMAT and SABR for palliation of uncomplicated spine metastases, current guidelines state conformal radiotherapy is not mandatory for this cohort of patients (Lutz *et al*, 2011). However IMRT, VMAT and SABR are known to provide improved target coverage, and better sparing of OAR than cEBRT is able to provide (Staffurth, 2010) and may be beneficial where metastases are localised or require re-irradiation (Ejima *et al*, 2015).

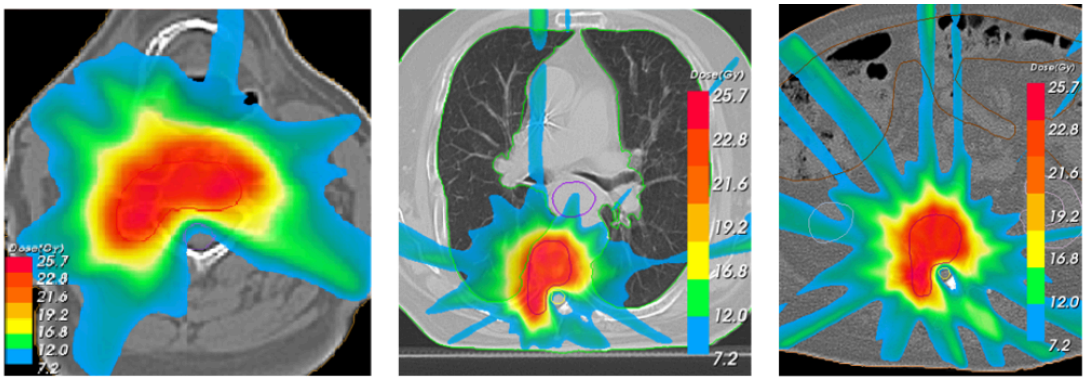

Figure 2.2: Single slice isodose distributions using IMRT in the cervical (left hand side), thoracic (centre) and lumbar (right hand side) regions of the vertebral spine (Rief *et al*, 2015, p.191).

Most of the literature on conformal radiotherapy for palliation of spine metastases focuses on SABR, and the impact of SABR on pain response and durability of pain control. Early single-institution, prospective, non-randomised, longitudinal cohort studies by Gerzten *et al* (2007) and Ryu *et al* (2008) described long-term pain relief in 86% and 84% of patients respectively. However van der Velden *et al* (2016) argue that SABR is increasingly being used without evidence of superiority over cEBRT through randomised controlled trial.

Results of randomised controlled trials are now emerging in the literature. Four randomised controlled trials which focus on pain response and durability of pain control have recently been published (Sprave *et* al, 2018; Ryu *et* al, 2019; Sahgal *et al*, 2021; Pielkenrood *et al*, 2021). Sprave *et al* (2018) in their single-institution, non-blinded, randomised, explorative trial with a primary end point of pain control at 3 months (n=60), found pain relief at 3 months was not significantly different between 24Gy in 1 fraction SABR (n=27) compared to 30Gy in 10 fractions cEBRT (n=28), but the authors felt durability of pain control was improved with SABR with statistically significant difference in pain control at 6 months. Ryu *et al* (2019) performed a phase 3 randomised controlled clinical trial (n=339) to compare cEBRT at 8Gy in 1 fraction (n=130) with SABR 16-18Gy in 1 fraction (n=209) with a primary endpoint of pain control and found no significant difference in pain response at 3 months. Pielkenrood *et al* (2021) in their phase 2 randomised controlled clinical trial for spine and bone metastases (n=110) found no significant difference in pain control between cEBRT (n=44) and SABR (n=45) for a number of fractionation regimes. But noted 27% of patients declined SABR and 16% of patients were unable to complete fractionated SABR due to severe pain or the presence of

additional spine metastases observed in magnetic resonance images (MRI). Those patients who declined SABR were offered cEBRT (4% of these patients also declined cEBRT). The authors hypothesised this was due to patients receiving additional clinical trial information and more rigorous informed consent that caused induced hesitation regarding the usefulness of SABR. Sahgal *et al* (2021) in their multi-centre phase 2/3 randomised controlled clinical trial (n=229) found SABR 24Gy in 2 fractions (n=114) compared to cEBRT (n=115) reported complete pain response at 3 months of 35% and 14% respectively.

Three out of the four randomised controlled trials reported no clinically significant difference in pain relief for SABR compared to cEBRT. Sahgal *et al* (2021) were the only investigators to report improved pain response with SABR.

All of these studies focussed on immediacy of pain response and durability of pain control for irradiation of uncomplicated spine metastases, with limited investigation into acute or late toxicities. None of these studies looked into re-irradiation of spine metastases using SABR, or the rate of re-irradiation following cEBRT or SABR. In 2019 NHS England published an evidence review on the efficacy, toxicity and cost-effectiveness of SABR in patients undergoing re-irradiation of spine metastases (NHS England, 2019). The evidence review identified a single systematic review on re-irradiation of spine metastases with SABR performed by Myrehaug *et al* (2017). Myrehaug *et al* (2017) describe how SABR is emerging as an effective and safe means of re-irradiation following cEBRT for local control and pain relief but acknowledge the evidence is limited to low-quality data.

A review of the literature indicates that single and multi-fraction conformal radiotherapy approaches, particularly SABR, have the potential to improve the efficacy of radiotherapy for pain relief of spine metastases, extend duration of pain control and reduce toxicity. However, conformal approaches are labour and resource intensive (Mayles, 2010; Abolaban *et al*, 2016) and it has not yet been established if these techniques are clinically advantageous for palliation of spine metastases (Buergy *et al*, 2017; Cellini *et al*, 2021; van der Velden and van der Linden, 2021). Lutz *et al* (2017) describe how conformal techniques such as SABR lack high-quality data and state that it should only be used as part of clinical trial or when results are collected in a registry. Guidelines caution that utilisation of these techniques for this cohort of patients should be limited to clinical trial (Lutz *et al*, 2011) or NHS England's CTE programme (NHS England, 2018), both of which require strict inclusion criteria. The preferred approach in the future for palliative

radiotherapy of uncomplicated spine metastases is likely to be conformal radiotherapy (IMRT, VMAT and SABR) (Cellini *et al*, 2021) and the use of cEBRT will likely decline.

Routine implementation of conformal radiotherapy treatment techniques for palliation of spine metastases in the clinical environment would be both labour and resource intensive. Automation, however, has the potential to provide improved efficiency of the treatment planning process so that this cohort of patients could begin to benefit from the improved target coverage, and better sparing of OAR that conformal radiotherapy provides (Mian *et al*, 2016; Foy *et al*, 2017; Buergy *et al*, 2017; Younge *et al*, 2018).

2.2. Auto-Segmentation for Conformal Radiotherapy Treatment Planning of Spine Metastases

Conformal radiotherapy uses advanced radiotherapy treatment planning to optimise coverage of the target volume while sparing adjacent OAR compared to cEBRT. As such accurate delineation of the target volume and OAR is an essential step in the radiotherapy treatment planning process. Delineation is routinely performed manually, by clinicians, on CT images following recommendations provided by the International Commission on Radiation Units and Measurements (ICRU) (ICRU, 2010). Manual delineation of target volumes and OAR is time consuming. It is acknowledged as one of the largest sources of variability in the radiotherapy treatment pathway (Altman *et al*, 2015) and prone to intra- and inter-observer variation (Sharp *et al*, 2014). Despite this, manual delineation by the expert clinician remains the universally acknowledged gold standard and is currently superior to any automated methods (Whitfield *et al*, 2013; Vrtovec *et al*, 2020). Sharp *et al* (2014) describe how automation of target volume and OAR delineation through auto-segmentation has the potential to provide time-saving and improved efficiency in the radiotherapy treatment planning process, as well as improved consistency of the delineation process. Valentini *et al* (2014) describe how it has the potential to increase adherence to ICRU target volume guidelines (ICRU, 2010).

There are three primary methods of auto-segmentation, image analysis (thresholding) approaches, atlas-based (deformable image registration) approaches and those based on machine learning (non-deep and convolutional neural network) approaches (Harrison *et al*, 2022).

Atlas-based auto-segmentation (ABAS) is the primary method employed by SmartSegmentation in the Varian Eclipse treatment planning system (TPS) (*Varian Medical Systems, Palo Alto, California*). SmartSegmentation was first described by Haas *et al* (2008). SmartSegmentation utilises an atlas and model-based approach to auto-segment structures using advanced image analysis to determine the structures location according to the Hounsfield unit (HU) gradients in the CT data set, followed by deformable image registration against a reference image from an atlas of delineated images (Gambacorta *et al*, 2013). ABAS uses prior knowledge from an atlas created from curated CT reference images with expert peer review of target volume and OAR contours.

There are no articles in the literature describing the clinical implementation of ABAS of target volumes or OAR using SmartSegmentation for radiotherapy of spine metastases.

2.2.1. Auto-Segmentation of Target Volumes

cEBRT is widely used in the clinical environment for radiotherapeutic palliation of spine metastases. cEBRT does not require advanced radiotherapy treatment planning and does not routinely require delineation of a target volume. However, for conformal planning, delineation of the target volume is required. Barton *et al* (2002) suggest a dose distribution that covers a clinical target volume (CTV) which includes the vertebral body, pedicles and spinal cord should achieve the aim of palliation. The International Spine Radiosurgery Consortium (ISRC) propose CTV delineation based on disease involvement within sectors of the vertebral body which for uncomplicated spine metastases include the vertebral body, pedicles, transverse processes, laminae and spinous process (Cox *et al*, 2012).

Sharp *et al* (2014) describe how highly accurate auto-segmentation is achievable for structures with reproducible anatomy and sufficient contrast in imaging. As such, it would be expected that the vertebral spine would be a suitable candidate for auto-segmentation. However, a number of authors have approached auto-segmentation of the spine using image analysis and ABAS approaches (using in-house ABAS solutions) and have suggested that this is not the case (Forsberg, 2015; Hutt *et al*, 2015; Ruiz-España *et al*, 2017; Fu *et al*, 2017). Forsberg (2015), Hutt *et al* (2015) and Ruiz-España *et al* (2017) utilised ABAS and advanced image analysis and image interrogation alone, whereas Fu *et al* (2017) used Eclipse to generate an

atlas for ABAS, but used a novel in-house solution to support articulated skeleton registration.

Fu *et al* (2017, p.2814) describe how despite the relative ease of identifying bone in CT images, due to high contrast between bone and soft tissue, that segmentation of bone is still difficult. They argue that "vertebrae segmentation is the most challenging among all bony structures due to their complex topology, irregular boundaries, and similarity between adjacent vertebrae". Spine metastases alter the shape of the vertebral body and vertebrae (Ruiz-España *et al*, 2017) and whereas a healthy vertebral body has a clear, high contrast, boundary between surrounding soft tissues this is not the case in the presence of metastases (Fu *et al*, 2017), and as such makes accurate and precise segmentation more difficult. Figure 2.3 shows a CT image of a patient with a spine metastasis prior to and following re-irradiation of spine metastases (Kawashiro *et al*, 2016, p.151).

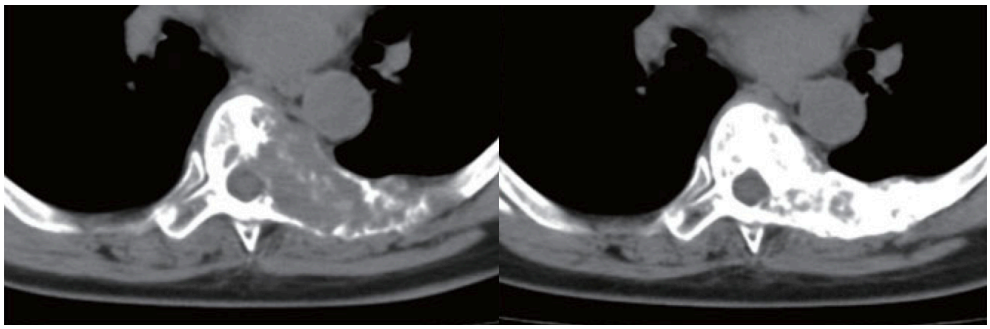

Figure 2.3: CT of a previously irradiated spine metastasis prior to re-irradiation (left hand side) and 5 months post re-irradiation (right hand side) (Kawashiro *et al*, 2016, p.151).

The spinal vertebrae alter in shape, size, position and vertebral centre of rotation throughout the cervical, thoracic, lumbar and sacral regions of the vertebral spine. There is variation between patients, and also variation as a result of patient positioning on CT images. The literature indicates that ABAS has had the most success for vertebrae delineation in the lumbar region (Ruiz-España *et al*, 2017), primarily due to the proximity of the ribs to the spinal vertebrae in the thoracic region as shown in figure 2.4. Figure 2.4 shows an example of ABAS compared to manual delineation of thoracic and lumbar vertebrae (Ruiz-España *et al*, 2017, p.4704).

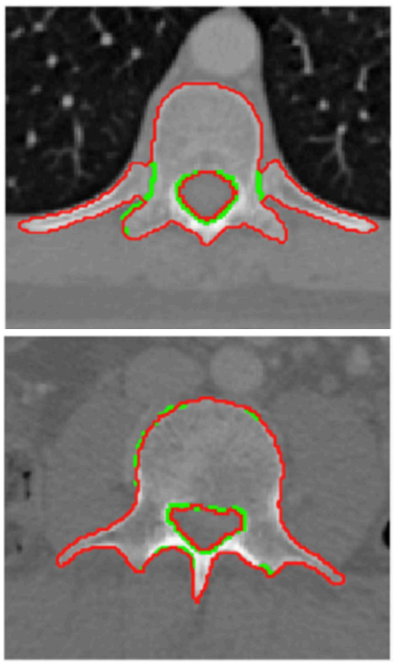

Figure 2.4: ABAS of vertebrae in thoracic region (top) and lumbar region (bottom) of the vertebral spine, the red outline indicating ABAS, and the green outline manual delineation (Ruiz-España *et al*, 2017, p.4704).

Saenz *et al* (2018), in their dosimetric analysis of spine SABR treatment planning, used Brainlab ABAS for contouring the affected vertebral body, pedicles and transverse processes. But have not commented on the quality of the auto-segmentation carried out.

2.2.2. Auto-Segmentation of OAR

For conformal radiotherapy treatment planning delineation of OAR is also required. In the thoracic and lumbar regions of the vertebral spine the OAR include the spinal cord, and may also include oesophagus, heart, lungs, kidneys and cauda equina (Wright *et al*, 2019). Lustberg *et al* (2018) describe auto-segmentation, through ABAS and machine learning, of OAR for radiotherapy treatment planning of lung cancer where a number of the OAR are in the same vicinity. The authors used Mirada auto-segmentation software (*Mirada Medical Ltd., Oxford, UK*) for ABAS and machine learning segmentation. They compared manually delineated heart, mediastinum, lungs, oesophagus and spinal cord contours with ABAS and machine learning generated contours. They also investigated two-stage delineation using the two auto-segmentation approaches followed by manual adjustment of the contours. Figure 2.5 shows manual contours (red), atlas-based contours (blue) and machine

learning generated contours (yellow), for the lung, oesophagus and heart, using Mirada (Lustberg *et al*, 2018, pp.314). While this work focussed on time-saving, the quality of auto-segmentation was assessed qualitatively with subjective scoring and quantitatively with evaluation of Dice similarity coefficient (DSC) and Hausdorff distance (HD). Both qualitatively and quantitatively the authors felt auto-segmentation showed promise but manual adjustment of contours was required in all instances. The authors concluded that both atlas-based and machine learning approaches followed by manual adjustment allowed for time-saving, with the exception of the oesophagus, which they argued was as a result of the low contrast boundary with surrounding soft tissues.

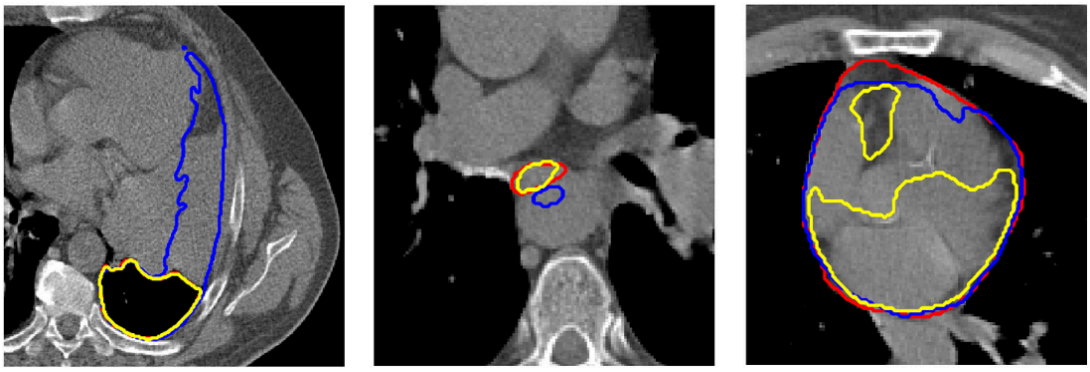

Figure 2.5: Manually delineated (red), ABAS generated (blue) and machine learning generated (yellow) contours for the lung (left), oesophagus (middle) and heart (right) (Lustberg *et al*, 2018, pp.314).

In 2017, an American Association of Physicists in Medicine (AAPM) grand challenge for auto-segmentation of structures in thoracic radiotherapy treatment planning evaluated auto-segmentation of the spinal cord, oesophagus, heart and lungs (Yang *et al*, 2018). Seven participants of the grand challenge performed auto-segmentation (n=5 machine learning, n=2 ABAS) on 12 CT scans using 36 delineated CT scans provided for training and atlas production. The quality of auto-segmentation was assessed quantitatively with evaluation of DSC, HD and mean surface distance. Generally participants using machine learning outperformed those using ABAS, ABAS participants placing 4th and 6th out of 7. The authors concluded both machine learning and ABAS were capable of auto-segmenting the heart and lungs to a reasonable degree of accuracy, but a high degree of variability was noted for oesophagus and spinal cord auto-segmentation, machine learning having less variability compared to ABAS for the oesophagus.

The literature indicates ABAS is achievable with varying degrees of success, with the exception of the oesophagus. The oesophagus however is widely known to be both difficult to manually delineate, with high variability between observers, and to auto-segment, as the boundaries between the oesophagus and other surrounding tissues are poorly defined (Bandeira Diniz *et al*, 2020).

2.3. Automated Conformal Radiotherapy Treatment Planning of Spine Metastases

Conformal radiotherapy uses advanced radiotherapy treatment planning to optimise coverage of the target volume while sparing adjacent OAR compared to cEBRT. Radiotherapy treatment planning for IMRT, VMAT and SABR techniques utilise inverse planning. Inverse planning is a computer driven process used to generate a radiotherapy treatment plan that best meets clearly defined objectives for target volume coverage and constraints for OAR sparing. Intervention and review by a treatment planner throughout the inverse planning process is required to generate high quality, deliverable treatment plans and as such treatment planning is labour and resource intensive. It is acknowledged that there is inter- and intra-planner variability in plan quality (Scaggion *et al*, 2018).

There are three primary methods of automated radiotherapy treatment planning, KBP, protocol-based automatic iterative optimisation, and multi-criteria optimisation (Hussein *et al*, 2018).

KBP is the method employed by RapidPlan in the Varian Eclipse TPS (*Varian Medical Systems, Palo Alto, California*). RapidPlan was developed using an approach described by Yuan *et al* (2012) and Appenzoller *et al* (2012). RapidPlan uses prior knowledge from curated radiotherapy treatment plans. The process of building a RapidPlan model is to first identify a set of manually planned treatment plans for site similar patients and use the patient geometry and dosimetry of these treatment plans to generate a dose volume histogram (DVH) estimation model (a range of achievable DVH parameters) for application to subsequent, new site similar patients (Varian, 2019b).

The use of RapidPlan KBP is widely reported in the literature, the greater part of which describes the use of RapidPlan KBP for radical radiotherapy treatment planning. Use of KBP for prostate cancer is readily described in the literature and was the focus of much of the early KBP publications and feasibility studies (Good *et*

al, 2013; Hussein *et al*, 2016; Schubert *et al*, 2017; Sheng *et al*, 2017; Kubo *et al*, 2017; Cagni *et al*, 2017; Alpuche *et al*, 2018; Ueda *et al*, 2018; Bossart *et al*, 2018; Scaggion *et al*, 2018; Castriconi *et al*, 2018). Furthermore, RapidPlan KBP treatment planning for cervix cancer (Li *et al*, 2017), lung cancer (Delaney *et al*, 2017; Faught *et al*, 2018; Hof *et al*, 2019), breast cancer (Wang *et al*, 2017; van Duren-Koopman *et al*, 2018; Rice *et al*, 2018), gastro-intestinal cancer (Berry *et al*, 2016; Chang *et al*, 2016; Wu *et al*, 2016a; Wu *et al*, 2016b; Jiang *et al*, 2017; Tran *et a*l, 2017; Wang *et al*, 2018; Yu *et al*, 2018), head and neck cancer (Delaney *et al*, 2015; Tol *et al*, 2015; Fogliata *et al*, 2017; Krayenbuehl *et al*, 2018; Tol *et al*, 2019) and brain cancer (Chatterjee *et al*, 2017) have been evaluated.

Together, these articles indicate that RapidPlan KBP has the potential to improve efficiency and reduce variability in the treatment planning process. Most also report that KBP improves quality of treatment plans, producing comparable or modest improvement to treatment plans than those produced manually. Many authors also report that RapidPlan KBP allows for better consistency of treatment plans, which has the potential to add value to clinical trial outcomes, as treatment plan quality can influence clinical trial outcome (Mian *et al*, 2016; Meyerhof *et al*, 2017; Younge *et al*, 2018; Kavanaugh *et al*, 2019; Tol *et al*, 2019). Assessment of plan quality in clinical trials is usually through determination of the planner's ability to meet target dose and homogeneity criteria and OAR dose constraints, but RapidPlan KBP may provide a more robust assessment tool for clinical trial quality control (Tol *et al*, 2015; Li *et al*, 2017). Improved consistency of treatment planning with RapidPlan KBP also has potential to reduce variation in plan quality as a result of variation in the experience of the treatment planner and/or the treatment centre (Good *et al*, 2013; Wang *et al*, 2017).

Much of the literature on automated treatment planning focuses on radical conformal radiotherapy. To date, very few studies have investigated the application of automated treatment planning for palliative radiotherapy treatment. Only four articles describe automated treatment planning for spine metastases. Two articles, from the same set of authors, describe RapidPlan KBP for SABR of spine metastases (Foy *et al*, 2017; Younge *et al*, 2018). A further study describes automated treatment planning for SABR using scripting (Mian *et al*, 2016). Automation for VMAT planning is addressed in only one study (Buergy *et al*, 2017).

The articles mainly use homogeneity index (HI) and conformity index (CI) as metrics to determine quality in terms of target coverage, with mean dose (D_{mean}) or maximum dose (D_{max}) to OAR for limiting dose outside of the target volumes.

HI is a method of quantitatively describing dose homogeneity in the PTV and is calculated using (D2%-D98%)/ D50%, where D2%, D98% and D50% are the doses received by the 2%, 98% and 50% volumes of the PTV (ICRU, 2010). A HI of 0 indicates total homogeneity of dose across the PTV, with HI increasing as homogeneity decreases. CI is a method of quantitatively describing conformity between the isodose distribution and the PTV volume. Feuvret *et al* (2006), in their critical analysis of conformity index and its use in radiotherapy treatment planning, review and compare all current methods of calculating CI. For the purposes of the research contained in this thesis, CI is calculated using V95%/VPTV, where V95% is the volume of the 95% isodose and VPTV is the volume of the PTV. The ideal value of CI is 1, indicating total conformity of the 95% isodose to the PTV volume, with CI increasing as conformity decreases. A limitation of CI calculated using this method however, is that CI does not provide any information as to whether the volumes of the 95% and PTV volume are coincident (Feuvret, 2006).

Buergy *et al* (2017) evaluated the quality of automated treatment plans generated with Erasmus i-Cycle, developed at the Erasmus MC-Cancer Institute in the Netherlands (Breedveld *et al*, 2007), against that of VMAT treatment plans manually produced with a commercially available TPS, for the irradiation of spine metastases. Erasmus i-Cycle utilises a multi-criteria optimisation approach. All manually produced treatment plans were produced by experienced treatment planners and reviewed by clinical oncologists. CTVs in the cervical, thoracic and lumbar regions of the spine were manually delineated for 32 patients, with an anisotropic margin to generate planning target volumes (PTVs). Plan quality, in terms of PTV coverage, was determined using calculation of HI and CI, and for OAR, through calculation of D_{mean} and D_{max} in the case of the spinal cord. This study found that the automated treatment plans outperformed the manual treatment plans in terms of OAR sparing, and produced favourable PTV coverage. The authors concluded that automated treatment planning might reduce workload while maintaining or improving quality of treatment plans when compared to manual VMAT treatment planning for spine metastases.

The remaining three articles focus on SABR for treatment of spine metastases in a clinical trial setting (Mian *et al*, 2016; Younge *et al*, 2018; Foy *et al*, 2017). The trial

in question, RTOG 0613, is a phase II/III study of image-guided SABR for localised spine metastases. Although the clinical trial does not investigate automated planning directly, the authors of the articles argue that automated planning can be used to meet the planning objectives of the clinical trial and improve quality and consistency of treatment planning. This in turn may have an impact on the quality of trial results. Mian *et al* (2016) describe pre-clinical validation of an automated, protocol-based automatic iterative optimisation inverse planning script to generate SABR treatment plans using the commercially available TPS, Pinnacle (*Philips Radiation Oncology Systems, Fitchburg, Wisconsin*). CTVs in the cervical, thoracic and lumber regions of the spine were manually delineated for 14 patients, with an isotropic margin of 2mm added for PTV. Conformity was assessed using CI and time to generate automated and manual treatment plans recorded. This study found that manually produced SABR treatment plans demonstrated reduced conformity and steeper dose gradients than those generated with the automated script, but the authors argued that this reduced conformity must be weighed against the benefit of speed of plan generation and the benefits of timely treatment delivery in urgent situations.

Younge *et al* (2018) describe the clinical validation of a RapidPlan KBP approach DVH estimation model of 40 manually optimised SABR plans for a further 11 cases. Plan coverage was assessed using CI and gradient index (GI). The authors reported all plans generated trial compliant treatment plans with increased PTV coverage over manually produced treatment plans, but noted that KBP increased PTV coverage at the expense of slightly increased dose to OAR (although still trial compliant). 2 of the 11 plans were trial compliant using KBP, but could not be made trial compliant through manual treatment planning. The authors concluded that a RapidPlan KBP model is capable of generating SABR treatment plans for treatment of spine metastases in a clinical trial setting. Figure 2.6 demonstrates how KBP improved dose conformity compared to manually planned highly conformal radiotherapy to a spine metastasis (Younge *et al*, 2018, p.1071).

The article by Foy *et al* (2017) was produced by the same authors as the Younge *et al* (2018) article described above. Both articles describe the clinical validation of RapidPlan KBP for SABR of spine metastases. However, in Foy *et al* (2017), they investigated a two-stage planning process, KBP followed by manual improvement. They compared manual treatment plans with 3 different DVH dose estimation models, 2 of which were created with intentional outliers included in the model,

resulting from inconsistent OAR delineation. They focused on whether the 3 models could produce treatment plans that met OAR dose constraints and found that all 3 models were able to achieve trial compliant plans in terms of OAR sparing (even those with outliers). All plans then achieved improvement by manual intervention in the second stage.

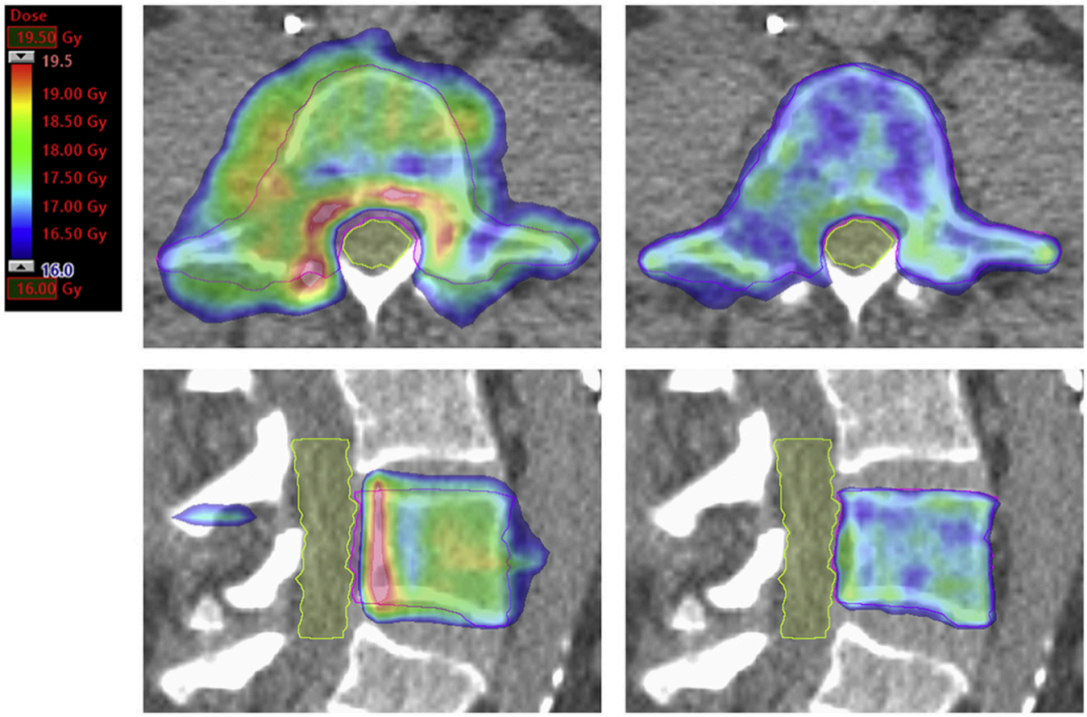

Figure 2.6: SABR dose distribution for radiotherapy of a spine metastasis using manual treatment planning (left) and RapidPlan KBP (right) for the same patient (Younge *et al*, 2018, p.1071).

Collectively, these articles show recent interest and potential for KBP for the palliation of spine metastases.

2.4. Summary and Implications

Radiotherapy techniques have developed extensively over the past few decades, and radical radiotherapy patients have benefitted from widespread clinical implementation of IMRT, VMAT and SABR. But these innovative and technological treatment approaches have not been employed routinely for palliative radiotherapy. Jones (2013, p.12) argues that "it is incumbent on the fields of palliative care and radiotherapy to continue to work to implement best practices in the treatment of patients with palliative radiotherapy". In 'Living with and beyond cancer: Taking action to improve outcomes' the adoption of practice that "minimises the risk of long-

term consequences by commissioning innovative treatments where these have been shown to be safe and effective" is recommended (National Cancer Survivorship Initiative, 2013, p.102). Walling *et al* (2017) argue the case for patient-centred quality improvement in the palliative treatment of uncomplicated spine metastases.

From a review of the literature, conformal radiotherapy treatment would appear to offer clinical advantages over cEBRT for palliation of spine metastases. There is however need for further investigation before widespread clinical implementation because there remain a number of unanswered questions. Does improved homogeneity of dose distribution across the target volume offer improved immediacy of pain relief and improved long-term pain control? If improved long-term pain control is realised, do fewer patients require re-irradiation? If re-irradiation is required and the first palliative treatment was conformal with spinal cord sparing, then can re-irradiation be performed without exceeding spinal cord dose tolerance? Does conformal radiotherapy reduce acute and late toxicity over cEBRT? Is conformal radiotherapy feasible for patients who are likely to be in considerable pain and therefore unable to be immobilised and/or maintain treatment position for the duration of treatment delivery?

Conformal radiotherapy is labour and resource intensive and therefore may present a challenge to implement in the clinical environment. From a review of the literature ABAS and KBP have potential to provide a method for delineation of target volumes and OAR, and optimisation of dose distribution that may make clinical implementation more feasible. However, a number of unanswered questions remain. Can ABAS produce accurate and consistent target volume delineation for the metastatic spine? Can ABAS accurately and consistently delineate adjacent OAR? Does KBP produce consistent treatment plans that provide improved coverage and improved homogeneity of coverage of the target volume, while better sparing OAR, over cEBRT?

3. Manuscript 1

This proffered manuscript describes the development and evaluation of SmartSegmentation ABAS of spinal vertebrae, and OAR in the thoracic and lumbar regions of the vertebral spine.

3.1. Introduction To Manuscript

This manuscript has been written with the aim of submission as a technical note for publication in the Journal of Applied Clinical Medical Physics. The guidance for authors has been followed. The manuscript follows the section format described in the author guidelines: introduction, methods, results, and discussion, there are no abstract or conclusion sections. A technical note describes "a specific development, technique or procedure, or it may describe a modification of an existing technique, procedure or device applicable to medicine" (Ng and Peh, 2010, pp.101). ABAS of the vertebral spine, including identification of specific thoracic and lumbar vertebrae, using SmartSegmentation has not been described in the literature. ABAS of OAR in the vicinity of the vertebral spine for radiotherapy treatment planning of uncomplicated spine metastases, using SmartSegmentation has not been described in the literature. Therefore this manuscript will add to the body of knowledge on auto-segmentation using SmartSegmentation.

3.2. Manuscript 1 - Atlas-Based Auto-Segmentation of Spinal Vertebrae and Organs at Risk in the Thoracic and Lumbar Regions

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Keywords: automation, atlas-based auto-segmentation, SmartSegmentation, spine metastases, organs at risk.

Introduction

Uncomplicated spine metastases primarily occur in the vertebral body of the spine [1] with an approximate distribution of 70% and 20% occurring in the thoracic and lumbar region respectively [2]. Spine metastases are routinely treated with conventional external beam radiotherapy (cEBRT), delivered as a single posterior, or two opposing anterior-posterior, open, un-modulated fields directed at the affected vertebrae, with little to no shielding of organs at risk (OAR) [3]. cEBRT is planned using virtual simulation, where field width is defined to encompass the transverse processes and laminae and field length to include the affected vertebra and the two vertebra immediately above and below. Target volumes and OAR are not routinely delineated and therefore target volume coverage and OAR dose statistics are not reported. Spine metastases result in considerable morbidity and can cause severe and debilitating effects, including pain. cEBRT is a widely established treatment to provide durable pain control, but 40% of patients fail to obtain pain relief [4] and 20% of patients require re-irradiation [5, 6]. As the disease progresses, further spine metastases may require additional cEBRT. Irradiation and re-irradiation of spine metastases presents a radiotherapy challenge, primarily due to the proximity of the spinal cord, which is the dose-limiting OAR. Other OAR in the vicinity of the thoracic and lumbar regions include the heart, oesophagus, lungs, kidneys and cauda equina. Toxicity following cEBRT has not been extensively reported on. Acute toxicity following cEBRT is usually resolved within 6 weeks of treatment completion and late toxicity is uncommon [7]. However, advances in combined modality treatment and treatment of local recurrences result in patients surviving longer with cancer which potentially places patients at greater risk of late toxicity, which can impact on quality of life [8]. It has been argued that patients with spine metastases should be treated with the most advanced radiotherapy techniques available [9] but current guidelines state that this is not mandatory [5]. Clinical implementation of the more advanced radiotherapy techniques is challenging. Conformal radiotherapy, which includes intensity-modulated radiotherapy (IMRT), volumetric-modulated arc therapy (VMAT) and stereotactic ablative radiotherapy (SABR), requires technically demanding and time consuming treatment planning, including target volume and OAR delineation [10, 11]. Manual

delineation of target volumes and OAR is routinely performed on computed tomography (CT) images following recommendations provided by the International Commission on Radiation Units and Measurements (ICRU) [12]. Auto-segmentation may aid clinical implementation of conformal radiotherapy for uncomplicated spine metastases and has the potential to facilitate dose reporting to target volumes and OAR providing useful information for re-irradiation and irradiation of subsequent spine metastases.

Atlas-based auto-segmentation (ABAS) is a method of auto-segmentation that uses prior-knowledge of previously delineated contours of target volumes and OAR from reference images within an atlas of images. This information is then used to inform delineation of the same contours on anatomically similar, new images [13]. While many commercial ABAS systems are available, we describe ABAS using Eclipse SmartSegmentation Knowledge Based Contouring version 15.5 (*Varian Medical Systems, Palo Alto, California*). SmartSegmentation utilises an atlas and model-based approach to auto-segment structures using advanced image analysis to determine the structures location according to the Hounsfield unit (HU) gradients in the CT data set, followed by deformable image registration against a reference image [14]. SmartSegmentation refers to the reference images within the atlas as expert cases. Use of SmartSegmentation for ABAS of thoracic and lumbar vertebrae has not been described in the literature but auto-segmentation for this site is acknowledged to be challenging. Spinal vertebrae exhibit complex topology and irregular boundaries, and similarity between adjacent vertebra makes distinction between, and identification of, individual vertebra difficult. Furthermore, spine metastases alter the shape of vertebrae, and reduce contrast against soft tissues on CT data sets [15, 16, 17, 18].

Here we describe the creation and evaluation of an expert case atlas of contoured thoracic (T1-T12) and lumbar (L1-L5) spinal vertebrae in SmartSegmentation, as well as specific OAR for cEBRT in the vicinity of these regions.

Method

A. Creation of SmartSegmentation expert case atlas

A selection of randomly selected CT image data sets of previously treated spine metastases patients were used to generate an expert case atlas in SmartSegmentation, CT data sets were excluded from addition to the atlas if there

was evidence of previous spinal surgery. All patients were imaged head first, supine. Patient position and immobilisation was variable across the CT data sets, see table 3.1 for the patient characteristics of the reference images used in the expert case atlas.

Atlas	Patient Characteristics					CT Reference Image Characteristics
Expert Case	Primary Cancer	M/F	Age at CT	Location of spine metastasis during course of palliative treatment	Deviation from 'normal' anatomy	Position/Immobilisation
1	Rectum	M	52	C6-T1		head on head rest, 1 mat under pelvis, hands by side, knee and foot support
2	Head and Neck	M	56	T4-T5, T6-T9, T11-L2	L1	2 mats under thorax and pelvis, hands by side, knee and foot support
3	Breast	F	68	C4-T1		head on non-slip mat, 2 mats under thorax and pelvis, hands by side, knee and foot support
4	Breast	F	55	T12-S2		head on 1 block, 3 mats under thorax and pelvis, hands on chest, knees straight, foot support
5	Lung	M	64	T11-L1	T12	head on 2 blocks, 2 mats under thorax and pelvis, hands by side, knee and foot support
6	Breast	F	55	L2-L4		head on 1 block, 2 mats under thorax and pelvis, hands by side, knee and foot support
7	Breast	F	68	L5-S3		head on 2 blocks and 1 wedge, head tilted to right, 2 mats under thorax and pelvis, hands by side, knee and foot support
8	Multiple Myeloma	M	77	T11-L3	L1	head on 1 block and 1 wedge, head tilted to right, 2 mats under thorax and pelvis, hands by side, knee and foot support
9	Breast	F	80	T3-T7	artifact in heart	head on 2 blocks and 1 wedge, 2 mats under thorax, hands by side, knee and foot support
10	Kidney	M	55	T3-T5	large mass in left kidney	head on 1 block and 1 wedge, 2 matts under thorax and pelvis, hands by side, knee and foot support
11	Lung	M	58	T4-T10	L4	head on 1 block, 2 mats under thorax and pelvis, hands by side, knee and foot support
12	Breast	F	76	T4-T10	L2	head on 1 block, 2 mats under thorax and pelvis, hands by side, knee and foot support
13	Bladder	M	72	L1-L5	artifact in heart	head on 1 block and 1 wedge, 2 mats under thorax, wedge under right shoulder, hands by side, knee and foot support
14	Liver	F	71	T8-L3	L1	head on 1 block and 1 wedge, 2 matts under thorax and pelvis, hands by side, knee and foot support
15	Lung	M	61	T3-T6, C2-C5	T5	head on 1 block and 1 wedge, 2 mats under thorax, wedge under right shoulder, hands by side, knee and foot support
16	Breast	F	76	T7-T12		head on 2 blocks and 1 wedge, 2 mats under thorax and pelvis, hands by side, knee and foot support

Table 3.1: Reference image expert case patient characteristics.

Anatomical changes to the vertebrae affected by spine metastases were present in most CT data sets, examples of which are shown in figure 3.1.

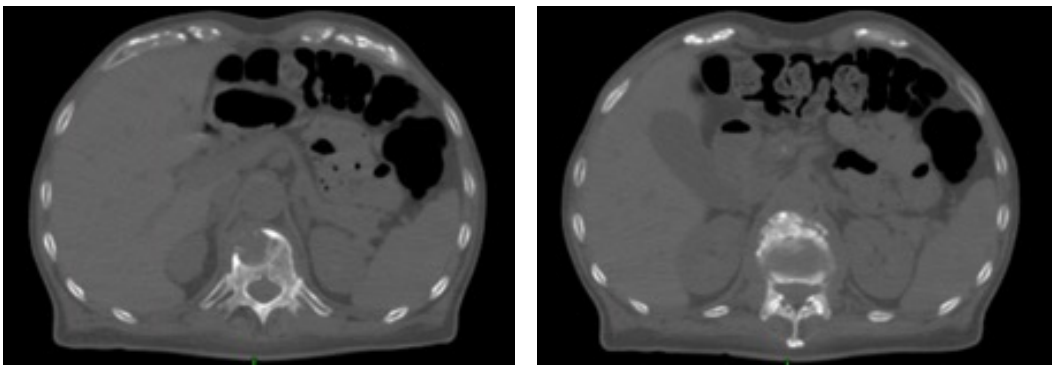

Figure 3.1: Anatomical changes to vertebrae as a result of spine metastases.

Manual delineation of the thoracic and lumbar vertebrae followed the guidelines of the International Spine Radiosurgery Consortium (ISRC) for delineation of spine metastasis for radiosurgery [19]. The ISRC propose clinical target volume (CTV) delineation based on disease involvement within sectors of the vertebral body. It was assumed for cEBRT of uncomplicated spine metastases the CTV therefore included the vertebral body (1), left and right pedicles (2 and 6 respectively), left and right transverse processes and laminae (3 and 5 respectively) and spinous process (4), as shown in figure 3.2.

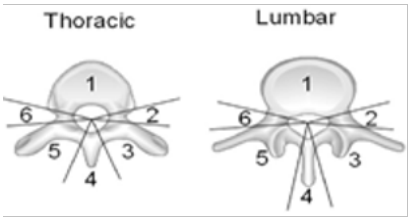

Figure 3.2: ISRC anatomic classification system for consensus target volumes (thoracic and lumbar regions) for spine radiosurgery [19, p.e599].

OAR selection followed the American Society for Radiation Oncology (ASTRO) consensus recommendations [20]. Delineation of OAR also followed the recommendations therein, specifically heart [21]; oesophagus [22]; lungs [23]; kidneys [23]; spinal cord [22]; and cauda equina [24].

Manual delineation was carried out on the axial plane using a variety of drawing tools available in SmartSegmentation, including ‘draw planar contour’, ‘brush’ - 2D adaptive and static, and ‘eraser’ - 2D adaptive and static. Spinal vertebrae T1-T12 and L1-L5 were delineated in the window/level range ‘bone’. OAR were delineated in a range suitable for the OAR. Contours were reviewed in the axial, sagittal and

coronal planes. Figure 3.3 shows a contoured expert case example included in the atlas.

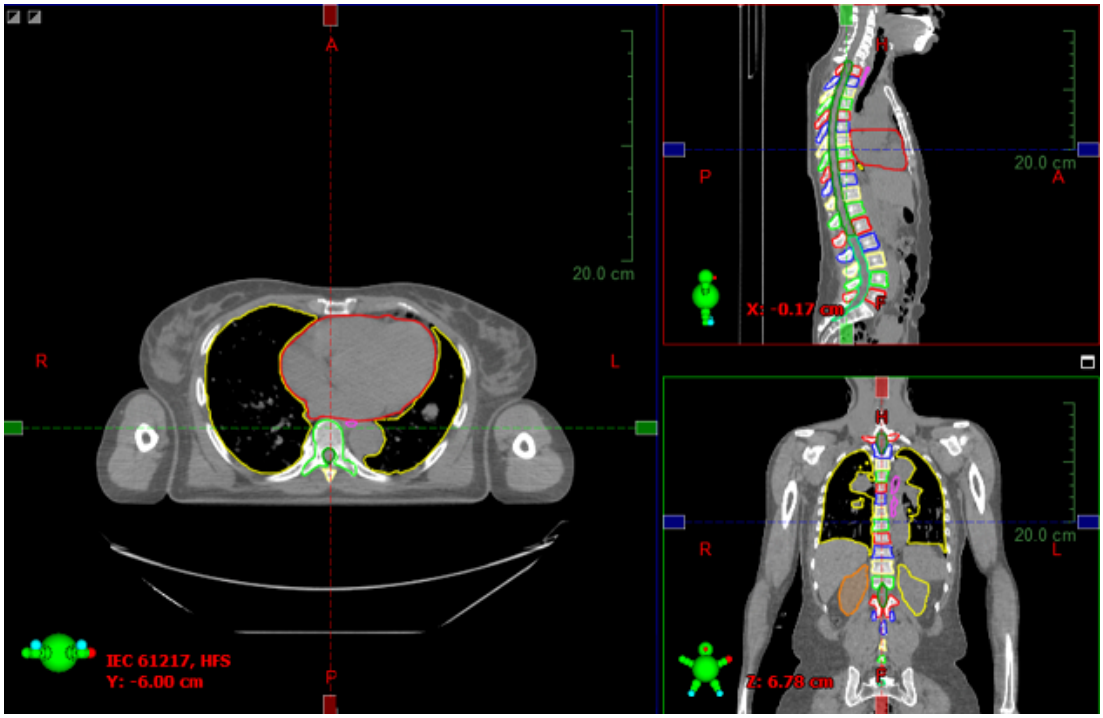

Figure 3.3: Expert case example with manual delineation of thoracic and lumbar vertebrae and OAR.

An initial 6 reference image expert case atlas (expert cases numbered 1-6 in table 3.1) was produced to evaluate the feasibility of SmartSegmentation on 10 randomly selected subsequent CT image data sets. SmartSegmentation scored reference image expert cases for appropriateness of application to subsequent CT datasets using a similarity scoring system of 1 to 5, where 5 indicated the greatest similarity with an expert case in the atlas. ABAS was performed on the single highest scoring expert case for all vertebrae and OAR, with the exception of the left and right lung which were auto-segmented using image thresholding segmentation (IS). All structures were manually delineated prior to ABAS to allow for comparison without bias. Time taken to manually delineate structures and perform ABAS were recorded. Evaluation of SmartSegmentation for ABAS of the thoracic and lumbar vertebral spine and OAR in their vicinity was carried out using the metric of Dice similarity coefficient (DSC). DSC is a widely used similarity metric where similarity is scored from 0 to 1, 1 indicating perfect overlap and similarity of comparative structures, 0 indicating no overlap or similarity [25, 26]. DSC>0.70 indicates good overlap [27]. A two-sample independent t-test (assuming unequal variances) with a significance

level of 0.05 was used to determine statistical significance for difference between means DSC of the vertebrae and OAR.

Following evaluation the manually delineated contours and the 10 evaluation CT images data sets were added to the expert case atlas once feasibility was established (expert cases numbered 7-16 in table 3.1).

B. Evaluation of SmartSegmentation ABAS

To evaluate the performance of the 16 reference image expert case atlas (expert cases numbered 1-16 in table 3.1), ABAS was performed on a further 9 CT image data sets for a selection of thoracic and lumbar vertebrae (T6, T7, T8, T10, T11, T12, L2, L3 and L4), and OAR (heart, oesophagus, left lung, right lung, left kidney, right kidney, spinal cord and cauda equina). ABAS was performed using the single expert case with the highest similarity score. All structures were manually delineated prior to ABAS to allow for comparison without bias.

To refine SmartSegmentation ABAS further, an additional structure review step was added for a further 10 CT image data sets. ABAS was performed using the single expert case with the highest similarity score, but reviewed to qualitatively assess the auto-segmentation of the structures. Any structures felt to have been inadequately auto-segmented by ABAS were put through SmartSegmentation ABAS again using an alternative, but similarly scored, expert case. This was repeated until the expert case providing the best qualitative match to the target volume or OAR was determined. Misidentified vertebrae were corrected by renaming the structures appropriately. ABAS/IS generated structures were compared with manually modified structures using ABAS/IS as a starting point for manual delineation. Time taken to perform ABAS, perform the additional structure review step, and manually modify ABAS structures were recorded. Evaluation of SmartSegmentation for ABAS was carried out using the metrics of DSC, volume change and centre of mass shift. A two-sample independent t-test (assuming unequal variances) with a significance level of 0.05 was used to determine statistical significance for difference between means DSC of the vertebrae and OAR.

Results

A. Creation of SmartSegmentation expert case atlas

DSC variation for ABAS of thoracic and lumbar vertebrae using a single expert case with the highest similarity score from a 6 reference image expert case atlas when applied to 10 CT image data sets is shown in figure 3.4. The bottom and top of the box plots indicate the lower and upper quartiles, with the median value indicated by the band in between. The interquartile range is the height of the box. Outliers, where present, are indicated with a circle, an outlier is considered as such if the value is less than or more than 1.5 times the interquartile range. The mean value is indicated by a cross. The whiskers indicate the minimum and maximum values excluding the outliers.

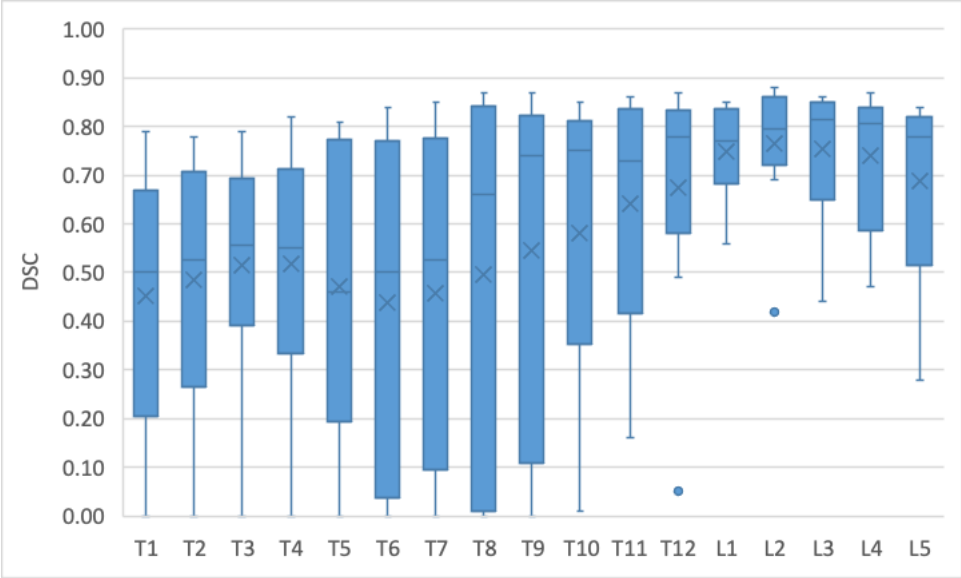

Figure 3.4: DSC for ABAS thoracic and lumbar vertebrae using a 6 reference image expert case atlas applied to 10 CT data sets.

Mean DSC for the combined thoracic vertebrae was 0.52±0.29 compared to 0.74±0.14 for combined lumbar vertebrae. There appears to be an upwards trend of improving DSC descending down the vertebrae, with the lumbar vertebrae achieving the higher mean DSC values. As well as higher DSC values for lumbar vertebrae, the standard deviation is smaller. There was a statistically significant difference between the DSC for the thoracic and lumbar vertebra ($p<0.01$).

Mean time to manually delineate T1-T12 was 133.9±27.0 minutes, approximately equivalent to 11.2 minutes per vertebra, compared to 1.6±0.2 minutes for ABAS. Mean time to manually delineate L1-L5 was 87.8±10.7 minutes, approximately equivalent to 17.6 minutes per vertebra, compared to 1.2±0.3 minutes for ABAS.

DSC variation for ABAS of heart, oesophagus (oeso), left and right kidneys, spinal cord (SC) and cauda equina (CE), and IS of left and right lungs is shown in figure 3.5.

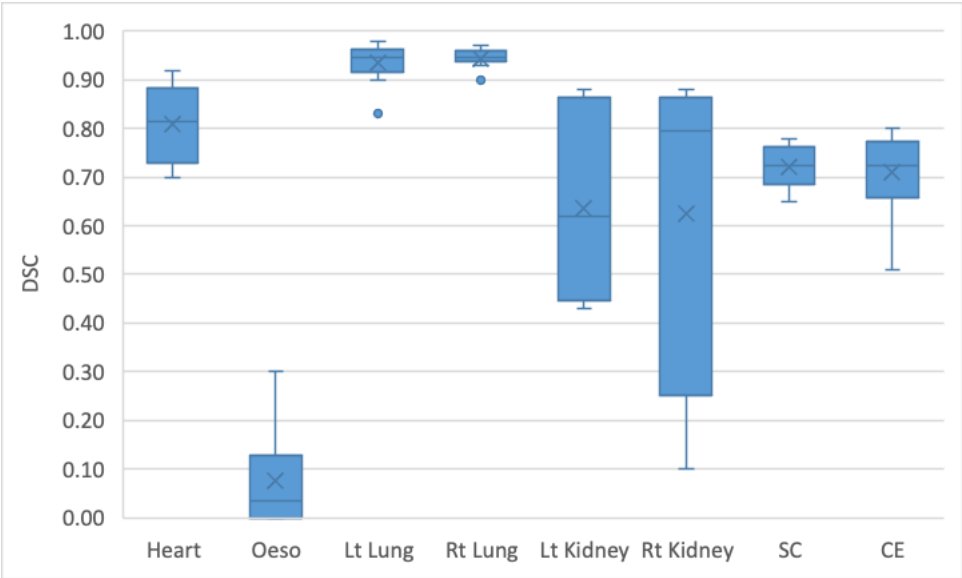

Figure 3.5: DSC for ABAS/IS OAR using a 6 reference image expert case atlas applied to 10 CT data sets.

Mean DSC for the OAR was heart 0.82±0.08, oesophagus 0.08±0.10, left lung 0.93±0.04, right lung 0.94±0.02, left kidney 0.66±0.19, right kidney 0.68±0.32, spinal cord 0.73±0.04 and cauda equina 0.70±0.09. IS was highly successful for the left and right lungs achieving the highest DSC with smallest standard deviation. ABAS for the heart, spinal cord and cauda equina all exceeded mean DSC≥0.70, indicating a degree of success. Less successful were the left and right kidneys which had greatest variation in DSC. The least successful ABAS occurred for the oesophagus.

B. Evaluation of SmartSegmentation ABAS

DSC variation for a selection of thoracic (T6, T7, T8, T10, T11 and T12) and lumbar (L2, L3 and L4) vertebrae for ABAS using a single expert case with the highest similarity score from a 16 reference image expert case atlas is shown in figure 3.6. Mean DSC for individual vertebrae was T6 0.48±0.33, T7 0.52±0.32, T8 0.54±0.33, T10 0.58±0.38, T11 0.61±0.34, T12 0.64±0.32, L2 0.68±0.37, L3 0.71±0.34 and L4 0.73±0.31. Similarly to figure 3.4 there appears to be a slight upwards trend of improving DSC descending down the vertebrae, with the lumbar vertebrae achieving

the higher mean DSC values. However, there was no statistically significant difference between the DSC for the thoracic and lumbar vertebra (p=0.08).

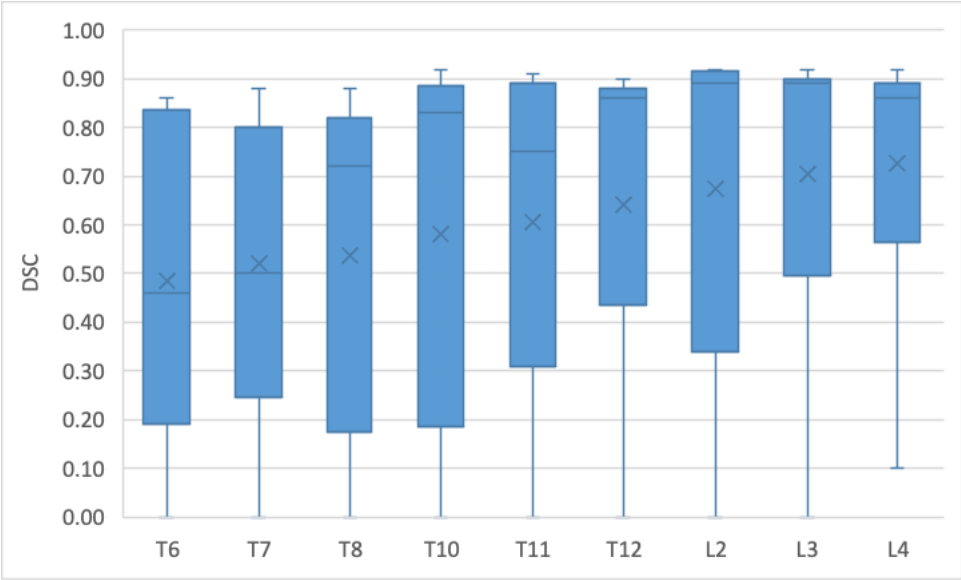

Figure 3.6: DSC for a selection of ABAS thoracic and lumbar vertebrae using the highest scored expert case from a 16 reference image expert case atlas applied to 9 CT data sets.

As indicated by the whiskers in figure 3.6, and also in table 3.2, most vertebrae had a minimum DSC=0, indicating no overlap or similarity between the manually delineated vertebrae and ABAS generated vertebrae. This has occurred where individual vertebrae were misidentified, where an individual vertebra was misidentified by ABAS as an adjacent vertebra.

DSC variation for ABAS of heart, oesophagus (oeso), left and right kidneys, spinal cord (SC) and cauda equina (CE), and IS of left and right lungs is shown in figure 3.7.

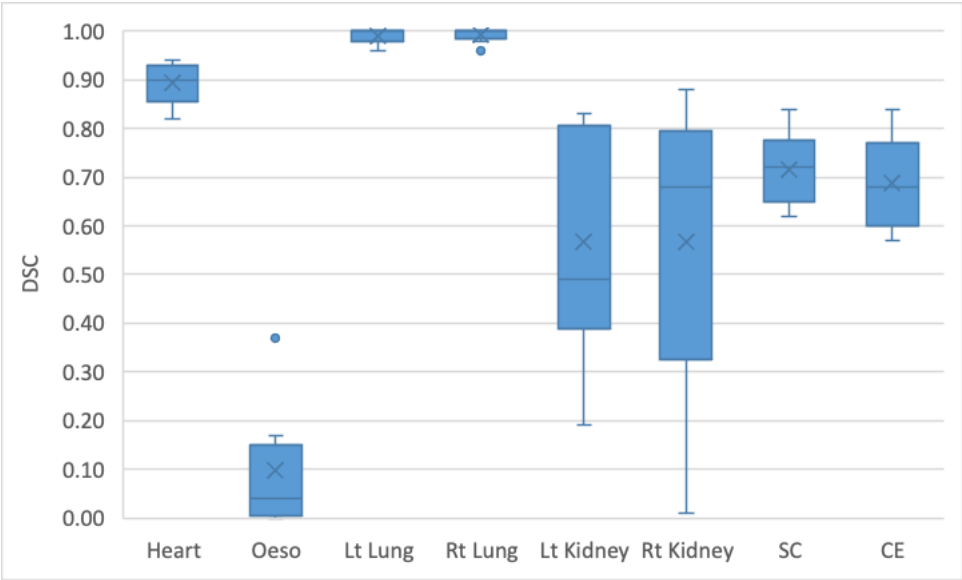

Figure 3.7: DSC for ABAS/IS OAR using the highest scored expert case from a 16 reference image expert case atlas applied to 9 CT data sets.

Mean DSC for the OAR was heart 0.89±0.04, oesophagus 0.10±0.12, left lung 0.99±0.02, right lung 0.99±0.01, left kidney 0.57±0.24, right kidney 0.57±0.32, spinal cord 0.72±0.08 and cauda equina 0.69±0.09. Again IS was highly successful for the left and right lungs achieving the highest DSC with smallest standard deviation. ABAS for the heart and spinal cord exceeded mean DSC≥0.70, indicating a degree of success. Less successful were the left and right kidneys which again had greatest variation in DSC. Once more the least successful ABAS occurred for the oesophagus. Table 3.2 summarises the similarity metrics for ABAS/IS.

Structure (target/ OAR)	Mean DSC	Standard Deviation	Min DSC	Max DSC	Mean centre of mass shift (cm)	Volume difference range (cm^3)
T6	0.48	0.33	0	0.86	1.03	-28.4 to 3.0
T7	0.52	0.32	0	0.88	0.91	-6.0 to 6.9
T8	0.54	0.33	0	0.88	0.87	-5.4 to 12.0
T10	0.58	0.38	0	0.92	0.86	-7.6 to 11.1
T11	0.61	0.34	0	0.91	0.80	-1.8 to 7.0
T12	0.64	0.32	0	0.90	0.84	-5.4 to 20.2
L2	0.68	0.37	0	0.92	0.88	-3.9 to 20.9
L3	0.71	0.34	0	0.92	0.78	-25.9 to 11.1
L4	0.73	0.31	0.1	0.92	0.76	-8.2 to 5.9
Heart	0.89	0.04	0.82	0.94	0.48	-10.1 to 252.5
Oesophagus	0.10	0.12	0	0.37	4.40	6.6 to 15.4
Left Lung	0.99	0.02	0.96	1.00	0.16	-110.8 to 54.5

Structure (target/ OAR)	Mean DSC	Standard Deviation	Min DSC	Max DSC	Mean centre of mass shift (cm)	Volume difference range (cm^3)
Right Lung	0.99	0.01	0.96	1.00	0.11	-93.1 to 43.0
Left Kidney	0.57	0.24	0.19	0.83	2.70	-66.5 to 92.1
Right Kidney	0.57	0.32	0.01	0.88	3.01	-106.6 to 91.3
Spinal Cord	0.72	0.08	0,62	0.84	1.66	-25.2 to 25.9
Cauda Equina	0.69	0.09	0.57	0.84	0.98	-14.0 to 8.9

Table 3.2: DSC, centre of mass shift and volume difference for ABAS/IS of a selection of vertebrae and OAR using the highest scored expert case from a 16 reference image expert case atlas.

Mean centre of mass shifts were variable, with the direction of the shifts primarily being in the superior-inferior direction. The greatest centre of mass shifts occurred for the left and right kidneys. Volume difference was variable, with the larger volume structures exhibiting the greatest difference and variation.

There was no statistically significant difference between the DSC values for ABAS using a 6 reference image expert case atlas compared to a 16 reference image expert case atlas, p=0.59 for thoracic and lumbar vertebra and p=0.88 for OAR. Indicating that additional expert cases in the atlas did not improve ABAS similarity against equivalent manually delineated structures.

Figures 3.8 and 3.9 show DSC following an additional structure review step on a further 10 CT image data sets. ABAS was performed using all expert cases with the highest similarity score, with each structure reviewed to determine the best qualitative match to the anatomical vertebrae or OAR. Misidentified vertebrae were renamed. No structure however was manually modified and all structures remained ABAS/IS generated. Table 3.3 summarises the similarity metrics for ABAS/IS with the additional structure review step.

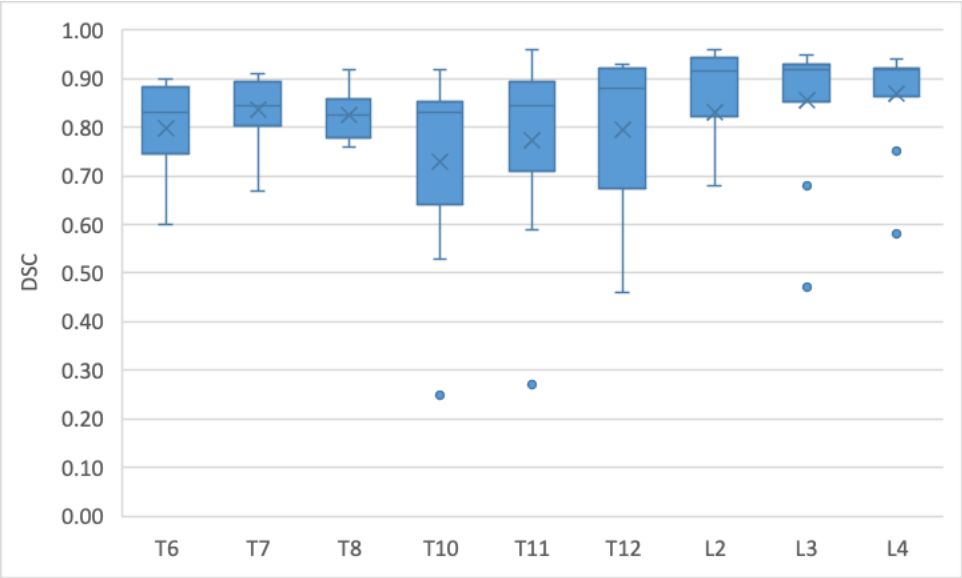

Figure 3.8: DSC of ABAS thoracic and lumbar vertebrae following an additional structure qualitative review step applied to 10 CT data sets.

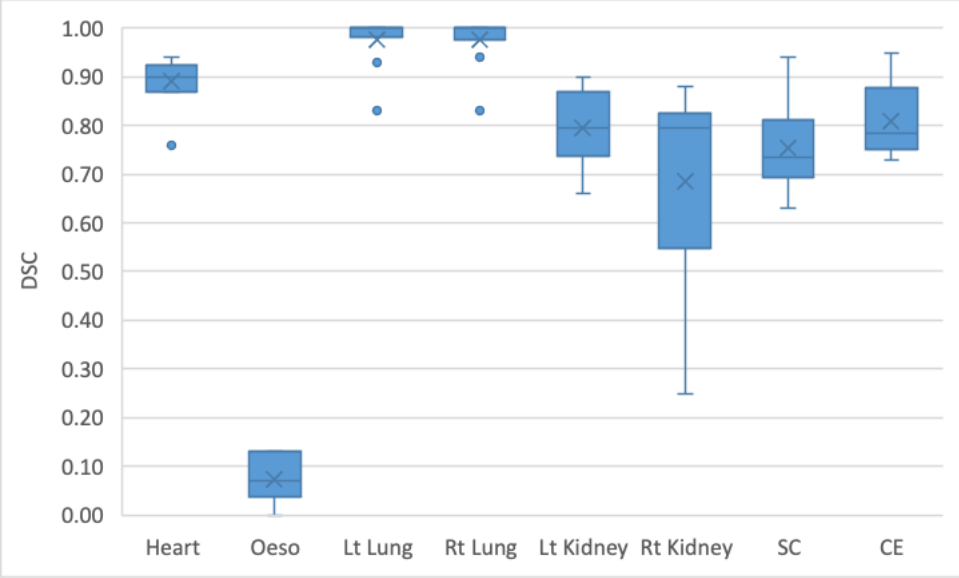

Figure 3.9: DSC of ABAS/IS generated OAR following an additional qualitative structure review step applied to 10 CT data sets.

Structure (target/ OAR)	Mean DSC	Standard Deviation	Min DSC	Max DSC	Mean centre of mass shift (cm)	Volume difference range (cm³)
T6	0.80	0.10	0.60	0.90	0.39	-2.5 to 5.3
T7	0.84	0.07	0.67	0.91	0.29	-3.1 to 2.5
T8	0.83	0.05	0.76	0.92	0.40	-6.0 to 5.1
T10	0.73	0.20	0.25	0.92	0.56	-13.9 to 13.5
T11	0.77	0.21	0.27	0.96	0.40	-4.0 to 8.6

Structure (target/ OAR)	Mean DSC	Standard Deviation	Min DSC	Max DSC	Mean centre of mass shift (cm)	Volume difference range (cm^3)
T12	0.80	0.18	0.46	0.93	0.45	-11.4 to 15.1
L2	0.83	0.22	0.26	0.96	0.37	-0.2 to 12.2
L3	0.86	0.16	0.47	0.95	0.38	-4.7 to 6.8
L4	0.87	0.11	0.58	0.94	0.32	-29.1 to 7.0
Heart	0.89	0.05	0.76	0.94	0.60	-59.5 to 186.0
Oesophagus	0.07	0.05	0	0.13	1.90	15.9 to 121.8
Left Lung	0.98	0.06	0.83	1.00	0.26	-127.0 to 154.6
Right Lung	0.98	0.05	0.83	1.00	0.23	-94.4 to 123.6
Left Kidney	0.79	0.08	0.66	0.90	0.79	-94.1 to 84.4
Right Kidney	0.68	0.23	0.25	0.88	1.91	-85.2 to 135.3
Spinal Cord	0.76	0.09	0.63	0.94	2.10	-21.8 to 40.1
Cauda Equina	0.82	0.08	0.73	0.95	1.03	-5.2 to 9.0

Table 3.3: DSC, centre of mass shift and volume difference for ABAS/IS of a selection of vertebrae and OAR with an additional qualitative structure review step.

Mean centre of mass shifts were variable, with the direction of the shifts primarily being in the superior-inferior direction, but the additional structure review step did reduce the shift. Volume difference again was variable, with the larger volume structures exhibiting the greatest difference and variation.

The addition of the structure review step has significantly improved mean DSC for the thoracic and lumbar vertebrae with an increase from DSC=0.56 to DSC=0.79 for thoracic vertebra ($p<0.01$) and an increase from DSC=0.70 to DSC=0.85 for lumbar vertebrae ($p<0.05$). However the impact of a structure review step on OAR is less significant, with no statistically significant improvement in DSC for heart, oesophagus, left lung, right lung, right kidney and spinal cord, but some improvement for left kidney ($p<0.05$) and cauda equina ($p<0.05$).

The additional structure review step and application of ABAS using multiple expert cases added additional time to the ABAS process. Mean time to perform ABAS of T6, T7, T8, T10, T11, T12, L2, L3 and L4 and all OAR was 2.5±0.3 minutes. Mean time to perform the additional structure review step was 12.1 ±7.9 minutes.

Discussion

SmartSegmentation ABAS was more successful for lumbar vertebrae than thoracic vertebrae, this is statistically significant for ABAS generated from a 6 reference image expert case atlas ($p<0.01$) in figure 3.4, but not statistically significant for ABAS generated from a 16 reference image expert case atlas ($p=0.08$) in figure 3.6. Other researchers investigating ABAS of the vertebral spine, with an alternative auto-segmentation solution, have also indicated that ABAS has had the most success for vertebrae delineation in the lumbar region [16]. As shown in table 3.1, there is wide variation in patient position and immobilisation in the reference image expert cases in the atlas, and this appears to have more impact on the thoracic vertebrae position compared to the lumbar vertebrae position which appears more consistent between all 16 expert cases. The use of a varying head rests, blocks and wedges appears to significantly alter the thoracic vertebral spine, an example of this is shown in figure 3.10.

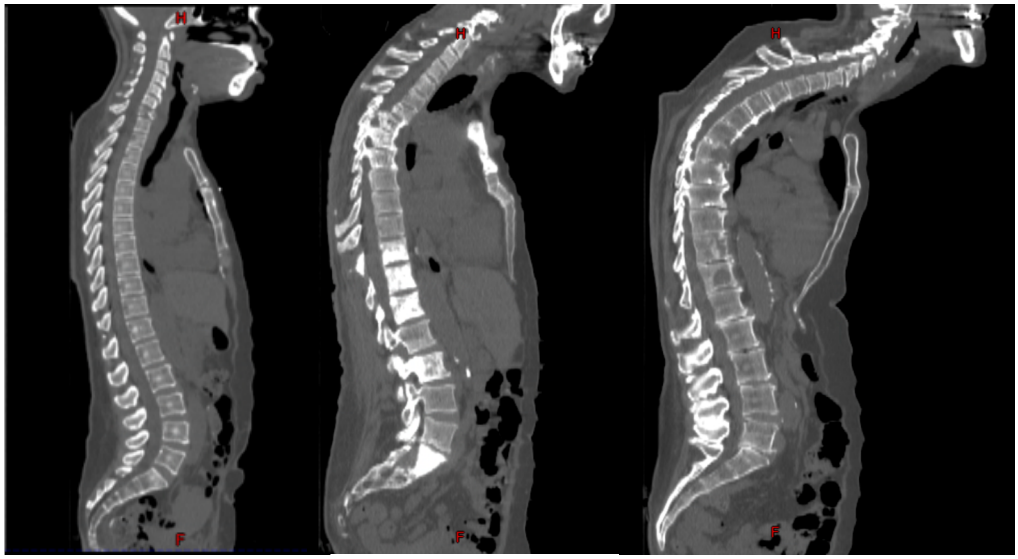

Figure 3.10: Varying use of head rests, block and wedges altering the spinal vertebrae position and angle in the thoracic region.

The addition of a structure review step reduces the difference between ABAS for thoracic and lumbar vertebrae and improves DSC for both significantly. Misidentification of vertebrae, leading to DSC=0 indicating no overlap or similarity, was frequent and this indicates that it is not reasonable to perform ABAS without review of vertebra labelling. Review, and renaming vertebra appropriately, improves mean DSC significantly ($p<0.01$), as shown in figure 3.8 compared with figure 3.6.

IS for left and right lungs was highly successful and achievable in all instances. SmartSegmentation ABAS for OAR, with the exception of the oesophagus, had

varying levels of success. The addition of a structure review step had no statistically significant improvement on DSC for OAR, with the exception of the left kidney and cauda equina ($p<0.05$). The heart was auto-segmented with great success with a mean DSC value of 0.89 indicating good overlap and similarity between the ABAS generated heart contour and then manually modified heart contour. The structure review step did improve the DSC of the left kidney, but did not statistically significant impact DSC for the right kidney, the range of DSC values for both kidneys however was reduced, as well as the mean centre of mass shifts. It was observed that the kidneys were highly variable in size and position between the reference image expert cases and potentially the addition of further expert cases to the atlas may improve ABAS for the kidneys. DSC values indicate some success for delineation of spinal cord and cauda equina, but as indicated by mean centre of mass shifts, the determination of the start and end positions of the spinal cord and cauda equina were highly variable, the centre of mass shift primarily being in the superior-inferior direction. Review of the expert case atlas showed consistent practice in the delineation of spinal cord and cauda equina, with consistent start and end positions, but high variability when ABAS was performed, this is also likely due, in part, to the variability of patient position and immobilisation shown in figure 3.10. ABAS of the oesophagus was unsuccessful and likely the addition of further expert cases would not improve on this. SmartSegmentation failed to auto-segment the oesophagus successfully in all instances. The oesophagus is however widely known to be both difficult to manually delineate, with high variability between observers, and to auto-segment, as the boundaries between the oesophagus and other surrounding tissues are poorly defined [28].

It is likely the 16 reference image expert case atlas is insufficient for successful ABAS of vertebrae, in particular when there is such high variation in patient position and immobilisation. All reference images in the expert case atlas exhibit anatomical changes to vertebrae anatomy due to the presence of spine metastases, that may or may not be present when applying to new CT image data sets, further expert cases may limit the impact this has on ABAS. Increasing the expert case atlas may also benefit ABAS of OAR where the OAR are known to have high variability of size and position in the reference image expert case atlas.

Despite the limitations described, SmartSegmentation ABAS, as expected, was able to generate entire structure sets of thoracic and lumbar vertebrae and OAR in a timely manner, significantly faster than would be achievable manually. Although all

structures would require manual modification before they would be suitable for conformal radiotherapy planning. SmartSegmentation ABAS and manual modification of structures would facilitate reporting dose to target volumes and OAR, and assist in determining dose to structures for re-irradiation or irradiation of subsequent spine metastases.

Conflict of Interest

This work was partly funded by Varian Medical Systems.

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4. Manuscript 2

This proffered manuscript describes the development of RapidPlan KBP for conformal VMAT treatment planning of uncomplicated spine metastases in the thoracic and lumbar regions of the vertebral spine.

4.1. Introduction To Manuscript

This manuscript was written with the aim of submission as an original article for publication in the Journal of Applied Clinical Medical Physics. The guidance for authors was followed. The mission of this journal is to publish papers that will help medical physicists and other health professionals perform more effectively and efficiently, for increased patient benefit and as such this is an appropriate journal to target for publication of this work. Automated treatment planning approaches to reduce the labour intensive nature of treatment planning have been steadily gaining momentum (Hussein *et al*, 2018). This manuscript describes VMAT KBP using a widely used commercial TPS for a clinical treatment site not extensively reported on in the literature. Therefore this manuscript will add to the body of knowledge on RapidPlan KBP for spine metastases and automation of treatment planning for spine metastases.

4.2. Manuscript 2 - Development of Knowledge-Based Treatment Planning for Radiotherapeutic Palliation of Spine Metastases

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Keywords: knowledge-based planning, RapidPlan, spine metastases, VMAT

Abstract

Purpose: To develop and validate a RapidPlan DVH estimation model for volumetric-modulated arc therapy (VMAT) of uncomplicated spine metastases, and evaluate if knowledge-based planning (KBP) is feasible for VMAT of uncomplicated spine metastases.

Materials and Methods: A 60 plan RapidPlan DVH estimation model was developed for application of KBP for VMAT of uncomplicated spine metastases in the thoracic and lumbar regions of the vertebral spine. PTV volumes ranged from 154.8 to 529.4cm^3 (mean=295.9cm^3). OAR included spinal cord, oesophagus, heart, lungs, kidney and cauda equina. The model was validated through cross validation.

Results: RapidPlan VMAT KBP generated plans met the optimisation objectives of the RapidPlan DVH estimation model. The mean PTV Dmean dose was 7.98±0.01Gy (mean Dmin=6.90±0.22Gy and Dmax=8.52±0.06Gy) for the RadpidPlan VMAT KBP generated plans compared to PTV Dmean of 7.95±0.01Gy (mean Dmin=6.57±0.24Gy and Dmax 8.60±0.08Gy) for the plans in the RapidPlan model. The dose limiting structures, spinal cord and cauda equina, had a mean Dmax dose of 7.75Gy and 7.94Gy for RapidPlan VMAT KBP generated plans, compared to 7.55Gy and 7.68Gy for the plans in the RapidPlan model respectively, where mean Dmax is across all regions of the thoracic and lumbar spine for spinal cord, and for the lumbar region only for cauda equina. All other OAR Dmax and Dmean doses were lower for RapidPlan VMAT KBP generated plans.

Discussion: The results indicate that this RapidPlan DVH estimation model for VMAT KBP of uncomplicated spine metastases can be used to generate RapidPlan KBP generated VMAT treatment plans with greater consistency than manual VMAT radiotherapy treatment planning. The generated plans meet the optimisation objectives of the RapidPlan model.

Conclusion: The RapidPlan DVH estimation model for VMAT KBP of uncomplicated spine metastases can be used to generate consistent RapidPlan KBP generated VMAT treatment plans of sufficient quality for mid thoracic to lumbar PTVs. This provides an automated optimisation solution for conformal radiotherapy treatment planning.

Introduction

The use of radiotherapy for palliation of uncomplicated spine metastases is well established [1, 2, 3]. The most widely used radiotherapy treatment approach is conventional external beam radiotherapy (cEBRT). cEBRT can be broadly defined as the application of a single-applied posterior field, or parallel-opposed anterior-posterior fields directed at the affected vertebrae [2], as shown in figure 4.1. cEBRT is typically virtually simulated, as opposed to conformally planned. Field size is defined to ensure the treatment field covers the affected vertebra and the adjacent vertebrae above and below. Treatment fields are usually open with no shielding, except in the lower thoracic and upper lumbar regions, where multi-leaf collimators (MLC) may be used to shield the kidneys if they are directly within the treatment field and can be shielded without compromise to the coverage of the vertebrae. The fields are typically un-modulated. Energy selection and prescription depth are chosen by considering the depth of the most anterior aspect of the spinal cord in the centre of the treatment field. The spinal cord is the dose-limiting organ at risk (OAR). Dose is prescribed to a point on the most anterior aspect of the spinal cord in the centre of the treatment field. The anterior aspect of the spinal cord typically lies >5cm beneath the skin surface [4] and therefore cEBRT with a single-applied posterior field can result in high doses to the skin and para-spinal musculature [5], this is shown in figure 4.1.

cEBRT is therefore a non-conformal radiotherapy technique. Current guidelines state conformal radiotherapy is not mandatory for this cohort of patients [6]. Despite the clinical benefit of conformal radiotherapy over cEBRT not being fully demonstrated [5, 7], it has been argued that spine metastases should be treated with the most advanced radiotherapy techniques available [8]. Advanced radiotherapy techniques include intensity-modulated radiation therapy (IMRT), volumetric-modulated arc therapy (VMAT) and stereotactic ablative body therapy (SABR). Results of randomised controlled trials which focus on pain response of SABR for irradiation of spine metastases are emerging in the literature. There is some evidence that the immediacy and durability of pain response with SABR is improved compared to that achieved with cEBRT [9, 10, 11, 12]. Additionally, re-irradiation of spine metastases is common, with 20% of patients requiring re-irradiation following cEBRT [6, 13]. A recent systematic review on re-irradiation of spine metastases with SABR describes SABR as emerging as an effective and safe means of re-irradiation following cEBRT for local control and pain relief [14].

Advances in primary treatment and treatment of local recurrences mean patients are surviving longer with cancer [15]. As such it is not unreasonable to assume that the incidence of uncomplicated spine metastases requiring irradiation and re-irradiation may also increase. IMRT, VMAT and SABR are known to provide improved target coverage, and better sparing of OAR than cEBRT is able to provide [16]. They are increasingly being used, with SABR in particular becoming an emerging treatment option for irradiation and re-irradiation of spine metastases [2].

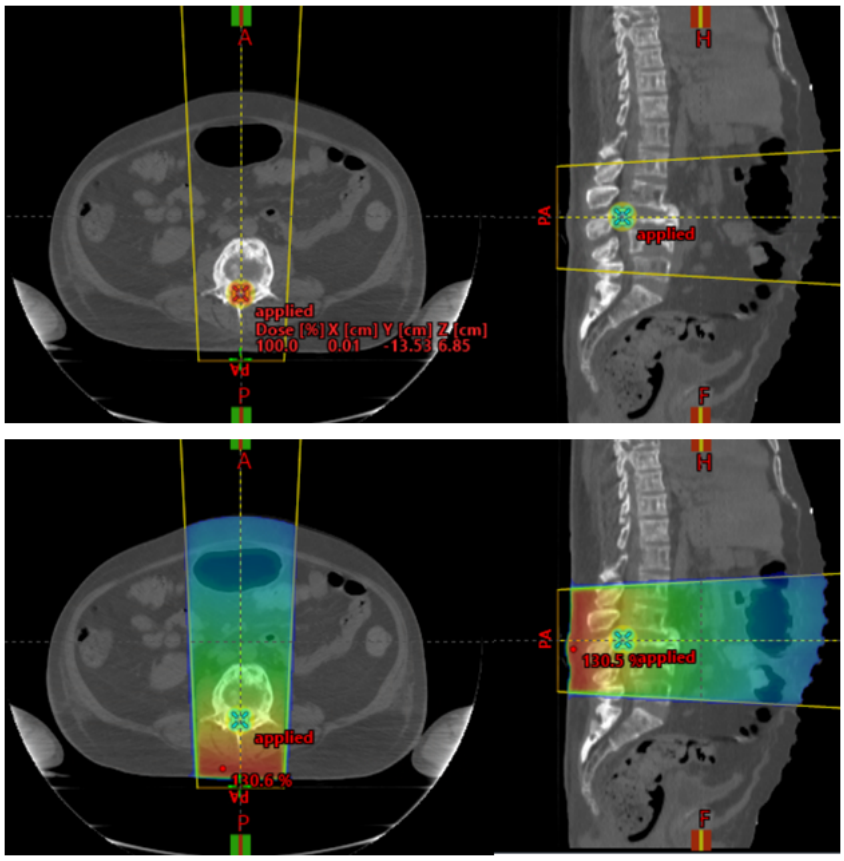

Figure 4.1: An example of cEBRT of uncomplicated spine metastases in the lumbar region of the vertebral spine.

Implementation of conformal treatment approaches in the clinical environment is difficult due to the time-consuming, technically challenging and labour intensive nature of treatment planning [5]. Automated approaches to overcome this have been steadily gaining momentum [17]. The potential for automated treatment planning of VMAT for spine metastases has been assessed using Erasmus-iCycle, an *a priori* multi-criteria optimisation approach [7]. Erasmus-iCycle was able to produce clinical acceptable VMAT treatment plans with superior target volume coverage and sparing of OAR than what could be achieved with manual treatment planning. Additionally, potential for automated treatment planning of SABR for spine

metastases has been explored by a number of investigators [18, 19, 20]. Automated treatment planning of SABR using an in-house developed inverse planning script using Pinnacle has been investigated [18]. The inverse planning script produced inferior SABR treatment plans, in terms of target volume coverage, compared to those generated using manual treatment planning, but the authors stated these plans remained dosimetrically acceptable. Automated treatment planning of SABR for spine metastases has also been explored using RapidPlan, a commercial model-based, knowledge-based planning (KBP) solution [19, 20]. RapidPlan was found to produce clinically equivalent or clinically superior SABR treatment plans compared to manual treatment planning (in terms of target volume coverage and OAR sparing). Where measured, the automated treatment planning process introduced time-saving over the manual conformal treatment planning process [18, 20]. This however, was at the cost of increasing the time taken for radiotherapy treatment delivery [7]. Furthermore, automated treatment planning improved the consistency of treatment planning and ensured protocol compliance in a clinical trial setting [19]. All of these studies indicate that automation of conformal treatment planning for spine metastases is feasible in terms of plan quality, target volume coverage and OAR sparing, and may introduce time-saving in the treatment planning process.

Here we describe the development of KBP for VMAT radiotherapy treatment planning of uncomplicated spine metastases using the RapidPlan (DVH Estimation Model Configuration version 15.6.06) module of Eclipse (*Varian Medical Systems, Palo Alto, California*). KBP uses prior knowledge from clinically acceptable treatment plans to predict achievable dose volume histograms (DVH) for new treatment plans using these achievable DVHs to define optimisation objectives [17].

Materials and Methods

A. Development of RapidPlan DVH Estimation model

The development of a RapidPlan KBP DVH estimation model is a two-stage process consisting of data extraction and model training [21].

A.1. Data Extraction

RapidPlan DVH estimation models described in the literature and used in the clinical environment are generally developed using a knowledge-base of clinically approved

and delivered radiotherapy treatment plans. As such, the models are curated to ensure that the treatment plans meet all the requirements of the clinical protocol. This includes patient positioning and immobilisation for imaging, target volume and OAR delineation, dose constraints, plan optimisation, plan review and radiotherapy treatment deliverability. In our institution uncomplicated spine metastases are treated with cEBRT, and therefore no VMAT radiotherapy treatment plans were available for the development of the RapidPlan KBP model. Data extraction from clinical data was therefore not an option. Instead, 20 CT image data sets of previously treated cEBRT spine metastases patients were retrospectively contoured and planned. The spinal vertebrae in the thoracic (T1-T12) and lumbar (L1-L5) regions were delineated and used to define clinical target volumes (CTVs), the spinal cord, oesophagus, heart, lungs, kidneys and cauda equina were delineated as OAR. 60 VMAT radiotherapy treatment plans were produced on these CT image data sets (n=20 in the mid thoracic T6-T8, n=20 in the lower thoracic T10-T12 and n=20 in the lumbar L2-L4 regions of the vertebral spine). These regions of the vertebral spine were selected as VMAT optimisation of dose distribution in these regions was particularly influenced by the presence of OAR (spinal cord, oesophagus, heart, lungs and kidneys in the mid thoracic to low thoracic regions, and spinal cord, kidneys and cauda equina in the low thoracic to lumbar regions). This was intentional in order to introduce plan heterogeneity into the model in terms of planning target volume (PTV) size and location and the varying influence of OAR on dose distribution. Additionally, while the CT image data sets provided imaging of the entire vertebral spine, patient positioning and immobilisation was highly variable across the datasets as these patients were treated with cEBRT introducing patient setup heterogeneity to the plans.

The CTV was delineated to include the vertebral body, left and right pedicles, left and right transverse processes and laminae and spinous process [22] of the affected vertebra, as well as the adjacent vertebrae above and below. This is in keeping with the aims of target volume coverage through field size definition in cEBRT. The PTV included a 5mm isotropic margin around the CTV excluding the spinal cord and cauda equina. Since PTVs are not delineated in cEBRT there were no established planning aims for PTV coverage. In cEBRT the aim is to ensure that the anterior aspect of the vertebral body is covered by the 80% isodose. For VMAT planning the International Commission on Radiation Units and Measurements (ICRU) aim of 95%-107% to the PTV was used for optimisation objectives [23].

OAR delineation followed the American Society for Radiation Oncology (ASTRO) consensus recommendations [24]. As OAR are not delineated for cEBRT and dose reporting therefore not provided, there were no established OAR dose constraints to use for optimisation and therefore optimisation was carried out with the aim of keeping the OAR dose as low as reasonably achievable and in keeping with the recommendations of UK consensus guidelines on normal tissue dose constraints for SABR [25] and the HyTEC organ specific guidelines for spinal cord [26, 27].

In keeping with our routine VMAT planning technique, all of the VMAT radiotherapy treatment plans were 6MV, single isocentre, two full rotation arc VMAT plans, with a fixed collimator angle and complement angle of 30° and 330° with jaw tracking. A normal tissue objective (NTO) and monitor unit (MU) objective (<1000MU per arc) were applied. The NTO was used in an attempt to improve dose conformity and constrain dose to the normal tissues that were not delineated. NTO is an optimisation objective used in Eclipse to vary the dose constraints spatially with respect to the PTV. An MU objective was applied in an attempt to limit the treatment time to be more in keeping with the treatment times achievable for cEBRT.

Dose distributions were calculated for the Varian TrueBeam linear accelerator with millennium 120 multi-leaf collimator (MLC) using Acuros External Beam version 13.6.23. All plans were normalised so the 100% isodose covered 50% of the target volume with a prescription of 8Gy in a single fraction.

A.2. Model Training

All 60 VMAT plans were used to train the DVH estimation model. PTV volumes ranged from 154.8 to 529.4cm^3 (mean=295.9cm^3). Model Analytics, a cloud-based tool developed by Varian Medical Systems to analyse RapidPlan DVH estimation models, provides information on each of the training plans and indicates where the plans do not fit the average for that of the model. Model Analytics indicated 3 of the 60 plans were potential outliers, suggesting that the dose homogeneity within the PTV seemed lower than average. The plans for the outliers were reviewed and found to remain clinically acceptable, therefore no further action was taken and the plans were not removed from the model. Figure 4.2 shows the DVH range for PTV coverage for the 60 VMAT plans used to train the model.

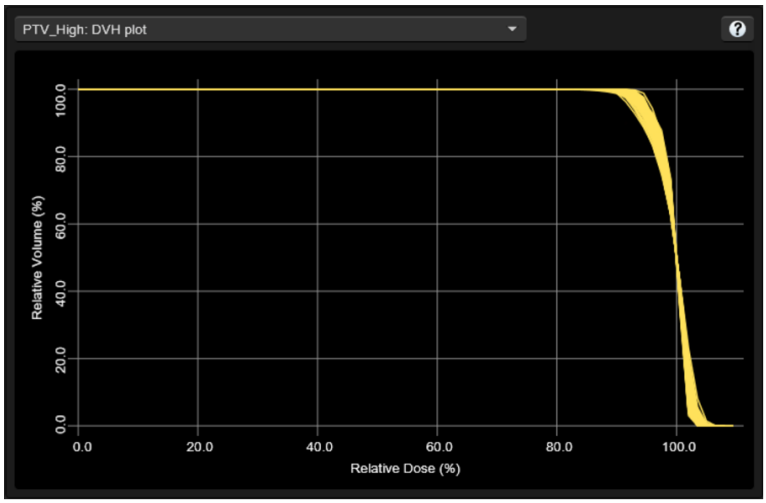

Figure 4.2: Screenshot from RapidPlan model configuration window showing the distribution of the PTV DVH for the 60 plans used in the model.

Figure 4.3 shows the DVH range for OAR and the residual plots for the 60 VMAT plans used to train the model (starting top to bottom: spinal cord, oesophagus, heart, lungs, kidneys and cauda equina).

The residual plots describe the relationship between the achieved OAR DVH and the predicted OAR DVH. Principal component analysis (PCA) is applied to the DVH for each OAR during model training. The residual plots illustrate how well the DVH estimation model fits the training data. The x axis is the first PCA score of the estimated DVH, and the y axis is the first PCA score of the actual DVH. Each data point shown in figure 4.3 represents a training plan in the model. If a data point is above the confidence interval identity line (dashed line in figure 4.3), it indicates the DVH for that OAR in that training plan is worse than expected, and if the data point is below it indicates it is better than expected.

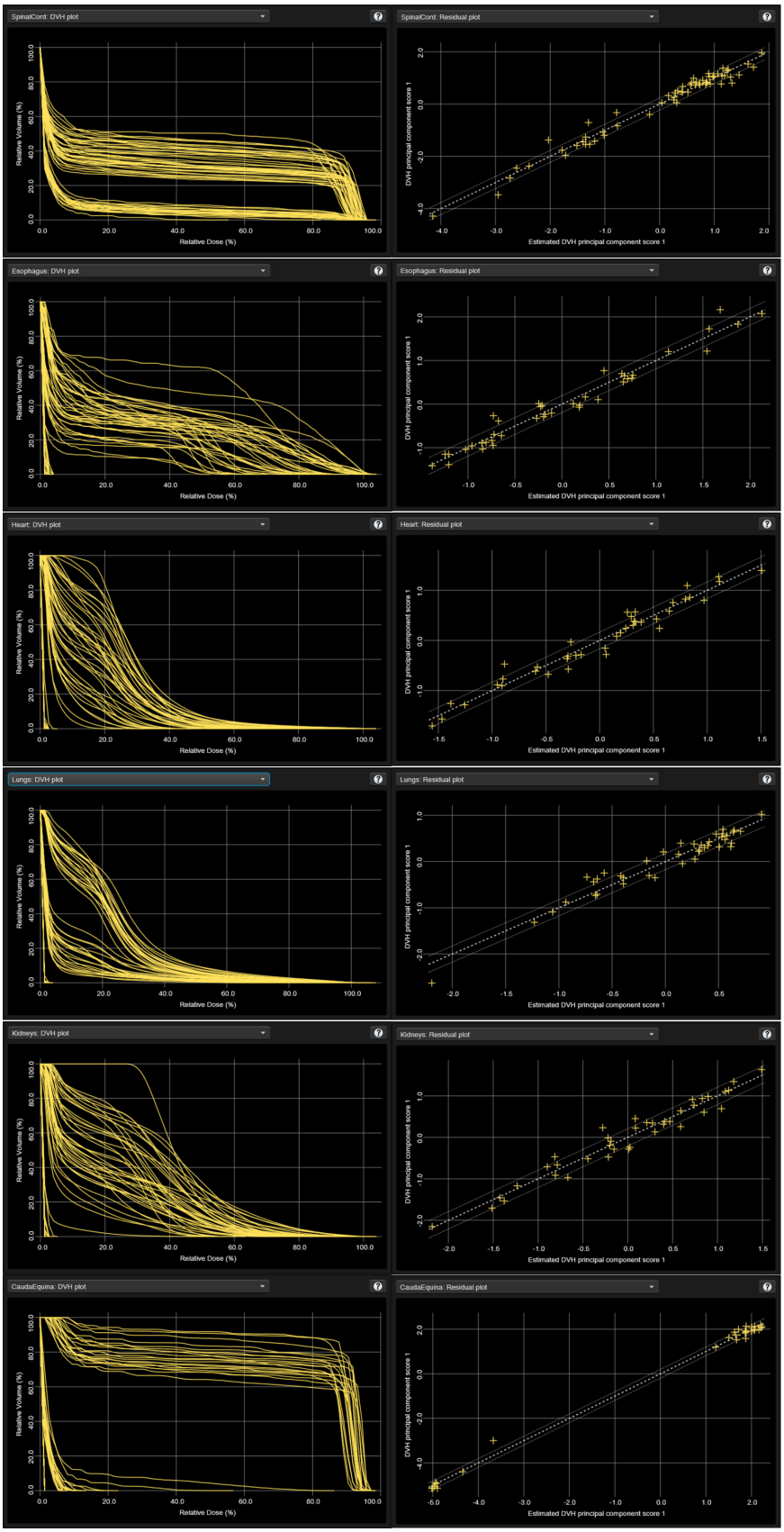

Figure 4.3: Screenshot from RapidPlan model configuration window showing the distribution of the OAR DVHs for the 60 plans used in the model and the residual plots (starting top to bottom: spinal cord, oesophagus, heart, lungs, kidneys and cauda equina).

OAR volumes for the oesophagus ranged from 7.1-27.4cm^3 (mean = 15.8cm^3), heart 495.8-1259.0cm^3 (mean = 671.7cm^3), kidneys 206.8-1902.0cm^3 (mean = 395.4cm^3), lungs 1634.1-3573.5cm^3 (mean = 2654.8cm^3), spinal cord 27.8-60.6cm^3 (mean = 40.0cm^3) and cauda equina 13.6-31.3cm^3 (mean = 21.1cm^3). For OAR volumes, Model Analytics indicated 5/60 plans were potential outliers for oesophagus, 2/60 plans for the heart, 2/60 for kidneys, 1/60 for lungs, 4/60 for the spinal cord and 1/60 for the cauda equina. This suggests that the geometry of the OAR differed from the majority, or that the OAR may distort the shape and position of the estimated DVHs. The plans for the outliers were reviewed and found to remain clinically acceptable, therefore no further action was taken and the plans were not removed from the model.

PTV and OAR volumes and dose for the 60 model plans are summarised in table 4.1.

Structure	Volume (cm^3)				Dose (Gy/% prescribed dose)			
	Mean	StDev	Minimum	Maximum	Mean	StDev	Minimum	Maximum
PTV (target)	295.9	98.8	154.8	529.4	7.90/98.7	0.01/0.14	7.87/98.4	7.92/99.0
Oesophagus	15.8	4.4	7.1	27.4	1.20/15.0	1.1/13.2	0/0	3.7/46.8
Heart	671.8	165.4	495.8	1259.0	0.82/10.2	0.8/9.4	0/0	2.3/28.6
Kidneys	395.4	357.0	206.8	1902.0	1.1/14.0	1.0/12.5	0/0	3.0/36.8
Lungs	2654.8	644.8	1634.1	3573.5	0.7/8.9	0.7/9.0	0/0	2.1/25.9
Spinal Cord	40.0	7.9	27.8	60.6	1.9/23.2	1.1/13.6	0.2/1.9	3.5/43.2
Cauda Equina	21.1	4.8	13.6	31.3	2.0/24.5	2.7/33.8	0/0	6.6/82.7

Table 4.1: PTV and OAR volumes and dose for the 60 plans used to train the RapidPlan DVH estimation model.

The objectives of the RapidPlan model for application to subsequent patients are shown in table 4.2. While all OAR in table 4.2 were used to train the DVH estimation model, hard constraints were placed on the spinal cord and cauda equina OAR, and their respective planning OAR volumes (PRV). A hard upper constraint of 7Gy on the spinal cord and cauda equina, and 7.5Gy on the PRV were set in the optimisation objectives as these are the dose limiting structures for treatment planning. The reasoning for this was to ensure that a Dmax of 8Gy would not be exceeded by any VMAT KBP plans generated by the model, as demonstrated in figures 4.5, 4.6 and 4.7.

Structure	Objective	Volume (%)	Dose	Priority
PTV (target)	Upper	0	100%	Generated
	Upper	50	100%	Generated
	Lower	100	100%	Generated
	Lower	50	100%	Generated
Oesophagus	Upper	0	8.00Gy	Generated
	Line (preferring target)	Generated	Generated	Generated
Heart	Upper	0	8.00Gy	Generated
	Line (preferring target)	Generated	Generated	Generated
Left Kidney	Upper	0	8.00Gy	Generated
Right Kidney	Upper	0	8.00Gy	Generated
Kidneys	Upper	0	8.00Gy	Generated
	Line (preferring target)	Generated	Generated	Generated
Left Lung	Upper	0	8.00Gy	Generated
Right Lung	Upper	0	8.00Gy	Generated
Lungs	Upper	0	8.00Gy	Generated
	Line (preferring target)	Generated	Generated	Generated
Spinal Cord	Upper	0	7.00Gy	Generated
Cauda Equina	Upper	0	7.00Gy	Generated
PRV	Upper	0	7.5Gy	Generated

Table 4.2: Optimisation objectives for the RapidPlan VMAT KBP model.

B. Knowledge-based planning validation

Validation of the DVH estimation model was carried out using a cross validation method. The 60 manually planned VMAT plans were randomly assigned into 3 folds. The RapidPlan model was retrained using the plans for the data sets in folds 1 and 2 (40 plans) and then tested on fold 3 (20 delineated CT images data sets), retrained again on folds 1 and 3 and tested on 2, and retrained again on 2 and 3 and tested on 1. Thus providing 60 scenarios for model validation. Cross validation is not widely used in RapidPlan model validation, with most researchers favouring train and test validation. Train and test validation ensures the trained model is not exposed to the test plans during the model training process and therefore the outcomes of the testing are indicative of the performance of the model. However, there is a risk of bias in models validated with train and test and the potential for inaccurate assumptions on model performance, when the models are generated with a small number of training plans. Cross validation was carried out as a preventative measure of this. Cross validation has the potential to overcome underfitting and overfitting to the model in these situations.

C. Plan evaluation and statistical analysis

DVH statistics were obtained for the RapidPlan VMAT KBP generated plans from cross validation and the manually planned VMAT plans used for training the RapidPlan DVH estimation model. For the target volumes, CTV and PTV, the parameters minimum dose (Dmin), maximum dose (Dmax) and mean dose (Dmean) were recorded. For OAR, the parameters Dmax and Dmean were recorded. Two-sample independent t-tests with a significance level of 0.05 were used to determine statistical significance for the difference in means between the cross validation VMAT KBP generated treatment plans and the plans used in the RapidPlan DVH estimation model training.

Results

Figure 4.4 shows the distribution of CTV and PTV, Dmin, Dmax and Dmean for the VMAT KBP generated plans for cross validation and the plans used in the DVH estimation model. The bottom and top of the box plots indicate the lower and upper quartiles, with the median value indicated by the band in between. The interquartile range is the height of the box. The mean value is indicated by a cross. Outliers (if the value is less than or more than 1.5 times the interquartile range) are indicated with a circle. The whiskers indicate the minimum and maximum values excluding the outliers.

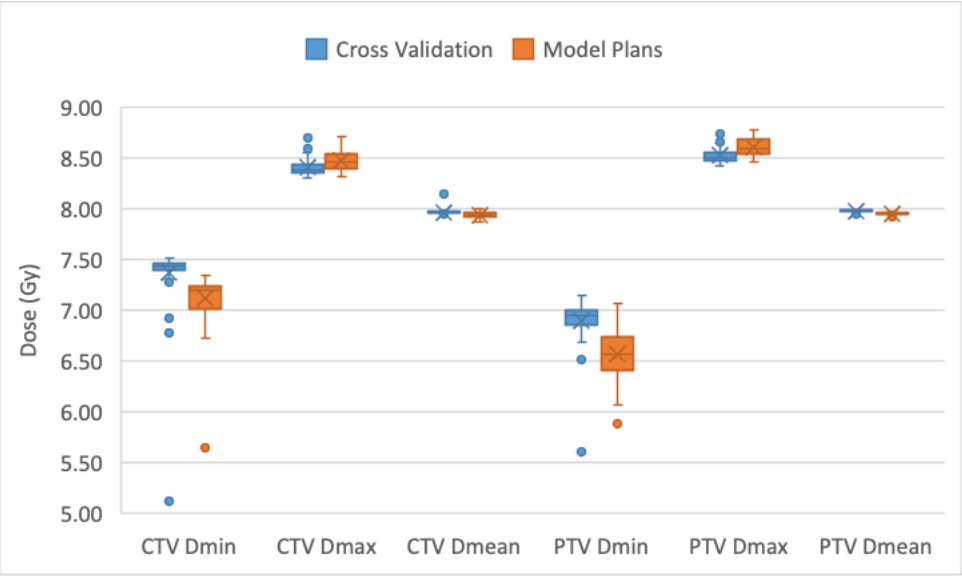

Figure 4.4: Distribution of CTV and PTV Dmin, Dmax and Dmean for the RapidPlan VMAT KBP generated plans for cross validation compared to the DVH estimation model plans.

The mean CTV Dmean dose was 7.97±0.03Gy (mean Dmin=7.37±0.32Gy and Dmax=8.40±0.08Gy) for the cross validation plans compared to a CTV Dmean of 7.94±0.03Gy (mean Dmin=7.12±0.24Gy and mean Dmax=8.47±0.09Gy) for the plans in the RapidPlan model. The mean PTV Dmean dose was 7.98±0.01Gy (mean Dmin=6.90±0.22Gy and Dmax=8.52±0.06Gy) for the cross validation plans compared to a PTV Dmean of 7.95±0.01Gy (mean Dmin=6.57±0.24Gy and Dmax 8.60±0.08Gy) for the plans in the RapidPlan model. This indicates that the RapidPlan model is capable of generating VMAT KBP treatment plans that meet the optimisation objectives of the model. The interquartile range, as indicated by the height of the box plot shown in figure 4.4, indicates that the VMAT KBP generated plans are more consistent than VMAT plans used to train the RapidPlan model. Additionally, the mean CTV Dmin and PTV Dmin for VMAT KBP generated plans used for cross validation is 92.1% and 86.3% of the prescribed dose respectively, which is greater that the cEBRT aim for coverage of the anterior vertebral body which is 80%, indicating that the target volume is covered to a higher dose than the aim of cEBRT.

Figures 4.5, 4.6 and 4.7 show the distribution of OAR Dmax and Dmean for the VMAT KBP generated plans for cross validation and the plans used in the DVH estimation model for the mid thoracic (T6-T8), lower thoracic (T10-T12) and lumbar (L2-L4) regions of the vertebral spine respectively.

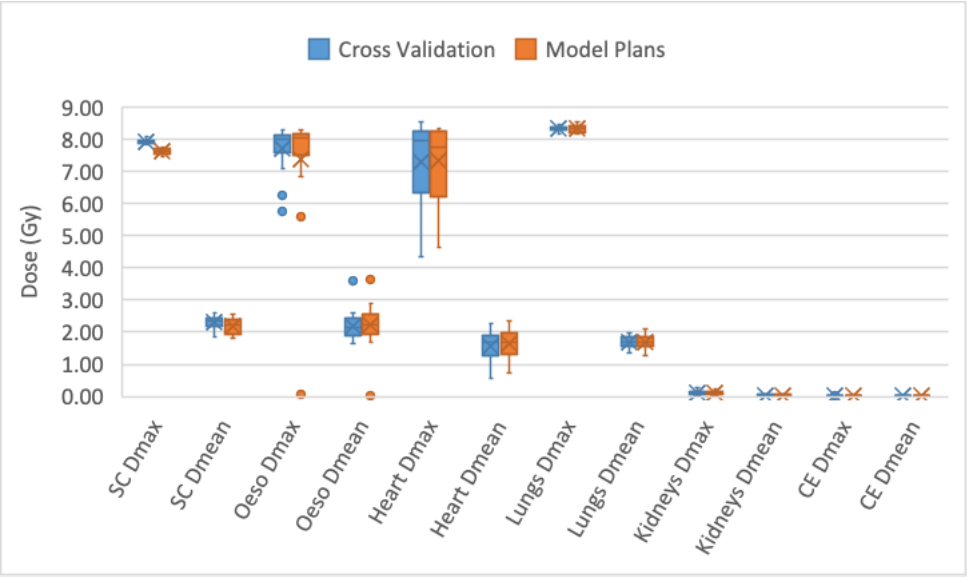

Figure 4.5: Distribution of OAR Dmax and Dmean for the RapidPlan VMAT KBP generated plans for cross validation compared to the DVH estimation model plans in the mid thoracic region of the vertebral spine.

In the mid thoracic region (T6-T8) the OAR in closest proximity to the PTV are the spinal cord, oesophagus, heart and lungs. There is a statistically significant difference ($p<0.01$) between the cross validation plans and the plans used to train the RapidPlan model for the spinal cord Dmax (7.93±0.07Gy and 7.63±0.09Gy), spinal cord Dmean (2.30±0.21Gy and 2.20±0.23Gy) and heart Dmean (1.58±0.44Gy and 1.64±0.45Gy). This indicates that the RapidPlan generated VMAT KBP plans results in higher dose (Dmax and Dmean) to the spinal cord compared to those plans used to generate the RapidPlan model. However, the spinal cord Dmax for VMAT KBP generated plans used for cross validation is 99.1% of the prescribed dose, which is less that the cEBRT aim for dose prescription which is 100%, indicating that the mean Dmax to the spinal cord is less than the prescription limit for cEBRT. However, a lower Dmean dose to the heart is achieved through RapidPlan VMAT KBP.

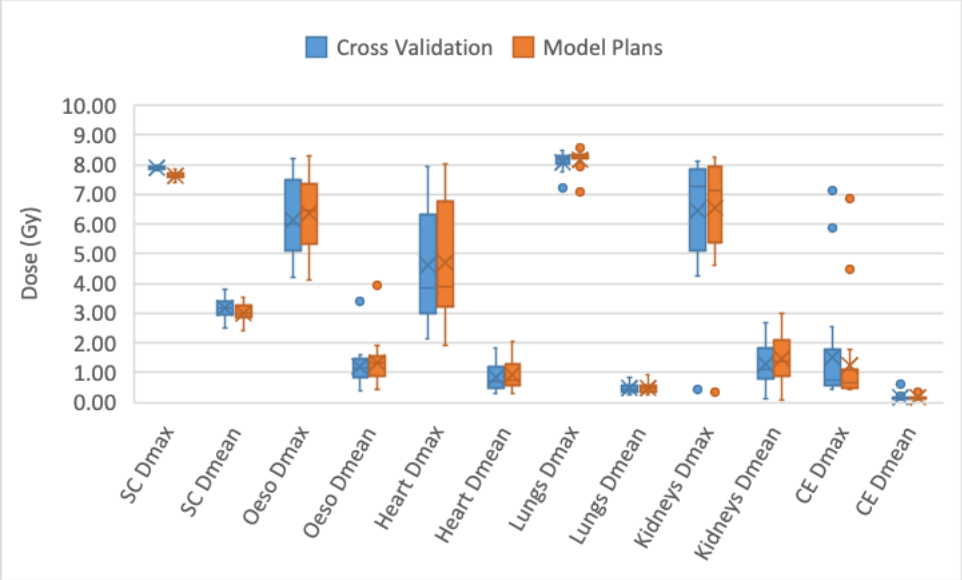

Figure 4.6: Distribution of OAR Dmax and Dmean for the RapidPlan VMAT KBP generated plans for cross validation compared to the DVH estimation model plans in the lower thoracic region of the vertebral spine.

In the lower thoracic region (T10-T12) the OAR in closest proximity to the PTV are the spinal cord, oesophagus, heart, lungs and kidneys. There is a statistically significant difference between the cross validation plans and the plans used to train the RapidPlan model for the spinal cord Dmax (7.89±0.05Gy and 7.63±0.10Gy), spinal cord Dmean (3.18±0.10Gy and 3.01±0.30Gy), oesophagus Dmax (6.13±1.31Gy and 6.38±1.23Gy), oesophagus Dmean (1.21±0.62Gy and 1.36±0.73Gy), heart Dmean (0.85±0.43Gy and 0.91±0.47Gy), lungs Dmean

(0.47±0.16Gy and 0.50±0.18Gy) and kidneys Dmean (1.28±0.70Gy and 1.45±0.79Gy). This indicates that the RapidPlan generated VMAT KBP plans results in higher dose (Dmax and Dmean) to the spinal cord and cauda equina compared to those plans used to generate the RapidPlan model. However, as with the spinal cord Dmax in the mid thoracic region for VMAT KBP generated plans used for cross validation is lower at 98.6% than the prescription tolerance for cEBRT of 100%. The Dmax and Dmean dose for the oesophagus OAR, and the Dmean doses for the heart, lungs and kidneys OARs are lower for the RapidPlan VMAT KBP plans than the plans used to generate the model, indicating that the model better spares these structures compared to the manual plans that formed the RapidPlan model.

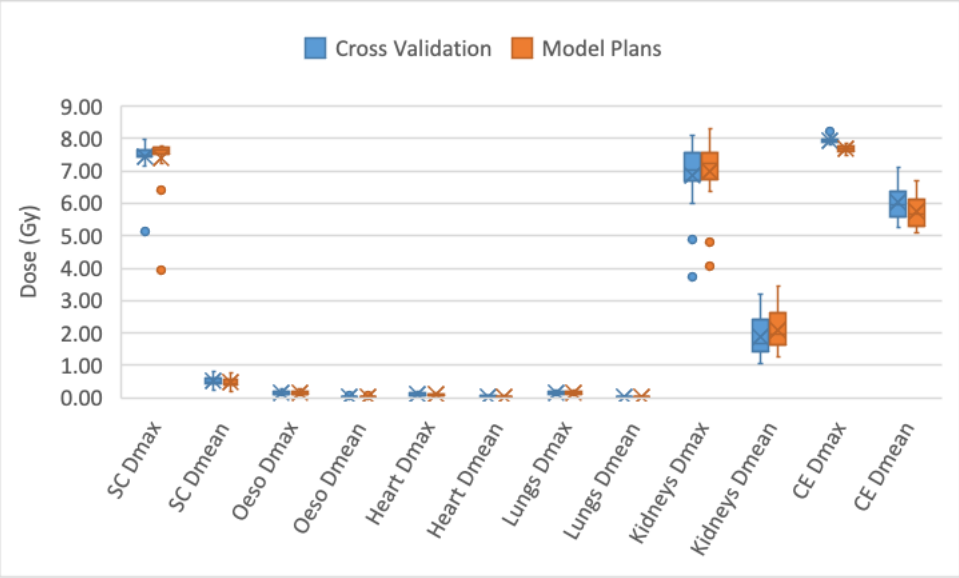

Figure 4.7: Distribution of OAR Dmax and Dmean for the RapidPlan VMAT KBP generated plans for cross validation compared to the DVH estimation model plans in the lumbar region of the vertebral spine.

In the lumbar region (L2-L4) the OAR in closest proximity to the PTV are the kidneys and cauda equina. There is a statistically significant difference between the cross validation plans and the plans used to train the RapidPlan model for the cauda equina Dmax (7.94±0.09Gy and 7.68±0.10Gy), cauda equina Dmean (6.03±0.54Gy and 5.75±0.51Gy) and kidneys Dmean (1.88±0.61Gy and 2.10±0.60Gy). This indicates that the RapidPlan generated VMAT KBP plans result in higher dose (Dmax and Dmean) to the cauda equina compared to those plans used to generate the RapidPlan model. However, a lower Dmean dose to the kidneys is achieved through RapidPlan VMAT KBP.

Region		Mid Thoracic					Lower Thoracic					Lumbar				
OAR		Mean (Gy)	SD	95% Confidence Interval		p	Mean (Gy)	SD	95% Confidence Interval		p	Mean (Gy)	SD	95% Confidence Interval		p
				Lower	Upper				Lower	Upper				Lower	Upper	
SC Dmax	Cross Validation	7.93	0.07	7.90	7.96	<0.01	7.89	0.05	7.87	7.91	<0.01	7.42	0.57	7.17	7.67	0.70
	Model Plans	7.63	0.09	7.59	7.67		7.63	0.10	7.59	7.68		7.38	0.87	7.00	7.77	
SC Dmean	Cross Validation	2.30	0.21	2.21	2.39	<0.01	3.18	0.10	3.04	3.33	<0.01	0.51	0.13	0.45	0.57	<0.01
	Model Plans	2.20	0.23	2.10	2.30		3.01	0.30	2.88	3.15		0.47	0.13	0.41	0.53	
Oeso Dmax	Cross Validation	7.73	0.68	7.43	8.02	0.38	6.13	1.31	5.56	6.71	0.01	0.15	0.07	0.12	0.18	<0.01
	Model Plans	7.40	1.84	6.59	8.21		6.38	1.23	5.84	6.92		0.14	0.06	0.12	0.17	
Oeso Dmean	Cross Validation	2.21	0.43	2.02	2.39	0.98	1.21	0.62	0.94	1.49	<0.01	0.04	0.02	0.03	0.05	0.02
	Model Plans	2.21	0.68	1.91	2.51		1.36	0.73	1.03	1.68		0.04	0.02	0.03	0.04	
Heart Dmax	Cross Validation	7.31	1.24	6.77	7.85	0.74	4.61	1.86	3.79	5.42	0.25	0.11	0.06	0.09	0.14	0.19
	Model Plans	7.34	1.13	6.85	7.83		4.72	1.90	3.89	5.55		0.10	0.03	0.08	0.11	
Heart Dmean	Cross Validation	1.58	0.44	1.39	1.77	<0.01	0.85	0.43	0.66	1.04	<0.01	0.05	0.01	0.04	0.05	0.11
	Model Plans	1.64	0.45	1.44	1.83		0.91	0.47	0.70	1.11		0.04	0.01	0.04	0.05	
Lungs Dmax	Cross Validation	8.32	0.07	8.29	8.35	0.89	8.09	0.35	7.93	8.24	0.05	0.16	0.06	0.14	0.19	0.09
	Model Plans	8.32	0.11	8.28	8.33		8.16	0.38	7.90	8.32		0.16	0.06	0.13	0.19	
Lungs Dmean	Cross Validation	1.69	0.18	1.61	1.77	0.49	0.47	0.16	0.40	0.55	0.01	0.03	0.01	0.03	0.03	0.02
	Model Plans	1.70	0.22	1.61	1.80		0.50	0.18	0.42	0.58		0.03	0.01	0.02	0.03	
Kidneys Dmax	Cross Validation	0.11	0.05	0.09	0.14	0.31	6.45	1.94	5.60	7.30	0.29	6.87	1.04	6.42	7.33	0.19
	Model Plans	0.11	0.05	0.09	0.14		6.55	1.89	5.72	7.38		7.00	1.04	6.54	7.46	
Kidneys Dmean	Cross Validation	0.04	0.01	0.03	0.04	0.58	1.28	0.70	0.98	1.59	<0.01	1.88	0.61	1.61	2.14	<0.01
	Model Plans	0.04	0.01	0.03	0.04		1.45	0.79	1.10	1.80		2.10	0.60	1.84	2.37	
CE Dmax	Cross Validation	0.03	0.01	0.03	0.04	0.17	1.53	1.82	0.73	2.32	<0.01	7.94	0.09	7.90	7.98	<0.01
	Model Plans	0.03	0.01	0.03	0.04		1.26	1.60	0.56	1.96		7.68	0.10	7.64	7.73	
CE Dmean	Cross Validation	0.01	0.01	0.01	0.02	0.14	0.19	0.13	0.13	0.24	0.02	6.03	0.54	5.80	6.27	<0.01
	Model Plans	0.01	0.01	0.01	0.01		0.17	0.10	0.12	0.21		5.75	0.51	5.52	5.97	

Table 4.3: OAR dosimetric statistics for the VMAT KBP generated plans for cross validation compared to the DVH estimation model plans.

Table 4.3 shows the OAR dosimetric statistics for the RapidPlan VMAT KBP generated plans for cross validation compared to the DVH estimation model plans, $p<0.05$ indicating a statistically significant difference. Where $p>0.05$ there is no statistically significant difference between the cross validation plans and the plans used to train the RapidPlan model and therefore the optimisation objectives of the

RapidPlan DVH estimation model have been met and comparable to that achieved in the manual VMAT plans that were used to train the model.

Figure 4.8 shows an example of a RapidPlan KBP generated VMAT treatment plan for spine metastases.

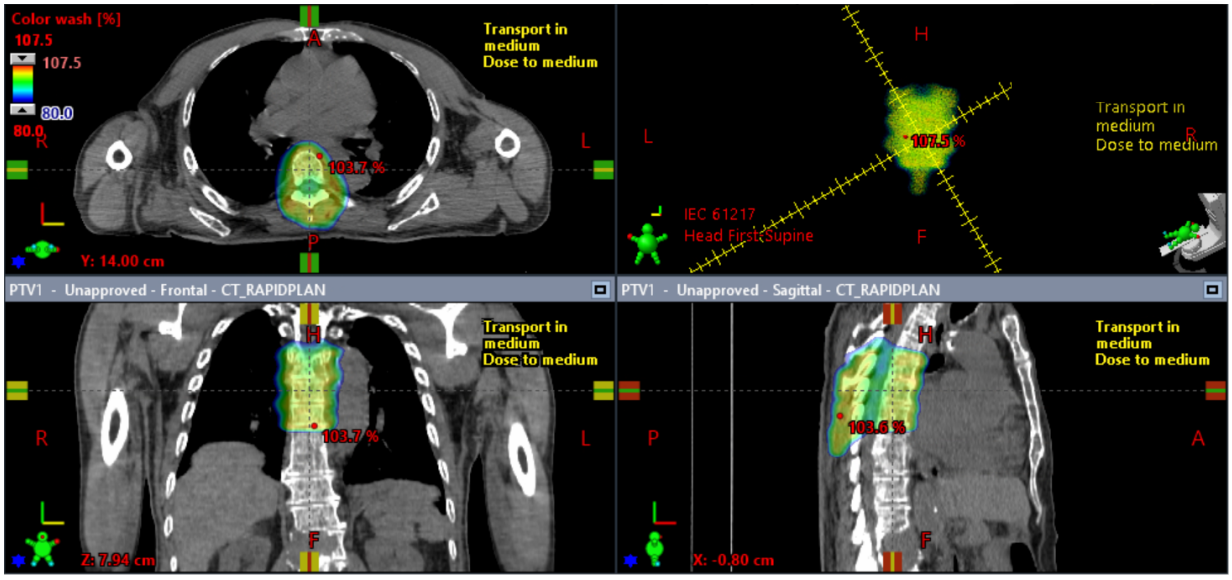

Figure 4.8: An example of a RapidPlan KBP generated VMAT treatment plan for spine metastases.

Discussion

The results indicate that this RapidPlan DVH estimation model for VMAT KBP of uncomplicated spine metastases can be used to generate RapidPlan KBP generated VMAT treatment plans. The RapidPlan VMAT KBP plans have more consistency between individual plans than that achieved with the manual VMAT planning for model training. This is shown by the reduced interquartile range, as indicated by the height of the box in figure 4.4. The results indicate that the RapidPlan DVH estimation model is stable for mid thoracic to lumbar PTVs. The CT image datasets and PTVs were intentionally generated for a heterogenous patient population in terms of patient setup, PTV size and location (T6-L5) and OAR geometry with respect to the PTV location, with varying locations and sizes of OAR. The cross validation showed that the model was stable across these regions and there was no requirement to refine the model further. Additional work is required to establish if the model is stable for the thoracic regions T1-T5.

The treatment plan outliers were not removed or replanned from the model. Removal of outliers would reduce the number of plans in the model, which in theory

could decrease the robustness of the model. As the outlier treatment plans were considered clinically acceptable they were left in the model. Model analytics indicated that the outliers for PTV were due to dose homogeneity within the PTV being lower than the average, while outliers for OAR were due to the geometry of the OAR differing from the majority, or that the OAR might distort the shape and position of the estimated DVHs.

The RapidPlan KBP generated VMAT treatment plans were of sufficient clinical quality for mid thoracic to lumbar PTVs. CTV and PTV Dmin coverage was 92.1% and 86.3% of the prescribed dose respectively, which is greater that the cEBRT aim for target volume coverage, which is to ensure the 80% isodose covers the anterior vertebral body (and therefore the most anterior aspect of the CTV). This indicates that the target volume is covered to a higher dose with RapidPlan VMAT KBP than the aim of cEBRT, although this requires additional work to confirm. The mean CTV Dmean dose was 99.6% of the prescribed dose (mean Dmin=92.1%, mean Dmax=105.0%). The mean PTV Dmean dose was 99.8% of the prescribed dose (mean Dmin=86.3%, mean Dmax=106.5%). There was no statistically significant difference in homogeneity or conformity of dose distribution between the cross validation plans and model plans shown in figure 4.4 through to 4.7. This indicates that the RapidPlan model is capable of generating VMAT KBP treatment plans that meet the optimisation objectives of the model, although the Dmin dose does not meet the ICRU aim for radiotherapy of greater than 95% of the prescribed dose (ICRU, 2010). This may be due to the proximity of the transverse processes and laminae, and spinous process to the posterior skin surface, or the presence of close proximity OAR, this requires further investigation.

The spinal cord and cauda equina are the dose-limiting OAR for uncomplicated spine metastases. The aim of cEBRT is to not exceed a Dmax dose of 8Gy to either of these structures, none of the RapidPlan KBP generated VMAT treatment plans exceeded this. This indicates that the RapidPlan KBP generated VMAT treatment plans were able to meet the dose constraint for the spinal cord and cauda equina. Comparison with cEBRT is required to determine which technique results in the lowest dose to these OAR.

OAR dose to spinal cord, oesophagus, heart, lungs, kidneys and cauda equina for conformal radiotherapy prescribed to 8Gy in 1 fraction meets the recommendations of UK consensus guidelines on normal tissue dose constraints for SABR [25] and the HyTEC organ specific guidelines for spinal cord [26, 27]. Further analysis of the

DVH estimation model is required to determine if the model is capable of equivalent OAR dose compared to cEBRT. In particular with respect to the dose to the kidneys. It is expected cEBRT will result in a lower dose to kidneys than VMAT, due to the nature of treatment delivery. VMAT results in a low dose bath that will envelop the kidneys if they are in the vicinity of the PTV, whereas cEBRT will not, additionally in cEBRT there is an active attempt to shield kidney with MLC.

The results indicated a stable model for RapidPlan VMAT KBP of sufficient quality for mid thoracic to lumbar CTVs for this energy and beam geometry combination.

Conclusion

The RapidPlan DVH estimation model for VMAT KBP of uncomplicated spine metastases can be used to generate consistent RapidPlan KBP generated VMAT treatment plans of sufficient quality for mid thoracic to lumbar PTVs. This provides an automated optimisation solution for conformal radiotherapy treatment planning.

Conflict of Interest

This work was partly funded by Varian Medical Systems.

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5. Manuscript 3

The aim of this research was to develop and evaluate a comprehensive automated workflow for VMAT treatment planning of uncomplicated spine metastases using ABAS and KBP. The automated workflow developed uses SmartSegmentation ABAS for auto-segmentation of target volumes and OAR (see chapter 3) and RapidPlan KBP for automated VMAT treatment planning (see chapter 4). This proffered manuscript describes the application of ABAS and KBP for VMAT of uncomplicated spine metastases and provides dosimetric evaluation of the automated approach compared to cEBRT.

5.1. Introduction To Manuscript

This manuscript was written with the aim of submission as an original article for publication in Practical Radiation Oncology. The guidance for authors was followed. The mission of this journal is to improve the quality of radiation oncology practice and the editors strive to provide readers with content that emphasises knowledge with a purpose and as such this is an appropriate journal to target for publication of this work.

Despite cEBRT being readily utilised to treat uncomplicated spine metastases (Gerszten *et al*, 2009) it has been argued that the most advanced radiotherapy techniques should be available (Rief *et al*, 2014). Currently the use of advanced radiotherapy techniques for this cohort of patients is not feasible in the clinical environment due to technically demanding and labour intensive treatment planning (Westhoff *et al*, 2018). Automated approaches using ABAS and KBP have the potential to facilitate this in the future (Buergy *et al*, 2017; Mian *et al*, 2016; Younge *et al*, 2018; Foy *et al*, 2017). A fully automated approach to auto-segmentation and treatment planning for uncomplicated spine metastases has not been reported in the literature. As such this manuscript will add to the body of knowledge.

5.2. Manuscript 3 - Dosimetric Evaluation of Automated Treatment Planning of Spine Metastases Using Atlas-Based Auto-Segmentation and Knowledge-Based Planning Approaches

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Keywords: automation, atlas-based auto-segmentation, knowledge-based planning, RapidPlan, spine metastases

Abstract

Purpose: Uncomplicated spine metastases are routinely treated with conventional external beam radiotherapy (cEBRT). In cEBRT, there is no delineation of target volumes or organs at risk (OAR), or attempt to optimise dose distribution to deliver conformal, homogeneous dose distributions with sparing of OAR. Atlas-based auto-segmentation (ABAS) for target volume and OAR delineation, followed by knowledge-based planning (KBP) could facilitate conformal planning and dose reporting of spine metastases.

Materials and Methods: ABAS using SmartSegmentation for delineation of thoracic and lumbar veterbrae, and OAR in their vicinity, provided target volumes and OAR for conformal treatment planning. 30 volumetric-modulated arc therapy (VMAT) treatment plans were produced using RapidPlan KBP. Plans produced using this automated approach were compared to the equivalent cEBRT treatment plans.

Results: Target volume coverage for RapidPlan VMAT generated plans was superior to cEBRT. PTV Dmean=7.86±0.16Gy, Dmin=3.46±1.79Gy, Dmax=8.56±0.05Gy for RapidPlan VMAT compared to Dmean=7.78±0.24Gy,

Dmin=1.83±1.08Gy, Dmax=10.46±0.41Gy for cEBRT. With homogeneity index and conformity index 0.236±0.215 and 1.201±0.121 respectively for RapidPlan VMAT compared to 0.508±0.137 and 1.789±0.437 for cEBRT. Dose to dose-limiting OAR spinal cord and cauda equina was reduced for RapidPlan VMAT, with Dmax of 7.91±0.16Gy and 7.94±0.13Gy respectively compared to 8.67±0.13Gy and 8.90±0.16Gy for cEBRT.

Discussion: RapidPlan VMAT KBP was superior to cEBRT in terms of target coverage, homogeneity and conformity and was achievable in a clinically acceptable time, with improved sparing of the spinal cord and cauda equina.

Conclusion: Implementation of automated treatment planning for uncomplicated spine metastases is feasible in the clinical environment with superior plan quality compared to cEBRT.

Introduction

Uncomplicated spine metastases are painful bone metastases unassociated with impending or existing pathologic fracture or existing metastatic spinal cord compression [1]. They are a common feature of advanced-stage malignancies [2], primarily occurring in the vertebral body of the spine [3] with an approximate distribution of 70%, 20% and 10% in the thoracic, lumbar and cervical regions respectively [4]. They result in considerable morbidity and can cause severe and debilitating effects.

Conventional external beam radiotherapy (cEBRT), applied or parallel-opposed, unmodulated fields, with little to no sparing of organs at risk (OAR), is a widely used and established technique for radiotherapeutic palliation of uncomplicated spine metastases [5]. cEBRT is delivered as 8Gy in 1 fraction, 20Gy in 5 fractions, or 30Gy in 10 fractions [6]. A number of randomised controlled trials, and subsequent systematic reviews and meta-analyses, have shown that there is no significant difference in the efficacy of cEBRT for pain relief between the three fractionation regimes [7, 8, 9, 10]. But despite considerable research on dose and fractionation, few studies have considered prescription depth and heterogeneity of dose across the target volume [11]. However, it has been suggested that the re-irradiation rate for recurrent pain post-cEBRT is 20% following a single fraction regime compared to 8% following a multi-fraction regime [12], but the relationship between re-irradiation rate and target volume coverage has not been investigated [13].

Advances in radiotherapy treatment planning and delivery such as intensity-modulated radiotherapy (IMRT), volumetric-modulated arc therapy (VMAT) and in particular stereotactic ablative body radiotherapy (SABR) are beginning to be utilised for treatment of uncomplicated spine metastases, albeit without evidence of superior outcome [14]. However, implementation of these advanced techniques is challenging in the clinical environment due to technically demanding and labour intensive treatment planning [15] compared to cEBRT. In recent years automated approaches to reduce the labour intensive nature of treatment planning have been steadily gaining momentum [16].

Automated approaches for VMAT and SABR treatment planning for uncomplicated spine metastases have been described [14, 17, 18, 19]. VMAT using an *a priori* multi-criteria optimisation approach with Erasmus-iCycle produced clinically acceptable treatment plans which demonstrated superior target volume coverage and some improvement in OAR sparing over manually produced VMAT treatment plans [14]. SABR using an in-house developed inverse planning script with Pinnacle [17] and also using knowledge-based planning (KBP) with Eclipse RapidPlan [18, 19] both demonstrated that automated treatment planning approaches resulted in significant time-saving over manual treatment planning. The Pinnacle script provided dosimetrically reasonable plans even though they were inferior when compared to manually produced treatment plans in terms target volume coverage [17]. Whereas those generated using RapidPlan were found to be clinically superior to manual treatment plans in terms of target volume coverage and sparing of OAR [18, 19]. These studies compared automated treatment planning approaches with manual treatment planning approaches, with manually delineated target volumes and OAR, for the same treatment technique.

Here we evaluate the feasibility of automation of the entire treatment planning process for VMAT of uncomplicated spine metastases, using model-based atlas-based auto-segmentation (ABAS) for target volume and OAR delineation followed by model-based knowledge-based planning (KBP) for treatment planning, as shown in figure 5.1.

ABAS uses an atlas of previously delineated target volumes and OAR on reference images to inform delineation of the same structures on anatomically similar, new images [20]. Here we use an atlas of previously delineated thoracic and lumbar vertebrae and OAR in the vicinity of the thoracic and lumbar regions (heart, oesophagus, lungs, kidneys, spinal cord and cauda equina) to perform ABAS on

new computed tomography (CT) image data sets using SmartSegmentation (Knowledge Based Contouring version 15.5) (*Varian Medical Systems, Palo Alto, California*). SmartSegmentation determines the location of structures using advanced image analysis of Hounsfield unit (HU) gradients in the CT data set followed by deformable image registration against the most similar reference image in the atlas [21]. KBP uses prior knowledge from clinically acceptable treatment plans [16]. Here we use a single centre RapidPlan (DVH Estimation Model Configuration version 15.6.06) (*Varian Medical Systems, Palo Alto, California*) DVH estimation model to predict achievable dose volume histograms (DVH) on new CT image data sets for structures generated with ABAS, using these achievable DVHs to define optimisation objectives.

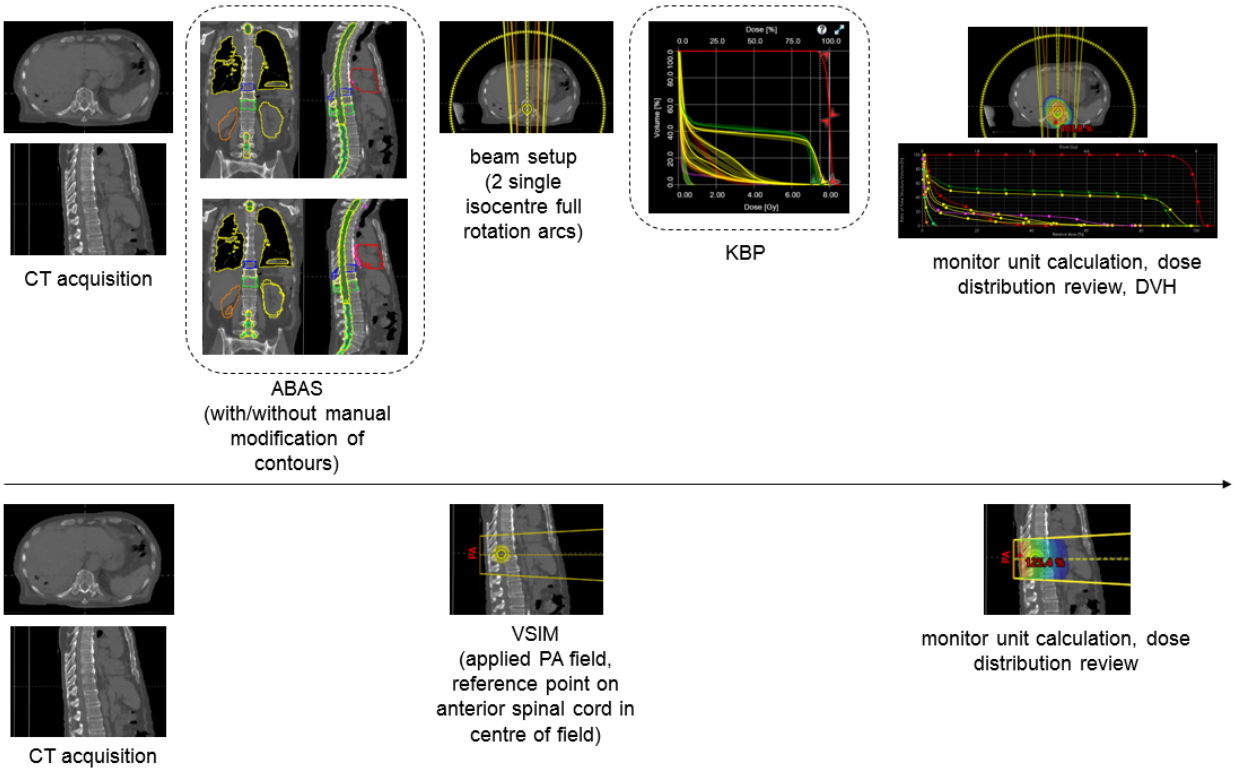

Figure 5.1: Automated workflow for VMAT of uncomplicated spine metastases (top) compared with workflow for cEBRT (bottom).

We describe how ABAS and KBP can be used to automate VMAT treatment planning for uncomplicated spine metastases and improve plan quality by providing superior target volume coverage and dose homogeneity over cEBRT.

Materials and Methods

A. Atlas-Based Auto-Segmentation

SmartSegmentation using a 16 reference image atlas was applied to 10 randomly selected CT image data sets from patients, 3 female and 7 male) previously treated with cEBRT in our institution for uncomplicated spine metastases. All thoracic (T1-T12) and lumbar (L1-L5) vertebrae, as well as the heart, oesophagus, kidneys, spinal cord and cauda equina were auto-segmented using ABAS, lungs were auto-segmented using automatic image segmentation (IS) with thresholding. Patient positioning and immobilisation was variable across the CT data sets with all patients imaged head first supine, typically with the head resting on blocks and/or wedges, with soft mats placed under the thorax and/or pelvis for patient comfort and using knee and foot support.

In cEBRT it is standard to treat not only the affected vertebra, but also the adjacent vertebrae above and below. Clinical target volume (CTV) was defined as the combination of three adjacent vertebrae. The approximate regions of the thoracic and lumbar vertebral spine where OAR involvement was greatest, due to the locations of the OAR with respect to the thoracic and lumbar vertebrae and beam geometry, were from mid thoracic level to lumbar level. Therefore 3 CTVs (mid thoracic T6-T8, lower thoracic T10-T12 and lumbar L2-L4) were defined for each patient to provide 3 planning scenarios per CT image data set (30 in total). The ABAS generated CTVs, and OAR were not modified in any way prior to RapidPlan treatment plan generation, but vertebrae were reviewed to ensure no vertebrae had been misidentified, where misidentification occurred vertebrae were renamed but not modified. Figure 5.2 shows an example of ABAS in the 3 regions.

An isotropic margin of 5mm was added to the CTV to generate planning target volume (PTV). The mean volume of PTV volumes were 229.0±43.4cm^3, 332.1±37.9cm^3 and 423.3±68.6cm^3 for T6-T8, T10-T12 and L2-L4 respectively. An isotropic margin of 3mm was also applied to the spinal cord and cauda equina structures to provide a planning OAR volume (PRV) for dose reporting and to drive any hot spots away from the PRV of the OAR and into the PTV.

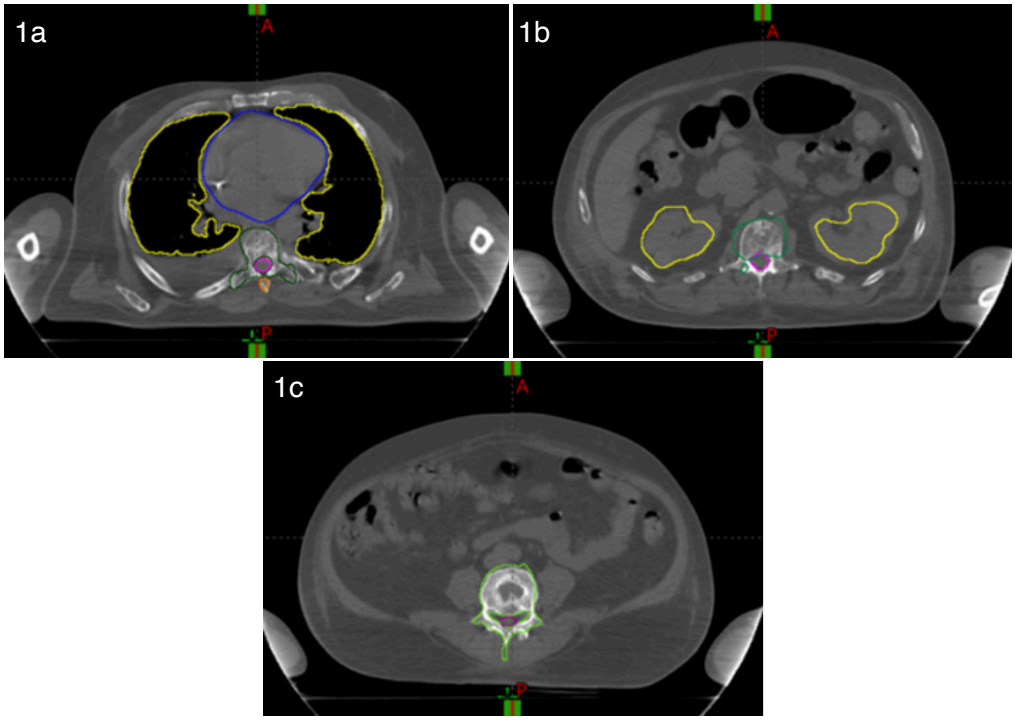

Figure 5.2: Example of ABAS of vertebrae and OAR in the mid thoracic (1a), lower thoracic (1b) and lumbar (1c) regions.

B. Knowledge-Based Planning

RapidPlan was applied to the 30 ABAS delineated CT datasets (10 PTVs in each of the mid thoracic, lower thoracic and lumbar regions) using a DVH estimation model consisting of 60 treatment plans for PTVs in the thoracic and lumbar region of the vertebral spine, with OAR of heart, lungs, oesophagus, kidneys, spinal cord and cauda equina. OAR determination and delineation followed consensus guidelines [22]. All plans generated were 6MV, single isocentre, two full rotation arc VMAT plans, with a fixed collimator angle and complement angle of 30° and 330° and jaw tracking, a normal tissue objective (NTO) and monitor unit objective (<1000MU per arc) were applied. Dose distributions for both the RapidPlan generated VMAT plans and the cEBRT plans were calculated for a Varian TrueBeam linear accelerator with millennium 120 multi-leaf collimator (MLC) using Acuros External Beam version 13.6.23 (*Varian Medical Systems, Palo Alto, California*). All plans were normalised so 100% isodose covered 50% of the target volume.

Following VMAT RapidPlan generation on structures generated with ABAS, the structures were manually modified to determine PTV dose coverage and dose to OAR for the true PTV and OAR structures. For comparison, cEBRT treatment planning was carried out through virtual simulation (VSIM). A 6MV single, applied,

posterior field was produced, prescribed to a reference point on the anterior spinal cord in the centre of the field. Field width and length were chosen to ensure coverage of the vertebrae. Manual MLC shielding was applied to shield kidneys if present in the field. Both VMAT and cEBRT were planned for 8Gy in 1 fraction. A dosimetric evaluation of PTV coverage and OAR dose was carried out. The following metrics were used to evaluate the quality of the treatment plans and determine the dosimetric difference between RapidPlan VMAT KBP and cEBRT for spine metastases, minimum dose (Dmin), maximum dose (Dmax), and mean dose (Dmean) to PTV, PTV homogeneity index (HI) and PTV conformity index (CI).

HI is a method of quantitatively describing dose homogeneity in the PTV and is calculated using (D2%-D98%)/ D50%, where D2%, D98% and D50% are the doses received by the 2%, 98% and 50% volumes of the PTV. The ideal value for HI is 0, indicating total homogeneity of dose across the PTV, with HI increasing as homogeneity decreases [23]. CI is a method of quantitatively describing conformity between the isodose distribution and the PTV volume and is calculated using V95%/ VPTV, where V95% is the volume of the 95% isodose and VPTV is the volume of the PTV. The ideal value of CI is 1, indicating total conformity of the 95% isodose to the PTV volume, with CI increasing as conformity decreases [24]. Dose to OAR was determined from DVH parameters, Dmax for serial OAR and Dmean for parallel OAR, both Dmean and Dmax was determined for OAR exhibiting both parallel and serial like behaviour.

Two-sample independent t-tests with a significance level of 0.05 were used to determine statistical significance for difference between means for RapidPlan VMAT KBP and cEBRT comparison.

The time to generate the treatment plans and calculate the dose distribution using RapidPlan was compared to the time taken to create a VSIM single applied field, with manual MLC shielding of kidneys where appropriate and calculate the dose distribution.

Results

Figure 5.3 shows the distribution of PTV Dmin, Dmax and Dmean, as well the distribution of HI and CI for the 30 RapidPlan VMAT KBP plans on ABAS generated PTV (T6-T8, T10-T12 and L2-L4) and OAR structures. The bottom and top of the box plots indicate the lower and upper quartiles, with the median value indicated by the band in between. The interquartile range is the height of the box. Outliers,

where present, are indicated with a circle, an outlier is considered as such if the value is less than or more than 1.5 times the interquartile range. The mean value is indicated by a cross. The whiskers indicate the minimum and maximum values excluding the outliers.

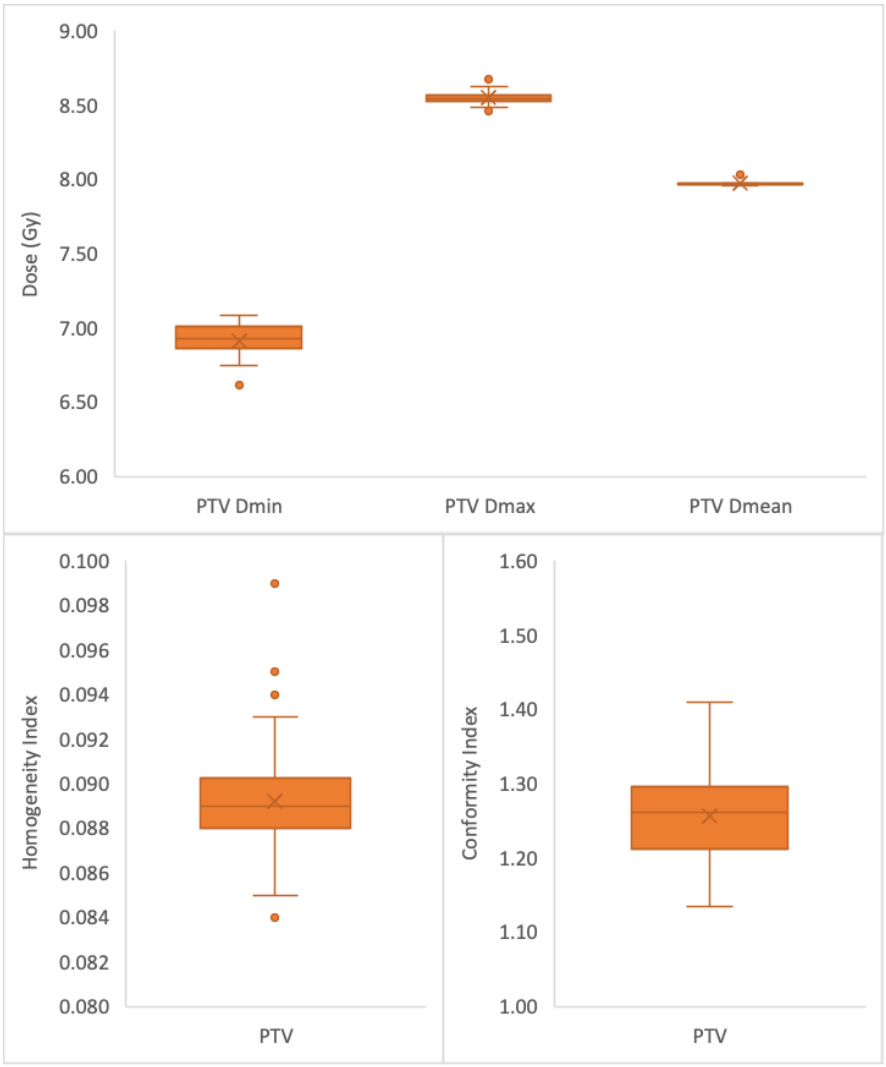

Figure 5.3: Distribution of PTV Dmin, Dmax and Dmean of RapidPlan VMAT plans (n=30) for thoracic and lumbar PTVs (n=10 T6-T8, n=10 T10-T12 and n=10 L2-L4), and distribution of PTV HI and PTV CI for ABAS generated PTV.

The mean PTV Dmean dose was 7.97±0.01Gy (mean Dmin=6.91±0.12Gy and Dmax=8.55±0.05Gy). The mean HI and mean CI were 0.089±0.003 and 1.257±0.219 respectively. Figure 5.4 shows a RapidPlan VMAT (left) and cEBRT (right) example isodose distribution for the same mid thoracic PTV.

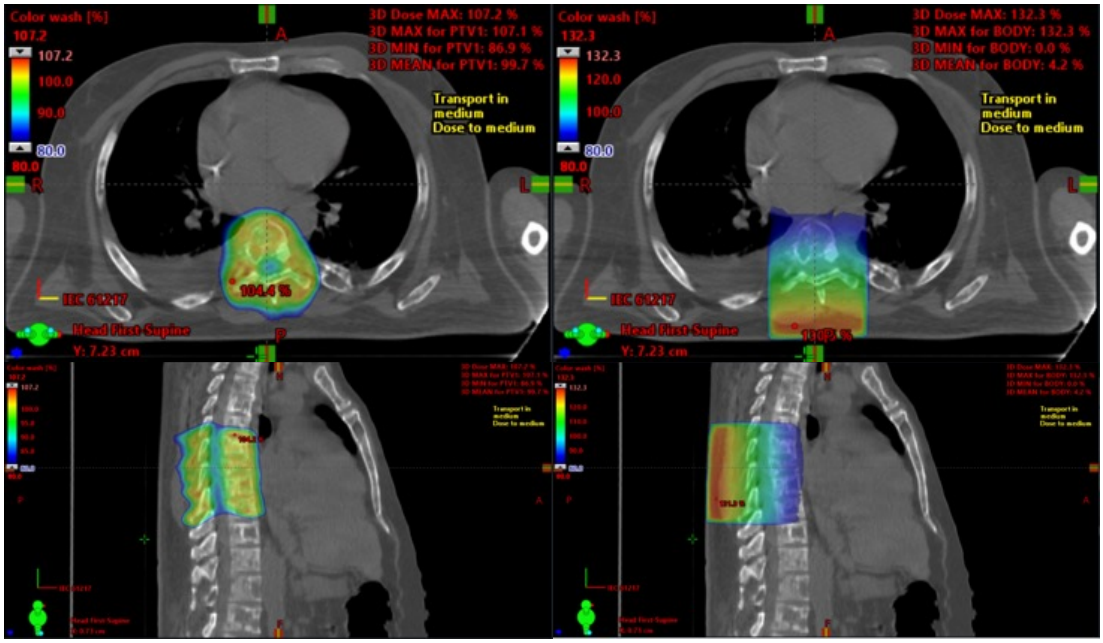

Figure 5.4: Example mid thoracic isodose distributions for RapidPlan VMAT (left) and the equivalent cEBRT (right).

Figure 5.5 shows the distribution of PTV Dmin, Dmax and Dmean, as well as the distribution of HI and CI for the same 30 RapidPlan VMAT generated treatment plans on the manually modified ABAS structures compared to the equivalent cEBRT treatment plans for the same structures.

The mean PTV Dmean dose was 7.86±0.16Gy (mean Dmin=3.46±1.79Gy and Dmax=8.56±0.05Gy) for RapidPlan VMAT generated plans compared to PTV Dmean of 7.78±0.24Gy (mean Dmin=1.83±1.08Gy and mean Dmax=10.46±0.41Gy) for cEBRT. The RapidPlan VMAT plans exhibiting more homogeneous and more conformal dose distributions than cEBRT for the same PTV with mean HI of 0.236±0.215 and mean CI of 1.201±0.121 for RapidPlan VMAT generated plans compared to 0.508±0.137 and 1.789±0.437 for cEBRT. Dmin coverage of the PTV for RapidPlan VMAT is significantly higher than that achieved with cEBRT. This is due to the nature of the treatment delivery, cEBRT being delivered as a single, applied radiation field, resulting in PTV in the skin sparing region not being covered appropriately.

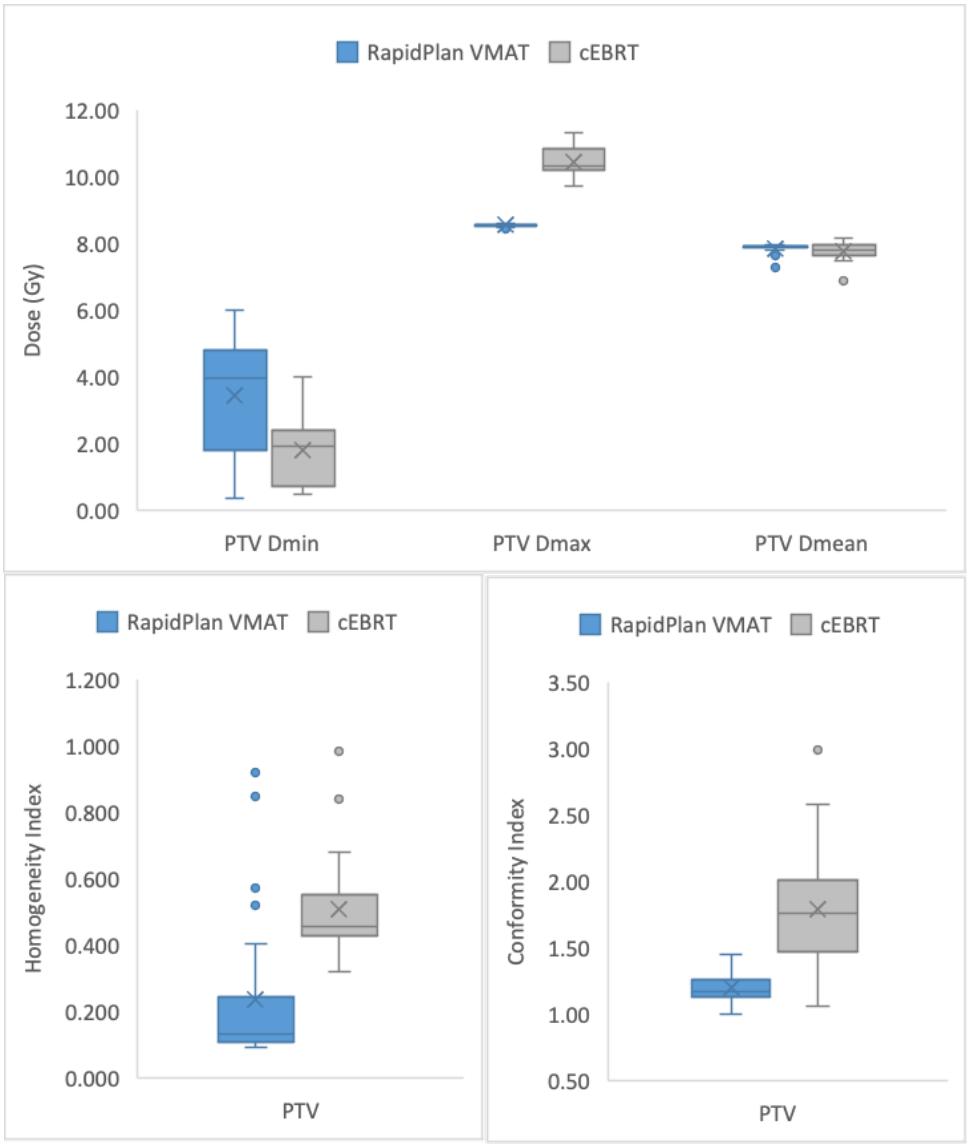

Figure 5.5: Distribution of PTV Dmin, Dmax and Dmean of RapidPlan VMAT and cEBRT treatment plans (n=30) for thoracic and lumbar PTVs (n=10 T6-T8, n=10 T10-T12 and n=10 L2-L4), and distribution of PTV HI and PTV CI for modified ABAS PTV.

Table 5.1 shows the dosimetric statistics for the distribution of PTV Dmin, Dmax and Dmean, as well as HI and CI, for the 30 RapidPlan VMAT and cEBRT plans.

Region		Thoracic-Lumbar (T6-T8, T10-T12 and L2-L4)				
PTV	Planning Technique	Mean (Gy)	SD	95% Confidence Interval		p
				Lower	Upper	
Dmin	VMAT	3.46	1.79	2.82	4.10	<0.01
	cEBRT	1.83	1.08	1.44	2.21	
Dmean	VMAT	7.86	0.16	7.81	7.92	0.13
	cEBRT	7.78	0.24	7.70	7.87	
Dmax	VMAT	8.56	0.05	8.54	8.58	<0.01
	cEBRT	10.46	0.41	10.31	10.60	
HI	VMAT	0.236	0.22	0.159	0.313	<0.01
	cEBRT	0.508	0.14	0.459	0.557	
CI	VMAT	1.201	0.12	1.158	1.244	<0.01
	cEBRT	1.789	0.44	1.632	1.945	

Table 5.1: PTV dosimetric statistics for 30 RapidPlan VMAT plans compared to the equivalent cEBRT plans.

Figure 5.6 shows the distribution of heart, oesophagus (oeso), lungs, kidneys, spinal cord (SC) and cauda equina (CE) OAR doses for the same 30 RapidPlan VMAT treatment plans on the manually modified ABAS structures compared to the equivalent cEBRT treatment plans for the same structures. To allow for comparison taking into account the location of the OAR with respect to the PTV and beam geometry figure 5.6 shows mid thoracic (T6-T8) (top), lower thoracic (T10-T12) (middle) and lumbar (L2-L4) (bottom).

Table 5.2 shows the dosimetric statistics for the distribution of OAR doses for the 30 RapidPlan VMAT and cEBRT plans.

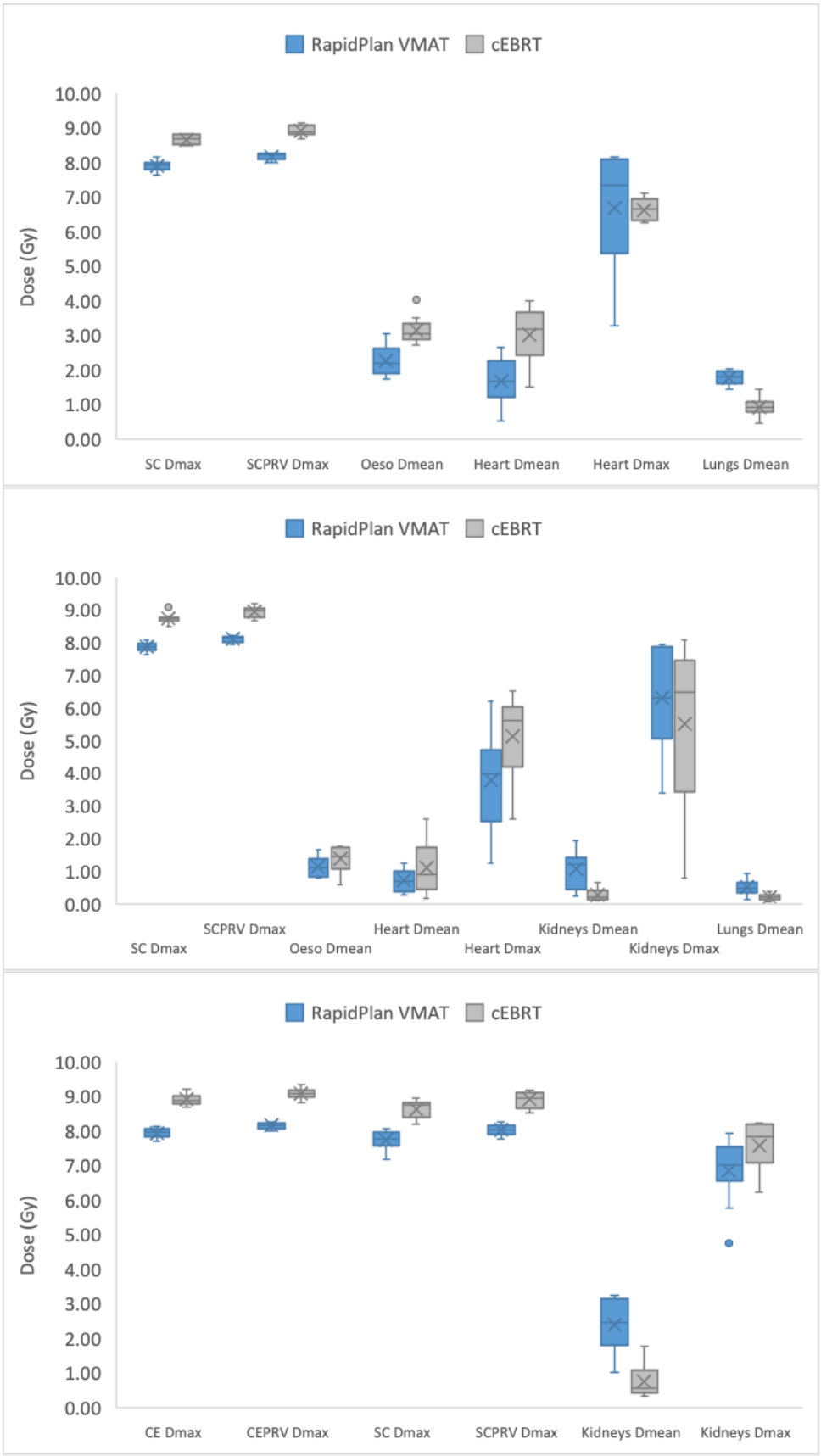

Figure 5.6: Distribution of OAR doses of RapidPlan VMAT and cEBRT plans (n=30), mid thoracic (top), lower thoracic (middle) and lumbar (bottom) for modified ABAS OAR.

Region		Mid Thoracic					Lower Thoracic					Lumbar				
OAR	Planning Technique	Mean (Gy)	SD	95% Confidence Interval		p	Mean (Gy)	SD	95% Confidence Interval		p	Mean (Gy)	SD	95% Confidence Interval		p
				Lower	Upper				Lower	Upper				Lower	Upper	
SC Dmax	VMAT	7.91	0.16	7.82	8.01	<0.01	7.88	0.14	7.79	7.97	<0.01	7.75	0.25	7.59	7.90	<0.01
	cEBRT	8.67	0.13	8.59	8.75		8.75	0.16	8.65	8.85		8.63	0.26	8.47	8.80	
SCPRV Dmax	VMAT	8.18	0.10	8.12	8.24	<0.01	8.11	0.10	8.05	8.17	<0.01	8.04	0.16	7.93	8.14	<0.01
	cEBRT	8.93	0.14	8.84	9.02		8.95	0.18	8.84	9.05		8.91	0.23	8.76	9.05	
Oeso Dmean	VMAT	2.27	0.44	2.00	2.54	<0.01	1.15	0.31	0.96	1.35	0.05					
	cEBRT	3.16	0.38	2.92	3.40		1.39	0.38	1.15	1.62						
Heart Dmean	VMAT	1.69	0.65	1.28	2.09	<0.01	0.72	0.35	0.50	0.93	0.06					
	cEBRT	3.02	0.78	2.53	3.50		1.10	0.78	0.62	1.59						
Heart Dmax	VMAT	6.69	1.70	5.64	7.75	0.92	3.80	1.48	2.89	4.72	<0.01					
	cEBRT	6.64	0.32	6.45	6.84		5.12	1.38	4.27	5.98						
Lungs Dmean	VMAT	1.78	0.20	1.66	1.91	<0.01	0.52	0.23	0.38	0.66	<0.01					
	cEBRT	0.94	0.26	0.78	1.10		0.23	0.10	0.17	0.29						
Kidneys Dmean	VMAT						1.07	0.56	0.72	1.41	<0.01	2.39	0.77	1.91	2.87	<0.01
	cEBRT						0.29	0.18	0.18	0.40		0.78	0.47	0.49	1.06	
Kidneys Dmax	VMAT						6.32	1.61	5.32	7.31	0.24	6.87	0.94	6.29	7.46	0.03
	cEBRT						5.52	2.57	3.92	7.11		7.59	0.72	7.14	8.03	
CE Dmax	VMAT											7.94	0.13	7.86	8.02	<0.01
	cEBRT											8.90	0.16	8.81	9.00	
CEPRV Dmax	VMAT											8.16	0.09	8.10	8.21	<0.01
	cEBRT											9.08	0.15	8.98	9.17	

Table 5.2: OAR dosimetric statistics for 30 RapidPlan VMAT plans compared to the equivalent cEBRT plans.

The mean time to perform ABAS of target volumes and OAR was 2.5±0.3 minutes. The mean time to perform RapidPlan followed by dose calculation was 18.7±2.2 minutes compared to 8.5±2.5 minutes to perform VSIM followed by dose calculation.

Discussion

All 30 RapidPlan VMAT KBP plans were generated on ABAS structures using a single DVH estimation model for the thoracic and lumbar regions. The DVH estimation model was used to predict achievable dose volume histograms (DVH) and define optimisation objectives for PTV and OAR.

Figures 5.3 and 5.4 indicate the DVH estimation model was successful at producing conformal and homogeneous dose distributions across the PTV, with minimal

variation between the 30 generated plans for PTVs in the thoracic and lumbar regions. The mean PTV Dmean was 7.97Gy (99.6% of prescribed dose). The mean PTV Dmin was 6.91Gy (86.4%). While for most radical conformal radiotherapy this Dmin might be considered low and less than International Commission on Radiation Units and Measurements (ICRU) recommendations of target coverage between 95%-107% [23], for cEBRT of uncomplicated spine metastases no PTV is defined and the clinical aim is simply to ensure the 80% covers the affected part of the vertebrae. 86.4% was comparable with the plans used to build the DVH estimation model, where the mean Dmin of the 60 plans in the DVH estimation model was 82.1%. The PTV Dmax was 8.55Gy (106.9%). Figure 5.3 also shows RapidPlan is capable of producing both homogeneous (mean HI 0.089±0.003) and conformal plans (mean CI 1.257±0.219) for thoracic and lumbar PTV. As such the DVH estimation model can be considered to be appropriate for use in these regions. Figure 5.3 shows the distribution of PTV Dmin, Dmax and Dmean for the RapidPlan VMAT plans generated for a PTV grown from a CTV generated with SmartSegmentation ABAS, although the CTV was reviewed to ensure no misidentification of vertebrae, it was not manually modified in any way prior to RapidPlan.

Figure 5.5 shows the dose distribution for the same plans with the DVH recalculated for the PTV grown from the manually modified, and therefore true, CTV, as well as the equivalent cEBRT doses for the same structure. Despite modification of the CTV and PTV used to calculate the DVH, the RapidPlan VMAT plans still achieve PTV Dmean 7.86Gy (98.3% of the prescribed dose), with PTV Dmin of 3.46Gy (43.3%) and PTV Dmax 8.56Gy (107.0%). PTV Dmin of 43.3% of the prescribed dose indicates that the PTV was not being covered sufficiently in a number of plans. Despite this, the RapidPlan VMAT plans remain superior to the cEBRT plans as demonstrated in figure 5.5 and table 5.1. There was no statistically significant difference for PTV Dmean between the RapidPlan VMAT and cEBRT plans ($p=0.13$), but PTV Dmin was higher and PTV Dmax was lower than that for the cEBRT plans ($p<0.01$). As expected HI and CI are superior for RapidPlan VMAT compared to cEBRT. In cEBRT no effort was made to improve homogeneity and conformity. The aim for cEBRT was to ensure the affected part of the vertebrae was covered by the 80% isodose and the only method of optimising PTV coverage was through energy selection or prescription depth change. As expected RapidPlan

VMAT was capable of shaping the isodose distribution around the vertebrae, cEBRT was incapable of delivering comparable isodose distributions to RapidPlan VMAT.

Figure 5.4 shows that the RapidPlan VMAT KBP plans remained superior in terms of PTV coverage compared to conventional radiotherapy plans. With cEBRT resulting in heterogeneity of dose across the PTV, and poor conformity across the PTV, as well as increased skin dose. HI and CI values were significantly improved for the VMAT plans compared to their equivalent cEBRT plans ($p<0.01$), as demonstrated by the isodose distribution example shown in figure 5.4.

Figure 5.6 and table 5.2 show the distribution of OAR dose for RapidPlan VMAT plans for manually modified, and therefore true, OAR, as well as the equivalent cEBRT plans for the same structure. Throughout the thoracic and lumbar regions the dose-limiting OAR are the spinal cord and cauda equina. For all plans in the mid thoracic, lower thoracic and lumbar regions dose to spinal cord, cauda equina and their respective PRVs is significantly lower for RapidPlan VMAT compared to cEBRT ($p<0.01$). In the mid thoracic the mean Dmax to spinal cord was 8.67Gy (108.4% of prescribed dose) for cEBRT, and although no PRV was defined for cEBRT, mean Dmax to spinal cord PRV was 8.93Gy. Through optimisation, RapidPlan VMAT attempts to restrict dose to both the spinal cord and spinal cord PRV, and does so successfully, reducing Dmax to 7.91Gy and 8.18Gy respectively. In the lower thoracic, mean Dmax to spinal cord was 8.75Gy (109.4% of prescribed dose) for cEBRT, with mean Dmax to spinal cord PRV of 8.95Gy, compared to 7.88Gy and 8.11Gy respectively for RapidPlan VMAT. In the lumbar region mean Dmax to spinal cord was 8.63Gy (107.9% of prescribed dose) for cEBRT, with mean Dmax to spinal cord PRV of 8.91Gy, compared to 7.75Gy and 8.04Gy respectively for RapidPlan VMAT. Mean Dmax to cauda equina was 8.90Gy (117.9% of prescribed dose) for cEBRT, with mean Dmax to spinal cord PRV of 9.08Gy, compared to 7.94Gy and 8.16Gy respectively for RapidPlan VMAT. In cEBRT the treatment was prescribed to deliver 8Gy to the anterior spinal cord in the centre of the treatment field, but this does not take into account that the spinal cord was rarely straight across the length of the field and as such the depth of the anterior spinal cord changes across the field length and the mean Dmax dose to the spinal cord exceeds the prescribed dose. In RapidPlan VMAT the optimisation was carried out with the intention of restricting the dose to both the spinal cord, cauda equina and their respective PRVs and would appear to do so successfully. Re-irradiation and irradiation of subsequent spine metastases can be challenging due to the dose

tolerance of the spinal cord and cauda equina. Not only does RapidPlan VMAT reduce dose to these structures but also enables dose reporting, which will assist the planning process for any re-irradiation or subsequent irradiation. Delineation of structures being a requirement for RapidPlanVMAT, but not for cEBRT.

In the mid thoracic region the OAR include oesophagus, heart and lungs. Dmean to oesophagus and heart is reduced for RapidPlan VMAT compared to cEBRT ($p<0.01$) but there is no significant difference for heart Dmax. Lung Dmean is higher for RapidPlan VMAT compared to cEBRT ($p<0,01$), due the fact that more lung is irradiated using 2 full arc rotations to deliver the dose to the PTV, than irradiated by cEBRT. In the lower thoracic region the OAR include oesophagus, heart, lungs and kidneys. Unlike plans in the mid thoracic region, the reduction of Dmean to oesophagus and heart for RapidPlan VMAT compared to cEBRT in the lower thoracic region is not statistically significant. ($p=0.05$ and 0.06 respectively). Unlike the mid thoracic region heart Dmax is reduced using RapidPlan VMAT ($p<0.01$) for plans in the lower thoracic region, however lung Dmean dose is increased using RapidPlan VMAT ($p<0.01$). Dose to kidneys is increased using RapidPlan VMAT, Dmean 1.07Gy and Dmax 6.32Gy compared to 0.29Gy and 5.52 Gy respectively for cEBRT, this difference is statistically significant for Dmean ($p<0.01$) but not for Dmax ($p=0.24$). In the lumbar region the OAR include the kidneys. The Dmean kidney dose is significantly increased for RapidPlan VMAT compared to cEBRT at 2.39Gy and 0.78Gy respectively ($p<0.01$). But for cEBRT kidney Dmax is 7.59Gy , which significantly higher than RapidPlan VMAT at 6.87Gy ($p=0.03$). In the 20 plans where kidneys where considered an OAR, it was expected that kidney dose would be higher for RapidPlan VMAT due to the nature of VMAT treatment delivery and because in cEBRT the kidneys are shielded with MLC if present in the treatment field. Further work is needed to reduce the dose to the kidneys for RapidPlan VMAT, specifically blocking the gantry angles that enter through the kidneys for VMAT, but this is currently outside the constraints of the DVH estimation model which is for fixed beam geometries.

Although not quantified, cEBRT skin dose is high and was reduced in all plans using RapidPlan VMAT due to the nature of VMAT treatment delivery compared to that of cEBRT.

ABAS of target volumes and OAR using SmartSegmentation, followed by KBP using RapidPlan and dose calculation was 2.5±0.3 minutes and 18.7±2.2 minutes

respectively, demonstrating that both could be achieved in a timely manner compared to VSIM and dose calculation for cEBRT of 8.5±2.5 minutes.

Conclusion

Automated treatment planning for uncomplicated spine metastases using SmartSegmentation ABAS and RapidPlan KBP approaches is feasible in the clinical environment. SmartSegmentation ABAS can be used to delineate target volumes and OAR to allow RapidPlan KBP to generate superior plans in terms of target volume coverage, homogeneity and conformity to cEBRT, with reduced dose to the dose-limiting structures, spinal cord and cauda equina. ABAS and KBP also allow dose reporting, currently not available for cEBRT.

Further work is required to refine ABAS and KBP, and establish methods of reducing OAR dose to the kidneys.

Conflict of Interest

This work was partly funded by Varian Medical Systems.

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5.3. ESTRO 2021 Poster Presentation

An abstract describing the development of this research was accepted as a poster presentation at the European Society for Therapeutic Radiation Oncology (ESTRO) 2021 meeting, held between 27-31 August 2021. The theme of ESTRO 2021 was 'Optimal Radiotherapy For All' and as such this poster presentation fitted the theme of this international meeting well. The poster is shown in appendix D of this thesis.

6. Critical appraisal

The research presented in this thesis describes the development of ABAS and KBP for automated VMAT radiotherapy treatment planning of uncomplicated spine metastases. It has been demonstrated in the introduction and literature review chapters of this thesis that the research presented is timely, of clinical interest, and of growing clinical importance. Additionally, this research was supported by a research grant from Varian Medical Systems, Inc, demonstrating that this work is also of commercial interest. The strengths and limitations of this work that merit comment are addressed in this chapter.

A strength of this research is that ABAS using SmartSegmentation, and VMAT KBP using RapidPlan DVH estimation model, is provided by the widely used and commercially available Eclipse TPS. As such this work could be easily replicated by other users of Eclipse for development of an automated solution for radiotherapy treatment planning of uncomplicated spine metastases for their own patients. Furthermore, the SmartSegmentation expert case atlas and RapidPlan DVH estimation model could be shared with other users, and potentially added to, to develop a multi-centre atlas and RapidPlan model that might facilitate a multi-centre clinical trial of automated VMAT KBP for uncomplicated spine metastases. Some early initial results of the work presented in this thesis were presented to the UK RapidPlan Consortium (UKRC) to determine interest in this application of RapidPlan KBP for a future multi-centre project. The UKRC are a consortium of nine UK radiotherapy centres formed to share expertise and experience of RapidPlan with each other, and to evaluate the potential for model sharing between centres.

The literature indicates that the radiotherapy techniques most commonly used for the radiotherapeutic palliation of uncomplicated spine metastases are cEBRT and SABR. cEBRT is widely established and available for all patients who present with uncomplicated spine metastases in the NHS. cEBRT requires no complex radiotherapy treatment planning and can be delivered in a timely manner to provide symptom control, often on the same day of clinical presentation. SABR is an emerging radiotherapy technique for uncomplicated spine metastases, and is only available on the NHS in England through NHS England's CtE programme (NHS England, 2015) for patients that meet the inclusion criteria. SABR requires specialist patient positioning and immobilisation, complex radiotherapy treatment planning and

treatment plan verification, and as such cannot typically be delivered on the same day of clinical presentation. These two radiotherapy techniques can be considered to be at opposite ends of the scale from each other in terms of complexity and deliverability.

Table 6.1 summarises the key differences between the two radiotherapy treatment techniques, along with the projected ABS and VMAT KBP workflow.

cEBRT	SABR	ABAS and VMAT KBP workflow
Same-day consultation, imaging, cEBRT treatment planning and treatment delivery	Minimum 7 day pathway, imaging, target volume and OAR delineation, IMRT/VMAT treatment planning, verification, pre-treatment imaging, treatment delivery	Anticipated same-day consultation, imaging, target volume and OAR ABAS, VMAT KBP treatment planning, verification, pre-treatment imaging, treatment delivery
Requires simple patient positioning and immobilisation	Requires specialist patient positioning and immobilisation	Requires simple patient positioning and immobilisation, but patient must be able to tolerate position for duration of VMAT treatment delivery
Requires CT imaging for treatment planning	Requires CT imaging for treatment planning (MRI imaging is sometimes additionally required)	Requires CT imaging for treatment planning
No target volume or OAR delineation required	Requires target volume and OAR delineation	SmartSegmentation ABAS of target volume and OAR with ABAS review step
Simple treatment planning (monitor unit (MU) dose calculation only)	Inverse treatment planning (IMRT or VMAT)	RapidPlan VMAT KBP
No dose reporting required	Requires dose reporting	Potential for dose reporting (ABAS structures)
Requires MU verification using MU check verification software	Requires MU verification using MU check verification software	Requires MU verification using MU check verification software
Non-conformal	Highly conformal	Conformal
Requires pre-treatment on board imaging	Requires pre-treatment on board imaging	Requires pre-treatment on board imaging
Single or multi-fraction treatment	Single or multi-fraction treatment	Single or multi-fraction treatment
No pre-treatment patient specific QC	Pre-treatment patient specific QC	Pre-treatment patient specific QC initially

Table 6.1: Comparison of cEBRT and SABR radiotherapy treatment techniques, with projected ABAS and VMAT KBP workflow.

The first proffered manuscript (manuscript 1, see chapter 3) in this thesis describes the development and evaluation of ABAS of the thoracic and lumbar vertebral spine and OAR in the vicinity of the thoracic and lumbar regions of the vertebral spine using SmartSegmentation. The second proffered manuscript (manuscript 2, see chapter 4) in this thesis describes the development and validation of a RapidPlan DVH estimation model for VMAT KBP of uncomplicated spine metastases. The third proffered manuscript (manuscript 3, see chapter 5) evaluates the application of both ABAS and VMAT KBP on subsequent patient CT image datasets and compares the achieved dose distributions against the equivalent cEBRT treatment plans.

Together these manuscripts demonstrate that ABAS and VMAT KBP can be used to produce VMAT radiotherapy treatment plans that are superior to the equivalent

cEBRT radiotherapy treatment plans in terms target volume coverage, homogeneity and conformity, while reducing dose to the dose-limiting structures (spinal cord and cauda equina). This may, with additional work, facilitate clinical implementation of VMAT for uncomplicated spine metastases for patients previously only offered cEBRT.

This research does not investigate if there is clinical benefit to VMAT over cEBRT. However, cEBRT must be acknowledged as an inferior radiotherapy treatment technique in terms of enhancement of the therapeutic ratio compared to IMRT, VMAT or SABR (Laine *et al*, 2017). The fundamental premise of radiotherapy is that the probability of tumour control increases with increasing radiation dose, and that the probability of normal tissue complications is reduced by decreasing the radiation dose to OAR. This is more easily achieved with the most conformal radiotherapy techniques. While it cannot be said that cEBRT is inferior for palliation of uncomplicated spine metastases at this stage, all indications in the literature and the emergence and growing use of SABR for this cohort of patients is beginning to lead the radiotherapy community towards that conclusion. 40% of patients treated with cEBRT fail to obtain pain relief (Huisman *et al*, 2015), and recurrent pain is common with 20% of patients requiring re-irradiation (Lutz *et al*, 2011; van der Velden *et al*, 2016). However, heterogeneity of dose distribution and conformity of dose coverage with cEBRT has not been investigated in terms of impact on pain control (Barton *et* al, 2002) and the requirement for re-irradiation rate (Andic *et al*, 2009). This alone suggests further research is required, and the research presented in this thesis may facilitate some of that investigation.

6.1. SmartSegmentation Atlas-Based Auto-Segmentation for Spine Metastases

Proffered manuscript 1 describes the development and evaluation of ABAS of the thoracic and lumbar vertebral spine using SmartSegmentation, additionally it describes the ABAS of OAR in the vicinity of these regions of the vertebral spine. Neither of which, to the best of the author's knowledge, has been described in the literature before. As such the research presented in this thesis adds to the body of knowledge on ABAS using SmartSegmentation and the application of ABAS for target volume and OAR delineation for radiotherapy treatment planning of uncomplicated spine metastases.

The focus of the research presented in this thesis is entirely on radiotherapy treatment planning of uncomplicated spine metastases in the thoracic and lumbar regions of the vertebral spine. Therefore, ABAS and VMAT KBP for treatment planning of metastases in the cervical and sacral regions have not been developed or evaluated. However, 70% and 20% of spine metastases occur in the thoracic and lumbar regions respectively (Nguyen *et al*, 2011). As such this this work focuses on the regions of the vertebral spine most affected, and therefore has the potential to benefit the majority of patients presenting with uncomplicated spine metastases. Furthermore, an automated solution for conformal radiotherapy treatment planning in these regions would be of most benefit, as the number of patients requiring treatment in these regions is greatest, and would be significantly labour and resource intensive without an automated solution.

This work does not extend to ABAS and VMAT KBP of spine metastases with soft tissue involvement. In some cases spine metastases may extend beyond the affected vertebra or vertebrae, and there may be an associated soft tissue mass. Manual adjustment of the ABAS generated CTV to include the soft tissue mass, followed by VMAT KBP may be feasible, but this has not been investigated. Additionally, this work does not extend to complicated spine metastases and MSCC. 10% of spine metastases patients can present with MSCC (Challapalli *et al*, 2020). MSCC is considered a medical emergency, and patients presenting with MSCC are managed differently to those with uncomplicated spine metastases.

The work presented in manuscripts 1 and 3 showed that ABAS, when used with an additional qualitative review step, provided delineated target volumes suitable for VMAT KBP of uncomplicated spine metastases. This was demonstrated by the results for the similarity metrics DSC, centre of mass shift and volume difference, shown in tables 3.2 and 3.3, and figures 3.6 and 3.8, where the additional review step improved the similarity scoring significantly. The qualitative review step was a necessary human intervention during ABAS. It was required to determine the most appropriate expert case atlas to use for ABAS and prevent misidentification of individual vertebrae. As such ABAS of target volumes and OAR was not an entirely automated task within the treatment planning process. ABAS target volume delineation appeared to be more successful in the lumbar region of the vertebral spine compared to that of the thoracic region, demonstrated in figure 3.4 and 3.6. One explanation for this is potentially the highly variable patient positioning and immobilisation used for the patient CT data sets that make up the expert case atlas,

as shown in figure 3.10, but this requires further investigation. ABAS was shown to be capable of auto-segmenting target volumes considerably more quickly than what could be achieved through manual delineation, when delineating all vertebrae in the thoracic and lumbar regions of the vertebral spine. Mean time to manually delineate T1-T12 being 133.9±27.0 minutes compared to 1.6±0.2 minutes for ABAS, and mean time to manually delineate L1-L5 being 87.8±10.7 minutes compared to 1.2±0.3 minutes for ABAS. To determine true time-saving of ABAS for this application however requires further investigation. All of the thoracic and lumbar vertebrae were delineated (primarily to add to the expert case atlas for future investigation or clinical implementation and use), when in reality it is more appropriate to delineate only those vertebrae requiring irradiation, which would take considerably less time to manually delineate. However, it is highly unlikely any manual delineation would be achieved in under 2 minutes, as was achieved with SmartSegmentation ABAS.

The work presented in manuscript 1 showed that ABAS for OAR had varying degrees of success, with some OAR being delineated highly successfully using ABAS, but other less so. Table 3.3 shows the evaluation of ABAS for the OAR. In terms of the DSC metric, ABAS was highly successful for the lungs, heart, spinal cord and cauda equina achieving DSC>0.70 indicating good overlap (Zou *et al*, 2006), but the centre of mass shifts for spinal cord and cauda equina (overwhelmingly in the superior-inferior direction) indicate that there is some ambiguity in the start and end points of the spinal cord and cauda equina. However ABAS of kidneys and the oesophagus were significantly less successful. It was observed that the kidneys were highly variable in size and position within the SmartSegmentation expert case atlas and additionally highly variable when ABAS was applied to subsequent patient CT image data sets. ABAS of the oesophagus was completely unsuccessful with SmartSegmentation failing to auto-segment the oesophagus in all instances. However, the oesophagus is widely known to be both difficult to manually delineate and to auto-segment, as the boundaries between the oesophagus and other surrounding tissues are poorly defined (Bandeira Diniz *et al*, 2020). The results presented in manuscript 1 and 3 indicate that adding to the expert case atlas may offer limited value (except in the case of the kidneys), but this would require further investigation to validate. Schipaaboord *et al* (2019) posed the question 'can ABAS ever be perfect?' and used extreme value theory to determine the optimum number of cases in an atlas used for ABAS. They calculated that in

order for ABAS to provide auto-segmentation to a performance level corresponding to clinical quality, the atlas would have to be made up of at least 5000 cases. What may instead offer more value is a more consistent patient set up for patient positioning and immobilisation, not only in terms of the atlas curation, but also in terms of imaging for radiotherapy treatment planning.

While these ABAS target volumes and OAR, shown in manuscripts 1 and 3, would not be clinically acceptable for radical radiotherapy treatment planning without the manual modification by the clinical oncologist, it was demonstrated in manuscript 3 that they could be used for VMAT KBP and that in this context, provided dosimetrically superior target volume coverage, conformity and homogeneity over cEBRT, as demonstrated in figure 5.5, and reduced dose to the dose-limiting structures (spinal cord and cauda equina). Additionally, target volume and OAR delineation facilitates dose reporting. It has been shown in manuscripts 1 and 3 that ABAS and VMAT KBP have the potential to provide dose reporting, which in turn may facilitate safe re-irradiation of spine metastases where required, or further irradiation of adjacent spine metastases. It is important to note however, that no investigation to determine how comfortable clinical oncologists would be with that has been carried out. The radiotherapy treatment planning process requires the clinical oncologist to approve the delineation of target volumes and OAR prior to conformal radiotherapy treatment planning. Clinical oncologists would likely be uncomfortable approving ABAS target volumes and OAR without manual modification, so clinical implementation would require additional work and further discussion. Removal of the approval of target volumes and OAR for this application might be feasible, or differentiation of the approval definition for this application might be required, or else human intervention to the automated workflow for manual modification of ABAS target volumes would be required. Due to the limited availability of clinical oncologists to participate in this research, qualitative metrics were not used to evaluate the quality of target volume and OAR delineation. Further assessment, using qualitative scoring of ABAS generated structures by clinical oncologists, might facilitate more confidence in its clinical use for VMAT KBP. Ultimately, manual delineation of target volumes is considered the gold standard and clinical implementation of auto-segmentation requires careful consideration to ensure patient safety and quality of radiotherapy is not compromised.

A key limitation of the work described in manuscript 1 is how the SmartSegmentation expert case atlas for ABAS was developed. Generally,

SmartSegmentation expert case atlases would be produced through curation of clinical cases, often delineated by multiple clinical oncologists and dosimetrists with a peer review process, with target volume and OAR contours that were delineated for the sole purpose of being used for radiotherapy treatment planning and treatment delivery. cEBRT does not require the delineation of target volumes or OAR, so no clinical cases were available for use as expert cases. Instead manual delineation of all of the target volumes and OAR for addition to the expert case atlas was carried out by a single physicist (the author) on CT image datasets of previously treated cEBRT patients. Training in manual delineation and peer review of contours was provided by a single, experienced dosimetrist. The delineation of the target volumes and OAR was discussed and agreed with by a consultant clinical oncologist and followed consensus guidelines. This limitation, while significant, was unavoidable. Clinical oncologist availability for research was limited, as such there was no option to have every case in the expert case atlas peer reviewed by a clinical oncologist or team of clinical oncologists. This would need to be rectified prior to clinical implementation.

The research presented in this thesis shows SmartSegmentation ABAS has potential to offer a time-saving approach to delineating the target volumes and OAR required for conformal VMAT KBP for uncomplicated spine metastases.

6.2. RapidPlan Knowledge-Based Planning for Spine Metastases

Proffered manuscript 2 describes the development and evaluation of VMAT KBP of uncomplicated spine metastases using RapidPlan. To the best of the author's knowledge, this has not been described in the literature before, although SABR KBP for uncomplicated spine metastases has been reported on (Foy *et al*, 2017; Younge *et al*, 2018). Additionally, the use of ABAS and VMAT KBP together for conformal radiotherapy treatment planning of uncomplicated spine metastases has not been reported on. As such the research presented in this thesis adds to the body of knowledge on KBP using RapidPlan and the application of RapidPlan for radiotherapy treatment planning of uncomplicated spine metastases. Additionally, the validation of the RapidPlan DVH estimation model was carried out using cross validation. Cross validation is not widely used in RapidPlan model validation, with most researchers favouring train and test validation. In this research both methods have been used, cross validation in manuscript 2, and the more conventional train and test in manuscript 3. Cross validation was carried out as a preventative

measure of overfitting to the model due to the relatively small number of training plans (n=60). Cross validation is considered more sophisticated than train and test for small data sets, but as demonstrated in manuscripts 2 and 3, both cross validation and train and test show validity of the RapidPlan model for VMAT KBP of thoracic and lumbar spine metastases.

As with ABAS expert case atlas development, a significant limitation of the work described in manuscript 2 is how the RapidPlan DVH estimation model for VMAT KBP was developed. Generally RapidPlan models would be produced through curation of clinical radiotherapy treatment plans that have met the requirements of the clinical protocol and delivered to a patient using a linear accelerator. These treatment plans would likely be planned by multiple dosimetrists, and reviewed and approved by multiple clinical oncologists. cEBRT does not require VMAT radiotherapy treatment planning, so no clinical treatment plans were available for addition to the model. Instead VMAT planning was carried out for the sole purpose of this research project. All treatment planning was carried out by a single physicist (the author) on CT image datasets of previously treated cEBRT patients. Training in VMAT planning and peer review of plans added to the model was provided by two, experienced dosimetrists. The planning aims and objectives were discussed with and agreed by a consultant clinical oncologist.

A minimum of 20 radiotherapy treatment plans are required to train a DVH estimation model in RapidPlan, but the addition of more increases the robustness of the model (Fogliata *et al*, 2014). The DVH estimation model, the development and validation of which is described in manuscript 2, consisted of 60 radiotherapy treatment plans produced on 20 CT image datasets. Three PTVs per CT image data set were manually planned for VMAT, each dataset consisting of 3 treatment plans for mid thoracic (T6-T8), lower thoracic (T10-T12) and lumbar (L2-L4). These locations were chosen due to the influence on dose distribution of OAR in the vicinity of these regions and to provide heterogeneity in the plans in terms of PTV size and location. No other combinations of vertebrae were added to the model or evaluated. All of the plans were 6MV, single isocentre, two full rotation arc VMAT plans, with a fixed collimator angle and complement angle of 30˚ and 330˚ with jaw tracking. All plans were normalised so the 100% isodose covered 50% of the target volume with a prescription of 8Gy in a single fraction. During planning, dose constraints were placed on the spinal cord and cauda equina, such that Dmax<8Gy, in keeping with the prescription aim of cEBRT. No other OAR constraints were

applied and instead the aim of treatment planning was to keep the dose to the remaining OAR as low as possible. Assessment of dose to OAR was carried out to ensure VMAT KBP was able to meet the constraints outlined in the appropriate recommendations (Hanna *et al*, 2018; Soltys *et al*, 2019; Sahgal *et al*, 2019). A limitation of this work is that the PTV and OAR doses (including those of the dose limiting structures) have been evaluated for Dmin and Dmax parameters. Dmin and Dmax are not a clinically meaningful for either optimisation or evaluation. In terms of optimisation, trying to achieve Dmin and Dmax doses can result in a heavily optimised and modulated VMAT plans. Dmin and Dmax are also very sensitive to differences in dose calculation. The near Dmin or near Dmax ($D0.03cm^3$) would be more clinically appropriate. Further work is required to establish more clinically meaningful dose evaluation for the appropriate OAR prior to clinical implementation.

A further limitation of this work is that the model was not evaluated for the vertebrae region T1-T5. Further work is required to evaluate the model in these regions, however it is not anticipated to be an issue in terms of planning due to similar vertebra topology throughout the thoracic region and the presence of fewer OAR in this vicinity.

The work presented in manuscripts 2 and 3 showed that RapidPlan VMAT KBP provided superior radiotherapy treatment plans in terms of target volume coverage, homogeneity and conformity, while reducing dose to the dose-limiting structures (spinal cord and cauda equina) when compared to the equivalent cEBRT dose distributions. However, VMAT KBP exhibited higher Dmean to the lungs and kidneys when present in the treatment plan, as shown in figure 5.6. This is to be expected due to the nature of VMAT treatment delivery and because in cEBRT the kidneys are shielded with MLC if present in the treatment field. Further work is needed to establish a method to reduce the dose to the kidneys for VMAT KBP. A solution might include blocking the beam entry for gantry angles within the arc that enter through the kidneys. However, the stability of the model has not been assessed for different beam geometries. Challapalli *et al* (2020) describe how improvements in overall survival and increases in life expectancy for patients with uncomplicated spine metastases require careful evaluation of late side effects, and this is anticipated to predominantly affect the kidneys for VMAT KBP of uncomplicated spine metastases in the lower thoracic and lumbar regions.

6.3. ABAS and VMAT KBP Radiotherapy Treatment Planning Workflow

A logistical barrier to offering conformal radiotherapy for uncomplicated spine metastases in the clinical environment is that conformal radiotherapy is technically challenging and labour intensive (Westhoff *et al*, 2018). Palliation of uncomplicated spine metastases often requires same-day consultation, imaging, treatment planning and treatment delivery (Dennis *et al*, 2021), as such cEBRT is the most commonly used radiotherapy technique. Dennis *et al* (2021) recently published their pre-clinical implementation study of same-day VMAT of spine metastases. They claimed they could complete all of the tasks in the treatment planning process, as well as quality control and treatment delivery, in under 2 hours. However this study was carried out on an anthropomorphic phantom with no evaluation on actual patients. Furthermore, this study did not exploit automation for any tasks in the planning process. They reported that time taken to manually delineate groups of vertebrae ranged from 5-13 minutes, and the time taken to perform manual VMAT planning ranged from 9-31 minutes. These timings are comparable to those presented in this thesis for automated ABAS and VMAT KBP. Automation of the radiotherapy treatment planning process may allow conformal radiotherapy of uncomplicated spine metastases in a timeframe comparable to cEBRT, and the work presented in this thesis therefore adds to the literature investigating the potential for this in the future.

While ABAS and VMAT KBP are automated methods for carrying out specific tasks in the treatment planning workflow, namely image segmentation and radiotherapy treatment planning, without the Eclipse scripting application programming interface (ESAPI) (Eclipse Scripting API version 15.6) function (*Varian Medical Systems, Palo Alto, California*)) to link the tasks together, the progress through the tasks in the treatment planning process remains human driven, rather than truly automated. Key stages of the treatment planning process are likely to require human intervention to ensure safe, effective and high-quality conformal radiotherapy treatment plans that are deliverable. Additional work is required to identify where this is likely to occur and have a truly automated radiotherapy treatment planning approach using ESAPI.

6.3.1. Clinical Implementation

The research presented in this thesis does not extend to clinical implementation of SmartSegmentation ABAS and RapidPlan VMAT KBP for radiotherapeutic palliation of uncomplicated spine metastases. Figure 5.1 show the radiotherapy workflow, for cEBRT and conformal radiotherapy treatment planning with ABAS and VMAT KBP, from imaging to treatment plan generation, but missing from this figure are the additional tasks in the radiotherapy process up to and including treatment delivery. Prior to clinical implementation a time and motion study needs to be carried out to determine the feasibility of completing all of these tasks on the same day of clinical presentation. Additionally, an investigation needs to take place on patient tolerance and compliance for conformal radiotherapy treatment delivery, in terms of patient positioning and immobilisation, pre-treatment imaging and treatment delivery. Clinical trials for SABR of spine metastases have shown that a high percentage of patients recruited are unable to tolerate SABR, in particular fractionated SABR, this is in part due to severe pain affecting their ability to maintain positioning and immobilisation for the duration of treatment delivery (Sprave *et al*, 2018; Ryu *et al*, 2019; Sahgal *et al*, 2021; Pielkenrood *et al*, 2021). While Dennis *et al* (2021) stated treatment delivery of VMAT for uncomplicated spine metastases ranged from 3-6 minutes and was quicker than delivery of cEBRT, their study did not assess patient setup times, and treatment delivery was carried out on an anthropomorphic phantom. Furthermore, VMAT treatment delivery, in the instance of a new technique requires pre-treatment dosimetric verification quality control, which is not a requirement for cEBRT. This requires assessment prior to clinical implementation.

As the clinical benefit of conformal radiotherapy for the irradiation and re-irradiation of spine metastases has yet to be evaluated and conformal radiotherapy is not considered mandatory (Lutz *et al*, 2011), clinical implementation might be most appropriate within a clinical trial setting. The implementation of conformal radiotherapy for uncomplicated spine metastases in the NHS should be evidence-based and therefore supported by clinical trial to ensure clinical efficacy and cost effectiveness. A randomised controlled clinical trial would allow this evaluation, but would likely be challenging. Palliative radiotherapy clinical trials often suffer from low accrual rates and high patient attrition (Bradley *et al*, 2006). Patients with advanced-stage malignancies often have multiple symptoms, and typically poor performance status. Other researchers have noted that a high percentage of patients recruited into palliative radiotherapy clinical trials are unable to complete

treatment due to severe pain (Sprave *et al*, 2018; Ryu *et al*, 2019; Sahgal *et al*, 2021; Pielkenrood *et al*, 2021). Furthermore, the presence of uncomplicated spine metastases is associated with limited life expectancy. Any clinical trial would require research ethics approval and the study design would have to follow consensus guidelines. Chow *et al* (2012b) provide international consensus on palliative radiotherapy endpoints for clinical trials for bone metastases. An automated radiotherapy treatment planning workflow that includes ABAS and VMAT KBP could enhance the study design and facilitate a randomised controlled trial. RapidPlan KBP allows for better consistency of treatment plans, which has the potential to add value to clinical trial outcomes, as treatment plan quality can influence clinical trial outcome (Mian *et al*, 2016; Meyerhof *et al*, 2017; Younge *et al*, 2018; Tol *et al*, 2019). Kavanaugh *et al* (2019) evaluated a single-institution RapidPlan KBP DVH estimation model as a dosimetric plan quality tool for a multi-institutional clinical trial and concluded that RapidPlan KBP improved overall plan quality and consistency in multi-institutional clinical trials. A multi-institution approach to clinical trial study design, for example through collaboration with the UKRC, might overcome some of the issues with accrual. Appropriate endpoints of the clinical trial might include immediacy and durability of pain relief, the requirement for re-irradiation, acute and late toxicity, and quality of life. While also investigating patient tolerance and compliance of conformal radiotherapy for uncomplicated spine metastases.

It could be argued that the adoption of IMRT for radical radiotherapy, in the NHS in particular, was hindered by the requirement to generate evidence to ensure clinical benefit and cost effectiveness (Castle-Clark, Edwards and Buckingham, 2017). Additionally, it is not unreasonable to say wide-spread adoption of IMRT across the NHS was hindered by treatment capacity challenges (Jeffries, Taylor and Reznek, 2009). Implementation of conformal radiotherapy for uncomplicated spine metastases is likely to suffer those same challenges. However, it could equally be argued that the clinical implementation of IMRT and VMAT were not thoroughly assessed through randomised controlled trial and neither is the CTE approach to implementing SABR for spine metastases. Conformal radiotherapy is known to be safe and effective, and superior to cEBRT, and as such potentially no further evaluation is required.

6.4. Future Work

As described in sections 6.1 and 6.2, future work is required to ensure that the ABAS and VMAT KBP workflow is suitable for clinical implementation. The proposed further work is outlined in this section.

Clinical oncologist qualitative peer review of the expert case atlas in SmartSegmentation and of the DVH estimation model in RapidPlan is required prior to clinical implementation. Clinical oncologist peer review may lead to refinement of the atlas and/or model, but significant adjustment or the addition of expert cases and/or training plans is not anticipated (see sections 4.2 and 5.2). Additional to peer review, the use of digital phantoms for benchmarking and quantitative peer review would further add robustness to this research project prior to clinical implementation and should be considered for future work (Hito *et al*, 2021).

Additionally, it is necessary to determine which patients might benefit most from this proposed workflow. Irradiation and re-irradiation of spine metastases might be first incidence of spine metastasis irradiation, re-irradiation of spine metastasis, or further irradiation of adjacent spine metastases. The RapidPlan DVH estimation model presented in chapters 4 and 5 of this thesis is constrained by the fixed beam geometries used in the training plans used to inform the model. As such, further irradiation of adjacent spine metastases might require additional work to investigate changes to collimator angle to minimise penumbra in the superior-inferior direction and make matching to previous irradiations easier.

An ambitious goal at the start of this research project was to have a fully automated treatment planning workflow with every stage of the workflow, shown in figure 5.1, automated. The aim was to facilitate this using ESAPI to link the key treatment planning tasks together. cEBRT for uncomplicated spine metastases and MSCC is often delivered outside normal clinical hours, as well as on weekends. The cEBRT process is often radiographer led through virtual simulation with simple MU calculation, the ambition was therefore to have a fully automated treatment planning workflow that could also be radiographer led. Unfortunately this was unachievable in the timeframe of this research project. Future work is required to produce the necessary Eclipse scripts, and determine whether they could be applied to patients all the way through to treatment delivery with little to no intervention by dosimetrists, physicists or clinical oncologists.

Any change in patient pathway which includes a change in the treatment planning and treatment delivery techniques for palliative spine metastases would require risk assessment and multi-disciplinary sign off before clinical implementation. As described in section 6.3.1, implementation of conformal radiotherapy for uncomplicated spine metastases in the NHS should be evidence-based and therefore supported by clinical trial to ensure clinical efficacy and cost effectiveness, and guided by health technology assessment. Future work should consider setting up a single or multi-centre clinical trial, which as well as providing evaluation, might additionally provide enthusiasm and ensure momentum for facilitating clinical implementation.

Finally, machine learning, which includes both ABAS and KBP, is having a growing impact in clinical radiotherapy and increasing presence in clinical and industry radiotherapy research (Field *et al*, 2021). Future technological advances in radiotherapy, specifically in imaging, auto-segmentation, automated adaptive radiotherapy treatment planning and increasing computation speeds have potential to further supplement the work in this research project.

7. Conclusions

Uncomplicated spine metastases are a common feature of advanced-stage malignancies and result in considerable morbidity (Lewandrowski *et al*, 2006). Radiotherapy for uncomplicated spine metastases is considered palliative. Patients who present with spine metastases often require same-day consultation, imaging, treatment planning and treatment delivery (Dennis *et al*, 2021) to provide them with timely and durable symptom control. As such cEBRT, prescribed to 8Gy in a single fraction, is the most readily used radiotherapy treatment approach, due to its effectiveness, tolerability and convenience (Dennis *et al*, 2020).

A review of the literature indicates that the use of conformal radiotherapy (IMRT, VMAT and SABR) for the irradiation and re-irradiation of uncomplicated spine metastases is increasing. Results of randomised controlled trials investigating SABR are emerging in the literature, with early indications that conformal radiotherapy, in particular SABR, may provide improved immediacy of pain relief and improved long-term pain control (Sahgal *et al*, 2021). Therefore, conformal radiotherapy for spine metastases is currently of considerable interest within the radiotherapy community. Conformal radiotherapy treatment planning is technically challenging and labour intensive (Westhoff *et al*, 2018). The research presented in this thesis describes the development of SmartSegmentation ABAS for auto-segmentation of thoracic and lumbar vertebrae and OAR in their vicinity, and RapidPlan KBP for VMAT radiotherapy treatment planning.

Proffered manuscript 1 (in chapter 3) describes the development and evaluation of SmartSegmentation ABAS. The manuscript demonstrates ABAS is capable of generating entire structure sets of thoracic and lumbar vertebrae target volumes and OAR in a timely manner, faster than would be achievable through manual segmentation. Although it achieves this with varying degrees of success, proffered manuscript 3 demonstrates that these auto-segmented target volumes and OAR can be readily used, without modification, for RapidPlan VMAT KBP.

Proffered manuscript 2 (in chapter 4) describes the development and validation of a RapidPlan DVH estimation model for VMAT KBP for uncomplicated spine metastases. The manuscript demonstrates that the model is capable of generating acceptable VMAT treatment plans that meet the optimisation objectives of the model

in a timely manner, with no human intervention or decision making during the optimisation process.

Proffered manuscript 3 (in chapter 5) evaluates ABAS and VMAT KBP in patient CT image datasets (of previously treated cEBRT patients). The ABAS and KBP tasks being used to generate treatment plans that were superior in terms of target volume coverage, homogeneity and conformity when compared to the equivalent cEBRT treatment plans, with reduced dose to the dose-limiting structures, spinal cord and cauda equina.

In conclusion, the research presented in this thesis demonstrates that the use of ABAS and VMAT KBP is feasible, and with additional work may provide a fully automated radiotherapy treatment planning solution for VMAT radiotherapy treatment planning of uncomplicated spine metastases. Providing patients with conformal radiotherapy as opposed to cEBRT, which in a clinical trial setting could establish if VMAT confers clinical benefit over cEBRT.

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Appendices

A. Taught and assessed elements of HSST DClinSci programme

Listed in table A.1 are the taught elements of the HSST DClinSci programme.

Section A Leadership and Professional Development was delivered and assessed by Alliance Manchester Business School at the University of Manchester.

Section B Specialist Scientific Clinical Programme in Medical Physics (Radiotherapy Physics) was delivered and assessed by the University of Manchester.

List of Alliance Manchester Business School (AMBS) A units and Medical Physics B units together with assignments – Emma-Louise Jones

AMBS – A Units		
Unit title	**Credits**	**Assignment word count**
A1: Professionalism and Professional Development in the Healthcare Environment	30	A1 – assignment 1 – 2500 words Group work/presentation – 10 minutes (10%) A1 – assignment 2 – 3000 words
A2: Theoretical Foundations of Leadership	20	A2 – assignment 1 – 3000 words A2 – assignment 2 – 3000 words
A3: Personal and Professional Development to Enhance Performance	30	A3 – assignment 1 – 1500 words A3 – assignment 2 – 4000 words
A4: Leadership and Quality Improvement in the Clinical and Scientific Environment	20	A4 – assignment 1 – 3000 words A4 – assignment 2 – 3000 words
A5: Research and Innovation in Health and Social Care	20	A5 – Group work/presentation – 15 minutes (25%) A5 – assignment – 4000 words
Medical Physics – B Units		
Unit title	**Credits**	**Assignment word count**
B1: Medical Equipment Management	10	Group presentation 1500 word assignment
B2: Clinical and Scientific Computing	10	Group presentation 1500 word assignment
B3: Dosimetry	10	Group presentation 1500 word assignment
B4: Optimisation in Radiotherapy and Imaging	10	Group presentation 1500 word assignment
B6: Medical Statistics in Medical Physics	10	3000 word assignment
B8: Health Technology Assessment	10	3000 word assignment
B9: Clinical Applications of Medical Imaging Technologies in Radiotherapy Physics	20	Group presentation 2000 word assignment
B10a: Advanced Radiobiology	10	Virtual experiment/1500 word report
B10c: Novel and External Beam Therapy	10	1500 word report
B10f: Radiation Protection Advice	10	1500 word report/piece of evidence for portfolio
Generic B Units		
Unit title	**Credits**	**Assignment word count**
B5: Contemporary Issues in Healthcare Science	20	1500 word assignment + creative project
B7: Teaching Learning Assessment	20	20 minute group presentation

Table A.1: Taught elements of the HSST DClinSci programme.

B. Innovation proposal element of HSST DClinSci programme

Proposal

Clinical implementation of the Hololens 2 mixed reality device for treatment mark-up and patient setup of multi-modality treatment for cutaneous T-cell lymphoma.

Executive Summary

Mycosis fungicides (MF) is a cutaneous T-cell lymphoma, a rare form of lymphoma affecting the skin. Patients require radiotherapy treatment of skin lesions that can appear anywhere on the skin surface. Recurrence in the vicinity of, directly adjacent to, or directly over previously treated lesions is common. This can create a radiotherapy challenge for subsequent treatments as re-irradiation of the skin above its radiation tolerance can cause radiation-induced skin injury. The clinician must therefore perform treatment mark-up taking into account all previous radiotherapy treatment. Hololens 2 is a head-mounted mixed reality (augmented and virtual reality) device already beginning to find widespread application in medicine. Hololens 2 may enhance the treatment mark-up of lesions by enabling a 3D photographic record of mark-ups which can be displayed as digital images blended on the physical patient with precision, accuracy and efficiency, using augmented and virtual reality. Radiotherapy is a fractionated treatment and patients are required to attend for daily treatment, the setup of which must be reproduced accurately and precisely to ensure the intended treatment outcome. Hololens 2 will assist with reproducible patient setup for radiotherapy treatment ensuring daily patient setup matches the treatment mark-up.

Background

St John's Institute of Dermatology is a research centre based at Guy's Hospital, which together with Guy's Cancer acts as a referral centre for MF. MF is a rare cutaneous T-cell lymphoma. MF is typically diagnosed as relatively low grade with expected long survival (Smith *et al*, 2015; Willemze *et al*, 2005) and initially treated with topical therapy, photochemotherapy and total skin electron beam radiotherapy (TSEBT) (Morris *et al*, 2013). As the disease progresses MF lesions are treated with multi-modality radiotherapy including superficial x-ray radiotherapy, electron beam radiotherapy, and/or superficial high dose rate (HDR) brachytherapy. The treatment is delivered with palliative intent. Patients undergo multiple radiotherapy treatments over the course of their disease progression, often directly adjacent to, or partially overlapping, previously irradiated lesions, and some lesions may require

complete re-irradiation. Clinical mark-up of lesions and modality selection is often a complex problem for the clinician. Radiation-induced skin injury is a risk of radiotherapy, particularly for re-irradiation. Treatment mark-up and modality selection consists of outlining the lesion and a suitable treatment margin on the patient's skin surface, considering the radiation dose from any previous irradiation by referring to diagrams and photographs of previous clinical mark-ups. Diagrams and photographs are stored in MOSAIQ Radiation Oncology, Elekta's cancer information solution (Elekta, 2021). MOSAIQ does not allow seamless viewing of medical records with diagrams and photographs, and it is often difficult to access the information required in a timely and straightforward manner. It is difficult for the clinician to visualise the locations of previous mark-ups on the patient's body from these diagrams and photographs. Hololens 2 (Microsoft, 2021) is a head-mounted mixed reality (augmented and virtual reality) device released by Microsoft in 2019. Hololens 2 has the potential to acquire 3D photographs of treatment mark-ups that can be redisplayed for subsequent mark-ups directly onto the patient using mixed reality technology, blending the digital images on the physical patient with precision, accuracy and efficiency.

Following treatment mark-up and modality selection the patient will proceed for treatment, with or without supportive medical imaging and treatment planning. Radiotherapy treatment is fractionated and patient setup must be reproduced accurately and precisely for every fraction to ensure expected treatment outcome. Hololens 2 can be used to visualise the treatment mark-up on the patient's skin for fractionated treatment, long after the clinician's original outline of the lesion has washed off the patient's skin surface. This has the potential to assist with accurate and precise daily patient setup. Hololens 2 can also be used to visualise treatment response during fractionated radiotherapy treatment, as well as disease progression after treatment, in subsequent follow-up appointments.

Hololens 2 has already been used in many medical applications including medical education and training, radiology and surgery. Virtual and augmented reality is an emerging and growing technological application in medicine (Eckert *et al*, 2019; Yeung *et al*, 2021) and we have identified an application in radiotherapy that has potential to enhance quality of treatment and patient safety.

Strategic Context

Introduction of Hololens 2 is consonant with the long-term strategic objectives of Guy's and St Thomas' NHS Foundation Trust by "delivering consistently excellent

care that is quality focused, best practice and data driven, efficient, consistent and supported by the latest digital technologies" (GSTT, 2021). Integration of mixed reality for this application may inspire further creative applications within Medical Physics, Radiotherapy, Oncology and across the Trust.

Guy's Cancer will contribute to the Data, Technology and Information Directorate's proof of concept investigation for Hololens 2 devices and associated applications across the Trust.

Proposal objectives

- Capital purchase of two Hololens 2 development edition devices.
- Creation, development and management of applications for treatment mark-up and patient setup.
- Clinical implementation of Hololens 2 for treatment mark-up and patient setup for multi-modality treatment of cutaneous T-cell lymphoma.

SWOT analysis

Hololens 2 provides Guy's Cancer with strengths, weaknesses, opportunities and threats for this application and beyond as outlined in table B.1.

Strengths	Weaknesses
• Provides the clinician with all the information they need to aid decision making for modality selection and treatment mark-up. • May facilitate shorter patient appointment times, and increased patient throughput in the clinic, by allowing the clinician to access the information required in a timely and straightforward manner. • May facilitate improved patient safety by allowing the clinician to visualise areas of overlap with previously irradiated areas at treatment mark-up. • May facilitate improved patient safety by providing an additional tool to assist with reproducible patient setup for fractionated radiotherapy treatment. • May enhance patient experience of the treatment mark-up process. • Provides a visual patient record of treatment response during fractionated radiotherapy treatment. • Provides a visual patient record of disease progression after treatment in subsequent follow-up appointments. • Could be used as a teaching tool to enable clinical teaching of the radiotherapy treatment mark-up process.	• Assumed to initially have a high impact on staffing resources due to the required creation, development and management of applications. • Assumed to initially have a high impact on staffing resources due to unfamiliarity with the technology. • Although Hololens 2 is not a medical device under Directive 93/42/EEV on medical devices (EU MDD, 1993), any developed applications will be if "it is intended to influence the actual treatment dose, sized of implant, time of treatment etc."(UK Government, 2021). • Clinical decision making will rely on this technology, so clinical implementation would require rigorous evaluation. • This is an immersive system and the clinician and radiographers will wear this device in the presence of, and while communicating with, patients. This may affect their interaction with patients and may not be inclusive for all.

Opportunities	Threats
• Consonant with the strategic objectives of the Trust and Guy's Cancer. • The Trust would be early implementers of this technology for radiotherapy applications, which may lead to positive patient and public opinion and in turn have a positive impact on the reputation of Guy's Cancer. • Collaborative approach to implementation across the Trust ensures a multi-disciplinary and multi-department approach which can be used as a role model for subsequent innovative technology implementation. • Integration of mixed reality for this application may inspire further creative applications within Medical Physics, Radiotherapy, Oncology and across the Trust.	• Patient information is stored on the device. Loss of the device and the information contained therein is a recognised risk. Information governance and General Data Protection Regulations (GDPR) (GDPR, 2018) failure to protect information can result in significant financial penalty to the Trust. • The use of the Hololens might not be suitable for all staff members and patients, therefore an alternative solution is also required. • A new electronic health records system will be introduced by the Trust in 2022. Hololens compatibility with this system has not been investigated. • There have been no clinical trials exploring the use of mixed reality devices in medicine (Eckert *et al*, 2019).

Table B.1: SWOT analysis for Hololens 2.

Financial Analysis

Capital costs are low. The Hololens 2 development edition is £3349.00 including VAT, and the capital cost for two devices can be funded through charitable donation, which has already been identified and agreed. Additionally, it may be possible to claim VAT back from this capital cost due to charitable funding. If required, additional headsets can be purchased at the same cost. Initial staffing costs are considered medium. Additional staffing costs for the creation and development of applications are anticipated to be up to £10,000. Additional funding sources include application for Topol digital fellowship (Topol, 2022) or application to the Institute of Physics and Engineering (IPEM) for an IPEM innovations grant (IPEM, 2021).

Stakeholder Support

The following stakeholders have been identified and initial consultation has started: Department of Medical Physics; Department of Radiotherapy; Department of Clinical Engineering; Department of Clinical Scientific Computing; and the Data, Technology and Information Directorate.

Patient and Public Engagement

The Guy's Cancer Patient Experience Team and the Patient and Public Engagement Team will participate in the evaluation of this technology prior to clinical implementation. Once clinically implemented, patient feedback will be collected to gather knowledge on the use of this technology and its impact on patient experience.

Project Management

A research and development proposal was submitted to the Radiotherapy Research and Development Team by Dr Stephen Morris, Consultant Clinical Oncologist and Emma Jones, Principal Clinical Scientist. The proposal was accepted. Project management, delivery and evaluation will be led by Eleanor Holden, 0.4WTE Radiotherapy Physicist and 0.6WTE Chief Scientific Office Fellow.

Implementation Planning

Table B.2 provides the proposed implementation timeline for Hololens 2.

Action	Schedule
Initial scoping exercise and innovation proposal meeting.	May 2021
Write up of research and development proposal.	June 2021
Present research and development proposal to the Radiotherapy Research and Development multi-disciplinary group (for Departments of Medical Physics, Radiotherapy and Clinical Oncology).	August 2021
Identify and request charitable funding for the purchase of two Hololens 2 devices.	August 2021
Identify stakeholders and propose initial engagement.	September 2021
Proof of concept collaboration for Hololens 2 implementation across multiple applications in the Trust, with the Data, Technology and Information Directorate.	November 2021 - July 2022
Present technology to the Guy's Cancer Patient Experience Team and the Patient and Public Engagement Team.	November 2021
Capital purchase of two Hololens 2 devices.	November 2021
Application for Topol digital fellowship (band 7 dosimetrist).	December 2021
Topol digital fellowship fellowship interviews and notification of funding, if successful.	January 2022
Initial training in the use of Hololens, and training in creation and development of applications.	February 2022
Creation, development and management of applications.	February - June 2022
Clinical training and writing of procedures and work instructions.	June 2022
Clinical implementation.	July 2022

Table B.2: Implementation timeline for Hololens 2.

Training Needs Analysis

Table B.3 provides the training needs analysis for Hololens 2.

All	Physicists/ Dosimetrists	Clincians	Radiographers
• General use of Hololens 2 (including capturing and storing patient images). • Use of Hololens 2 in the patient pathway. • Infection control requirements. • Information governance and GDPR requirements.	• Creation, development and management of applications. • Storing, archiving and retrieving patient information. • Integration of Hololens 2 into existing oncology information systems.	• Appropriate use of device. • Understanding and awareness of patient's experience of the device.	• Appropriate use of device. • Understanding and awareness of patient's experience of the device.

Table B.3: Training needs analysis for Hololens 2.

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C. Authors contributions

(1) Manuscript 1

Author's contributions are as follows:

The author of this thesis is the primary researcher of this work and the author of this manuscript, and has written all of the text therein contained. The author developed the methodology for fulfilling the aim and objectives of this research project. Specifically for this manuscript the author contoured the thoracic and lumbar vertebrae and OAR in the vicinity of these vertebrae (spinal cord, oesophagus, heart, lungs, kidneys and cauda equina) for 16 reference image expert cases and produced the expert case atlas in SmartSegmentation for ABAS. The author evaluated ABAS through application on subsequent multiple CT image data sets.

Additional authors' contributions are as follows:

Carolina Napoleone-Filho, Dosimetrist, Guy's St Thomas' NHS Foundation Trust. Peer reviewed contouring of thoracic and lumbar vertebrae and OAR for 6 reference images added to the expert case atlas in SmartSegmentation and provided guidance and assistance, where required, for the 10 additional reference images.

Dr Victoria Harris, Consultant Clinical Oncologist, Guy's and St Thomas' NHS Foundation Trust. Provided the author with the opportunity to discuss clinical implications of the work described in this manuscript.

Dr Christopher Golby, Radiotherapy Physicist, The Christie NHS Foundation Trust. Academic supervisor for HSST DClinSci research project. Provided the author with the opportunity to discuss the research described, and reviewed this manuscript.

Dr David Eaton, Head of Radiotherapy Physics, Guy's and St Thomas' NHS Foundation Trust. Provided the author with the opportunity to discuss the research described, and reviewed this manuscript.

Antony Greener, former Head of Radiotherapy Physics, Guy's and St Thomas' NHS Foundation Trust. Workplace supervisor for HSST DClinSci research project. With the author secured funding from Varian Medical Systems to carry out this research project. Provided the author with the opportunity to discuss the research described, advising on the direction and progress of the research, and reviewed this manuscript.

(2) Manuscript 2

Author's contributions are as follows:

The author of this thesis is the primary researcher of this work and the author of this manuscript, and has written all of the text therein contained. The author developed the methodology for fulfilling the aim and objectives of this research project. Specifically for this manuscript the author planned all the conformal VMAT plans for target volumes in the thoracic and lumbar regions of the vertebral spine. Using these plans, the author developed three RapidPlan DVH Estimation models, a thoracic RapidPlan model, a lumbar RapidPlan model and a combined thoracic and lumbar RapidPlan model. The author then validated the combined RapidPlan model.

Additional authors' contributions are as follows:

Caroline Sisodia, Dosimetrist, Guy's St Thomas' NHS Foundation Trust. Provided advice and training on VMAT planning of spine metastases. Peer reviewed a selection of treatment plans prior to addition to the RapidPlan DVH estimation model.

Mecaela Couper, Dosimetrist, Guy's St Thomas' NHS Foundation Trust. Provided advice and training on VMAT planning of spine metastases. Peer reviewed a selection of treatment plans prior to addition to the RapidPlan DVH estimation model.

Dr Christopher Golby, Radiotherapy Physicist, The Christie NHS Foundation Trust. Academic supervisor for HSST DClinSci research project. Provided the author with the opportunity to discuss the research described.

Dr Victoria Harris, Consultant Clinical Oncologist, Guy's and St Thomas' NHS Foundation Trust. Provided the author with the opportunity to discuss clinical implications of the work described in this manuscript.

Antony Greener, former Head of Radiotherapy Physics, Guy's and St Thomas' NHS Foundation Trust. Workplace supervisor for HSST DClinSci research project. With the author secured funding from Varian Medical Systems to carry out this research project. Provided the author with the opportunity to discuss the research described, advising on the direction and progress of the research.

(3) Manuscript 3

Author's contributions are as follows:

The author of this thesis was the primary researcher of this work and the author of this manuscript, and has written all of the text therein contained. The author developed the methodology for fulfilling the aim and objectives of this research project. Specifically for this manuscript the author produced the SmartSegmentation expert case atlas for ABAS and the RapidPlan DVH estimation model for KBP. The author randomly selected 10 patients on to which ABAS and KBP were applied to generate 30 VMAT plans for PTVs in the thoracic and lumbar regions of the vertebral spine. The author performed dosimetric evaluation RapidPlan KBP generated VMAT plans against cEBRT.

Additional authors' contributions are as follows:

Porsher Oppong, Dosimetrist, Guy's St Thomas' NHS Foundation Trust. Produced the cEBRT radiotherapy treatment plans.

Caroline Sisodia, Dosimetrist, Guy's St Thomas' NHS Foundation Trust. Provided advice and training on VMAT planning of spine metastases. Peer reviewed a selection of treatment plans prior to addition to the RapidPlan DVH estimation model.

Carolina Napoleone-Filho, Dosimetrist, Guy's St Thomas' NHS Foundation Trust. Peer reviewed contouring of thoracic and lumbar vertebrae and OAR for 6 reference images added to the expert case atlas in SmartSegmentation and provided guidance and assistance, where required, for 10 additional reference images.

Dr Victoria Harris, Consultant Clinical Oncologist, Guy's and St Thomas' NHS Foundation Trust. Provided the author with the opportunity to discuss clinical implications of the work described in this manuscript.

Dr Christopher Golby, Radiotherapy Physicist, The Christie NHS Foundation Trust. Academic supervisor for HSST DClinSci research project. Provided the author with the opportunity to discuss the research described, and reviewed this manuscript.

Antony Greener, former Head of Radiotherapy Physics, Guy's and St Thomas' NHS Foundation Trust. Workplace supervisor for HSST DClinSci research project. With the author secured funding from Varian Medical Systems to carry out this research project. Provided the author with the opportunity to discuss the research described, advising on the direction and progress of the research, and reviewed this manuscript.

D. ESTRO 2021 poster presentation

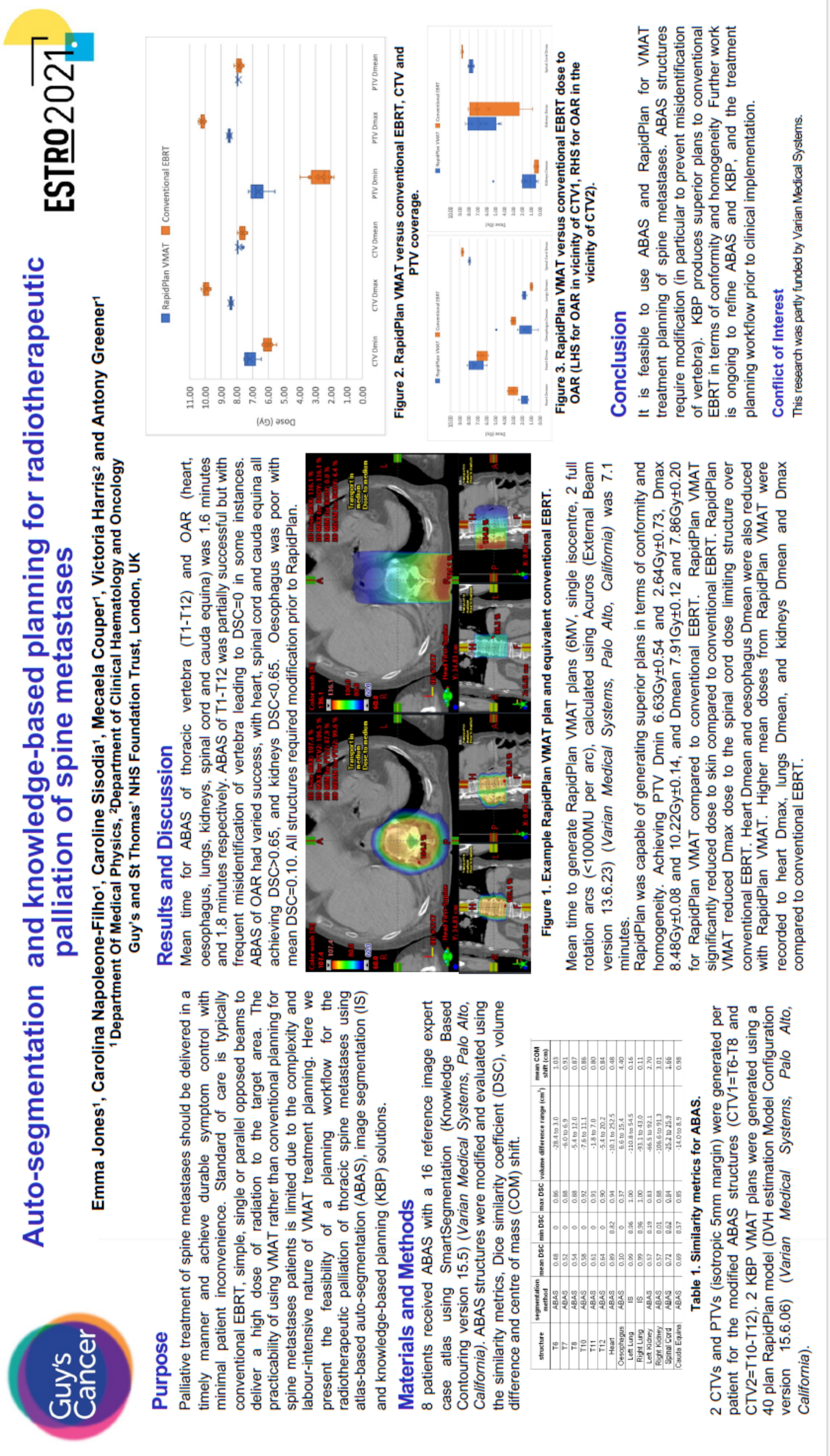

Figure D.1: ESTRO 2021 poster presentation.