IMPROVING RADIOTHERAPY TREATMENTS FOR HEAD AND NECK CANCER PATIENTS

A thesis submitted to the University of Manchester for the degree of

Doctor of Clinical Science

in the Faculty of Biology, Medicine and Health

2022

JULIE S. KIRK

SCHOOL OF MEDICAL SCIENCES

Contents

Word Count - 29,016

I. List of tables and figures

List of Figures

List of Tables

II. Abstract

Radiotherapy for head and neck cancer is a highly complex, multi-step process that requires input from many different staff groups. The timeliness and quality of radiotherapy for head and neck cancer patients is essential in reaching the aims set out in the radiotherapy operational delivery network service specifications (NHS England, 2019). This thesis addresses the issues of timeliness and quality in radiotherapy for head and neck cancer patients.

Timeliness has been addressed in a study of the impact waiting for radiotherapy to start has on overall survival and patient experience. The time between decision to treat with radiotherapy and the start of radiotherapy (TTS) was studied. A TTS greater than 30 days was found to be associated with a significant increase in death when compared to a TTS of less than 15 days. Patient responses to a questionnaire showed that the effect of waiting for radiotherapy to start is patient dependent and not time dependent. This study shows that focus should be on ensuring all patients are treated within a TTS of 30 days.

In radiotherapy of the head and neck it is common for the clinical target volume (CTV) to extend to the patient's skin. For inverse planning this results in excessive fluence being delivered to the build-up region and therefore the skin. A study has been carried out to determine a planning solution that gives superior plan quality when considering CTV coverage, skin dose and plan robustness. This study shows that a virtual bolus planning method was superior to the other common techniques considered.

In the planning study an accurate Eclipse Acuros XB calculation of dose at the surface and in the build-up region was assumed. A novel dosimeter for surface dosimetry has been used to study the differences in skin dose found in the planning study. DOSEmappers™ are a 2D array of Micro Silica Bead TLDs. This study has shown that the Bead TLDs have an effective depth of measurement of 0.7 mm and when constructed as a DOSEmapper™ make an ideal near surface dosimeter. Measurements using DOSEmappers™ confirm the dose differences from different planning approaches used in the planning study. This gives confidence in determining the most superior planning method for head and neck VMAT planning.

This work contributes to the field of head and neck cancer radiotherapy. The time head and neck cancer patients should be treated within and a planning method that gives superior plan quality have been determined and validated.

III. Declaration

The work contained in this thesis is the author's own original research. It has been written by the author and has not been previously submitted for examination for the award of a degree.

IV. Copyright Statement

V. Acknowledgement

This research project would not have been possible without the support, patience and advice of my supervisor Carl Rowbottom.

I would also like to thank my colleagues who have covered work and provided support and encouragement.

Also thanks to my supportive family, who have kept me going in this busy time. I could not have done this without the encouragement of my husband Tony, my children Izzy, Alex and Frankie and my Mum.

Thanks to my academic supervisor Julia Handley who has helped me stay positive and given me valuable feedback.

VI. Background to the Author

Academic Qualifications

- MPhys in Physics with Medical Physics, *The University of Sheffield*, 2000.
- MSc in Medical Physics, *The University of Leeds*, 2002.

Proffered Speaker

The results and conclusions from Paper B were presented at IPEM conference, *Radiotherapy Plan Robustness in clinical practice*, on 16th June 2022.

Research and Clinical Work

This work was completed during a two and half year period, this includes a nine month interruption in studies as discussed in the Covid statement. Throughout this time the author continued to work as a higher principal clinical scientist at The Clatterbridge Cancer Centre NHS FT.

VII. Statement for the Examiners

This research project was completed as a module within the Higher Specialist Scientific Training (HSST) programme. This is a five-year work-based scheme aimed to develop Clinical Scientists with the skills and knowledge they require to act as Consultants.

A degree of Doctor of Clinical Science (DClinSci) is the academic component of the HSST programme. The DClinSci award, is gained through a combination of taught academic modules and a research project. The taught modules have two components: leadership and management (section A) and medical physics (section B). Completed modules, assessment method and word count are included in Appendix A to support this submission. This thesis aims to cover the research component of the DClinSci degree.

The degree has been delivered on a part-time basis, one day a week away from workplace duties was allocated to study.

It is a requirement of the DClinSci to incorporate an innovation proposal into the thesis, this is included in Appendix B.

VIII. Rationale for Submission as Journal Format

This thesis has been submitted in journal format; this was approved by the thesis supervisors. The thesis was naturally separated into three publishable sections, each adding to the over-arching title of improving radiotherapy for head and neck cancer patients.

A journal format helps in making the research ready for publication. One of the aims of the HSST programme is to encourage clinical scientists to participate actively in research and published data. A journal format has given the author valuable experience in writing in this format and has offered a framework to further develop these skills in the future.

The papers included in this thesis have been prepared for publication; however at the time of submission, they have not been sent to journals for acceptance. Some aspects of the paper will need to be changed before being sent. For example, the referencing does not follow that of a published paper but has been kept consistent throughout the thesis.

In keeping with a journal format acknowledgements, author contributions and references have been added at the end of each chapter.

1. Introduction

1.1 Background

Approximately 12,400 new head and neck cancer cases are diagnosed each year in the UK (Cancer research UK, 2022). Radiotherapy services are an integral component of modern cancer care with four out of ten people that are cured of cancer having received radiotherapy as part, or the whole, of their treatment plan (Cancer Research UK, 2014). For head and neck cancers radiotherapy can be used alone or in combination with surgery and systematic therapy. The proportion of head and neck cancer patients having radiotherapy is strongly influenced by sub-group, stage at diagnosis and access (Cancer Research UK, 2022).

Radiotherapy is a highly complex, multi-step process that requires the input from many different staff groups in the planning and delivery of the treatment (BIR, 2008). Availability of radiotherapy for head and neck cancer patients requires the provision of advanced equipment and expert multi-disciplinary staff. The planning and delivery of radiotherapy for head and neck cancers is complex due to multiple dose levels and numerous organs at risk that are close to the target (Hansen et al, 2016). This requires the use of intensity modulated radiotherapy (IMRT) and image guided radiotherapy (IGRT) to ensure accurate dose delivery.

The timeliness and quality of radiotherapy for head and neck cancer patients is essential in reaching the aims set in the radiotherapy operational delivery network service specifications (NHS England, 2019). The aims set include improving the experience of care and reducing variation in quality.

This study attempts to address the issues of timeliness and quality in radiotherapy for head and neck cancer patients. This has been done by studying the impact of waiting for radiotherapy to start has on overall survival and patient experience, a study of planning methods used to compensate for excessive fluence in the build-up region and a study to validate these results.

1.2 Thesis Overview

The impact of waiting for radiotherapy treatment to commence has on a patient can be split into two categories; these being the effect on treatment outcome and patient experience. In 2014 NHS England and Cancer Research UK set a ten year vision for radiotherapy in the UK. One of the aims set out to improve survival and patient experience was to reduce waiting times from diagnosis to treatment (NHS England and Cancer Research UK, 2014). This was later supported by guidance from NHS England "*providers should aim to treat category 1 Service Users within seventeen days from decision to treat with radiotherapy to commencement*" (NHS England, 2019). The impact of waiting for radiotherapy treatment to start has on survival and patient experience for head and neck cancer is studied in Chapter 3. This is presented as a paper prepared for journal submission (Paper A).

Plan quality in the build-up region for head and neck cancer patients is studied in Chapter 4. Inverse planning in the build-up region can cause excessive fluence if not considered as part of the planning process. Solutions to overcome this issue have been studied here to determine the most superior and robust planning method for head and neck cancer patients. This is presented as a paper prepared for journal submission (Paper B).

The planning study assumes an accurate calculation of dose at the surface and in the build-up region. Calculated surface dose between plans differed in the planning study. Chapter 5 describes a study that aims to confirm these differences, therefore validating the results found in the planning study. This is presented as a paper prepared for journal submission (Paper C).

A section at the end of the thesis has been added to critically appraise the papers and research. This has enabled the author to comment on the methods used and discuss what research opportunities might follow from this work.

2 A review of the Available Literature

2.1 The Impact of Waiting for Radiotherapy Treatment to Commence

The Joint Collegiate Council for Oncology report into reducing delays in cancer treatment recommended a good practice target of fourteen days from the date of the first oncologist consultation to the start of radiotherapy, with a maximum acceptable time of 4 weeks (NHS England, 2019). Seventeen days recommended in the NHS England Service Specification allows for an additional weekend on top of the original JCCO recommendation. Reducing the time waiting for radiotherapy is thought to be an advantage; however, in both of these reports no evidence has been presented to support the stated recommended time from consultation to treatment.

The literature was therefore reviewed to determine the effect waiting for radiotherapy has on overall survival and on patient experience.

2.1.1. Effect of waiting on treatment outcome

In 2019 searches were carried out using The University of Manchester's library system and PubMed. The following terms were used "Radiotherapy", "waiting" and "delay". This returned 217 results after duplications were removed. The PRISMA process was then followed to aid selection.

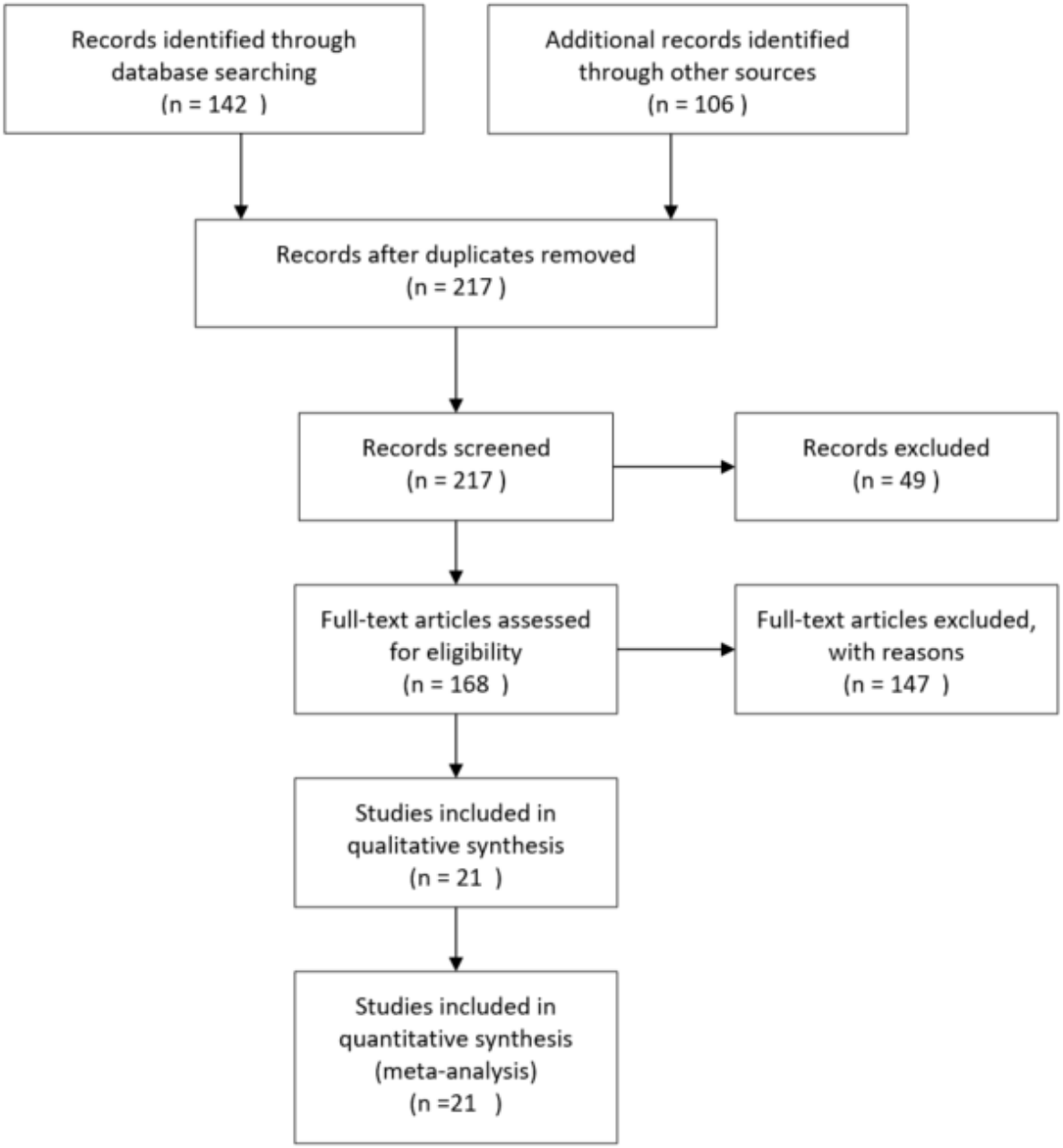

Figure 2.1 PRISMA flow diagram of systematic review for Waiting for Radiotherapy

The 21 studies included in the analysis are summarised in Table 2.1. In 2022 this table was added to using the terms “Radiotherapy”, “waiting” “delay” and “head and neck”, with a date ranging from 01/01/2019. For each study the treatment site, details of the analysis and outcome have been recorded. Additional sites to head and neck have been included in the table for reference but will not be discussed in the literature review.

Table 2.1. Summary of literature from systematic review of waiting for radiotherapy

Author	Year Published	Focus	Patient experience	Sample size	Effect	Time interval	Method of analysis	Outcome	How long is reasonable?
Fortin et al	2002	Early stage head and neck	No	623	Local failure Overall survival	Decision to treat with radiotherapy to treatment	Log-rank comparison of survival curves Cox regression	Significant link delay and local failure/ overall survival	As short as reasonably achievable. Less than 30 days
Leon et al	2002	Head and Neck	Yes	797	Local control Overall survival	Diagnosis to treatment	Chi2 Kruskal-Wallis Log-rank comparison of survival curves	No significant link	As short as reasonably achievable due to psychological distress
Marshak et al	2004	Laryngeal	No	44	Local control Overall survival	Surgery to treatment	Log-rank comparison of survival curves	No significant link	
Choan et al	2005	Cervix	No	195	Overall survival	Biopsy to treatment Action for radiotherapy to treatment	t-test analyses of variance Cox regression	Observed association, significance requires investigation	
Ravnbaek et al	2007	Squamous cell – Head and Neck	No	61	Tumour growth	Diagnostic scan to planning scan	Chi2 Spearman's	Evidence of tumour progression	
Chen et al	2008	Systematic review. Breast and H&N	No	44 studies	Local recurrence	Diagnosis to treatment Surgery to treatment	Meta-analyses	Significant	As short as reasonably achievable
Wang et al	2009	Non-small cell Lung	No	237	Overall survival	Diagnosis to treatment	Log-rank comparison of survival curves	Significant	

Author	Year Published	Focus	Patient experience	Sample size	Effect	Time interval	Method of analysis	Outcome	How long is reasonable?
Karlsson et al	2010	Breast	No	964	Local recurrence Disease-free survival Overall survival	Surgery to treatment	Log-rank comparison of survival curves	No significant link	
Downing et al	2011	Breast	No	18,158	Overall survival	Surgery to treatment	Path analysis	No significant link	
Barbieri et al	2011	Breast	No	387	Risk of local relapse	Surgery to treatment	Cox regression	No significant link	
Noel et al	2012	Glioblastoma	No	400	Overall Survival	5 different intervals examined	Cox regression	No significant link	
Wehming et al	2012	Glioma	No	153	Overall survival	Surgery to treatment	Log rank test Cox regression	No significant link	
Loureiro et al	2014	Glioblastoma	No	115	Overall Survival	Not stated	Chi2, Fisher and Mann-Whitney. Log-rank comparison of survival curves	No prognostic impact on increasing wait	
Loureiro et al	2016	Systematic review - Glioblastoma	No	12 studies 5212	Overall Survival		Meta-analysis	No significant link	
Liang et al	2016	Nasopharyngeal	No	9896	Overall survival	Diagnosis to treatment	Multivariate	Significant when increased beyond 30 days	As short as reasonably achievable
Chevalier et al	2016	Squamous cell – Head and Neck (N0)	No	63	Survival Recurrence Upstaging	Diagnosis to treatment	Chi2 and Fisher Kruskal-Wallis	No significance due to N0 and small sample size.	Less than 50 days
Bhattacharjee et al	2017	Squamous cell – Head and Neck	No	287	Overall survival	Diagnosis to treatment	p-value	Significant	20-45 days

Author	Year Published	Focus	Patient experience	Sample size	Effect	Time interval	Method of analysis	Outcome	How long is reasonable?
Polesal et al	2017	Squamous cell – Head and Neck	No	1616	Overall survival	Diagnosis to treatment	Cox regression	Significant link. Early stage affected greater by delay.	Less than 45 days
Harriset et al	2018	Stages III and IV head and neck cancer	No	25216	Overall survival	Surgery to RT treatment	Multivariable Cox regression	Significant but HR is low when comparing more to less than 50 days	Less than 50 days
Morse et al	2018	Oropharyngeal	No	4089	Overall survival	Diagnosis to treatment end	Cox regression	Significant link	
DeGraaff et al	2019	Head and Neck	No	633	Overall Survival	Diagnosis to treatment	Kaplan-Meier plots Cox regression	No significant link	42 to 60 days
Liao et al	2019	Head and Neck	No	956	Overall survival and recurrence	Diagnosis to treatment	Kaplan-Meier plots Cox regression	Significant	Less than 60 days
Zumer et al	2020	Head and Neck	No	262	Tumour growth	Diagnosis to treatment	Tumour volume doubling time Cox regression	No significant link	
Schoonbeek et al	2022	Head and Neck	No	245	Adverse events and recurrence	Decision to treat with radiotherapy to treatment	Multivariable Cox regression	No significant link	

Of the 24 papers summarised in table 2.1 only 14 are relevant to head and neck cancer patients.

Chen et al (2008) carried out a systematic review of local recurrence rates for breast and head and neck cancer patients. Chen et al used data from 44 studies to determine that a delay in starting radiotherapy is associated with an increase risk in local recurrence. Risk of recurrence was greater in head and neck cancer and could be associated with a decrease in survival. The waiting times studied ranged from a few days to 10 months. This range is beyond the range that is expected now in the UK, due to the 62 day maximum wait from GP referral to treatment (Cancer Research UK, 2013)

Waaijer et al (2002) and Jensen et al (2007) measured the increase in tumour volume between diagnostic and treatment planning CT scans for oropharyngeal cancers and determined the tumour volume doubling time. Jensen et al compared results to Waaijer et al; see Figure 2.2.

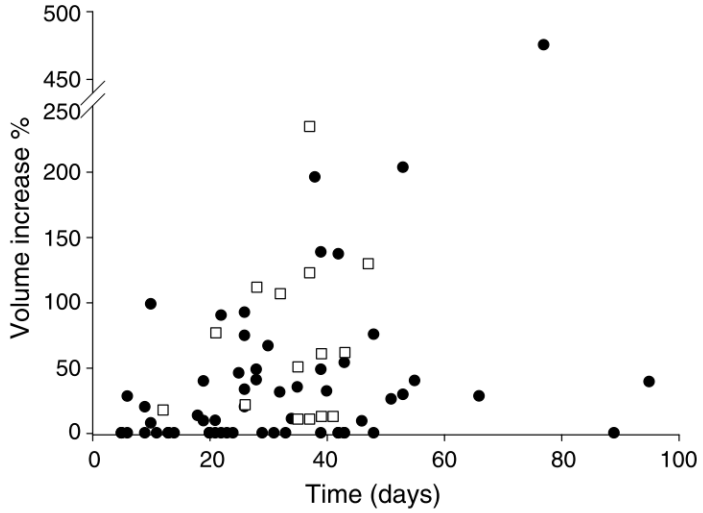

Figure 2.2. Taken from Jensen et al (2007) Tumour volume increase while waiting. Square data from Waaijer and circles from Jensen. Tumour volume doubling time calculated to be within the same range of 87 days (Jensen) and 96 days (Waaijer).

Waaijer et al used the increase in volume to calculate the reduction in tumour control probability (TCP) due to waiting a mean of 56 days. A mean increase in tumour volume of 70% gave an average control loss of 16-19% during the 56 days. For all of the 13 cases the tumour volume increased in size; however, the calculated tumour doubling time varied between 21 days and 256 days. This gives a range of TCP values, results for individual patients and small sample sizes (as in this study) must be considered with care. Both studies showed tumour progression while waiting for radiotherapy but could not define a threshold for acceptable intervals to avoid volume changes. For both studies, large differences in tumour doubling times were observed. The increase in tumour volume will

potentially have an impact on normal tissue complication probability (NTCP) due to the increase in volume irradiated; this has not been discussed in either study. Waaijer et al and Jensen et al show changes that occur while waiting for radiotherapy to start; however the link to patient survival has not been included. A similar study was carried out by Zumer et al (2020) for head and neck cancer patients. Tumour growth kinetics parameters were calculated by comparing differences in diagnostic scans and radiotherapy planning scans. A tumour doubling time of 19 days was calculated. This study also determined the hazard of cancer specific death. It was concluded that further research is needed to identify patients that are at an increased risk due to delay in starting radiotherapy treatment. To carry out this investigation on a large sample size would require a large resource from a multi-disciplinary team and is therefore not possible in this study.

Chevalier et al (2016) carried out a retrospective study on 63 head and neck cancer patients with no nodal involvement. Provided the waiting time was around 50 days, no significant increased risk of upstaging or recurrence was found. Leon et al (2003) findings were similar with a larger sample size of 797. Leon et al found that waiting time is not a significant factor in either local control or survival. Leon et al identified a non-controlled bias due to differences in waiting times in relation to the local extension of the tumour. This bias along with an insignificant variation in waiting times is likely to have affected the outcome of the study. At the time, Leon's finding was considered to confirm the results of earlier studies from other authors. Studies earlier than 2002 have not been included in this literature review, as changes in diagnosis and treatment make these earlier studies less relevant. Schoonbeek et al (2022) studied the effect of delaying treatment beyond 40 days from first consultation with an oncologist. It was found that a delay was not significantly associated with recurrence risk, this study was for patients older than 60 years and only included 93 patients.

DeGraaff et al (2019) studied the effect the time between diagnosis and the initiation of treatment (TTI) has on outcome for head and neck cancer patients. This was a single institution study of 633 patients. Cox regression hazard ratios showed a TTI of 42 to 60 days gave improved overall survival but a TTI of less than 42 days did not significantly reduce overall survival when compared to a TTI of more than 60 days. These results are not consistent with any other study discussed here. The study concluded that outcomes were not affected by delays in treatment initiation and this data should be used to alleviate patient anxiety. When studying the effect of waiting for radiotherapy on local control of

glottis laryngeal cancer Brouha et al (2000) also found no significant correlation between waiting time and outcome; this could be the result of studying a single head and neck cancer site. The cancer site within the head and neck region has an effect on how TTI impacts overall survival (Polesal et al, 2017).

Findings from Chevalier et al (2016), Leon et al (2003) and DeGraaff et al (2019) do not match other studies of head and neck cancer. Fortin et al (2002) and Polesal et al (2017) both had large sample sizes and included patients with different TNM staging. Fortin et al studied the time between evaluation by oncologist and the start of treatment. It was found that a delay of more than 40 days was significantly associated with an increased risk of local and neck failure and poorer survival relative to patients treated in less than 30 days or between 31 and 40 days. For a subgroup of patients with T2N0 disease, a delay of more than 30 days was associated with poorer outcome. Fortin et al therefore concluded that treatment should start within 30 days of oncologist evaluation. Polesal et al found similar results that survival probabilities increase if treated within 45 days of diagnosis. Both studies also found that early stage patients suffered the most from treatment delay.

In a study of 956 patients; Liao et al (2019) found that independent of other relevant factors, patients with a TTI exceeding 60 days had poorer survival and a greater risk of recurrence. A similar result was found by Harris et al (2018) when studying the overall survival as a function of time from surgery to start of radiation for 25,216 patients. A significant increase in mortality was found for a time of 50 days or more. Bhattacharjee et al (2017) found with a similar patient group that survival impact is reduced after 20 days from diagnosis and that radiotherapy should not exceed 45 days to get any benefit. Liang et al (2016) also looked at delays less than the 45 days studied by Polesal et al. This was for a large sample of patients with nasopharyngeal carcinoma. Increasing the time beyond 30 days was found to be detrimental to survival. Nasopharyngeal cancer is much less common in the UK than in far-eastern countries; this study is less relevant to UK practise. Bhattacharjee et al and Liang et al did not investigate the impact staging has on survival; this would have added to findings from Fortin et al and Polesal et al. Combining these studies shows that increasing waiting time after diagnosis beyond 45 days has an impact on survival.

One reason for delay in radiotherapy can be the impact of comorbidity. Stordeur et al (2000) investigated the relationship between comorbidities and therapeutic delay, post treatment mortality, overall survival and relative survival. This study of head and neck cancer patients in Belgium found that comorbidity was not only significantly related to survival but also therapeutic delay. This study also included other therapies in addition to radiotherapy, including surgery and chemotherapy without radiotherapy.

2.1.2. Effect of waiting on patient experience

There are a few studies investigating the physiological effect of waiting for radiotherapy. Patient support groups such as Macmillan give patients the forum to discuss experiences. The Macmillan website (Macmillan, 2019) has many patient stories of how waiting for radiotherapy causes patients to become frustrated and worried. Many patients describe waiting '*as the worst part of the cancer experience: waiting for diagnosis, waiting for treatment*' (Mulcahy et al, 2010). Mulcahy et al's research demonstrates that long waiting periods can create feelings of anxiety and depression for patients. This research was carried out in one centre in Canada with small patient numbers.

Studies on the mental well-being of patients diagnosed with low grade prostate cancer shows that even with a treatment option of active surveillance, waiting can cause depression and anxiety (Albertsen, 2009). This study reviewed the effect of increased prostate cancer detection and the various management approaches on quality of life. It is evident from this study that no matter the diagnosis or management of the disease; waiting for treatment has a large impact on a patient's quality of life.

Lehman et al (2004) carried out a survey of 255 patient's attitudes to waiting times. The study was conducted in three metropolitan radiotherapy centres and two rural centres in Canada. A range of cancer sites were included in the study. This study showed that patients are unlikely to trade-off effectiveness for convenience. The survey required patients to make difficult choices regarding how long they were prepared to wait before needing to travel further or accept a loss of treatment effectiveness. This survey did not address the impact waiting has on a patient and asked patients to accept a loss of treatment effectiveness which will add additional anxiety.

As seen in this review of the literature and highlighted by Jack (2010); increased waiting times for radiotherapy are highly likely to lead to stress, anxiety and depression for patients. Further qualitative studies are needed to confirm these findings.

2.1.3. Gap Analysis

When considering the impact of waiting for radiotherapy to start has on patient survival the evidence presented here is inconclusive. Chevalier et al (2016) and Leon et al (2003) both found that waiting time is not a significant factor in either local control or survival. Others found that survival decreases when treatment does not start within a certain time from diagnosis. Many of the studies measured the impact the time between diagnosis and treatment initiation has on survival. Times that had an impact on survival varied between 45 days and 60 days. Only Fortin et al (2002) and Schoonbeek et al (2022) studied the impact the time between decision to treat with radiotherapy and commencement of treatment. Fortin et al found that a time of greater than 30 days had a disadvantage on patient survival. This is greater than the guidance issued by NHS England in 2019 of seventeen days. It is unclear from the literature if reducing the time between decision to treat with radiotherapy and commencement to seventeen days would have an impact on overall survival. A study of the impact of waiting times on overall survival and patient experience would therefore add knowledge within the context of NHS England guidance.

There is evidence to suggest that any wait in a patient's cancer carepath adds stress and can increase a patient's anxiety. There is limited literature in this field and no evidence to suggest how long is an acceptable waiting time for patients.

Linking the impact of waiting for radiotherapy treatment to commence on overall survival and patient experience has not been previously studied. Considering both impacts is important when considering any quality improvement studies that may aim to reduce the waiting time for radiotherapy treatment.

2.2 Planning methods

In head and neck radiotherapy tumour control is achieved by irradiating clinical target volumes (CTVs) to a prescribed dose. CTVs for head and neck cancers are complex and individual to each patient. In many head and neck cancer patients the CTV can extend to or close to the patient's skin. When a margin is added for uncertainties in set-up and delivery a planning target volume (PTV) that extends beyond the patient surface is created. In inverse planning; dose objectives are added to structures to achieve target coverage, to reduce dose to normal tissues and to avoid hotspots. Coverage of the PTV is achieved by adding a minimum dose objective to the PTV. The treatment planning system (TPS) optimises the plan with the aim to achieve this minimum dose objective. In 2004, Thomas and Hoole demonstrated that PTV based optimisation in the head and neck region removes low doses within the PTV, even within the build-up region. This results in excessive fluence being delivered to the build-up region and therefore the skin. This can result in acute skin toxicity as seen by Lee et al (2002). Since the introduction of inverse planning a number of solutions have been considered to compensate for this problem.

Lee et al (2002) compared skin doses for head and neck cancer patients and concluded that the skin should be considered a sensitive structure when optimising IMRT plans. In this study CTVs that were to or close to the patient's skin were not included. Treatment volumes were delineated away from the patient's skin and dose in this region was not part of the patient's treatment. Lee et al did not investigate the effect that geometric errors have on target coverage. This planning method is considered similar to removing the skin structure from the PTV when optimising and similar to the approach of cropping the PTV away from the patient surface. This solution is described in a number of UK and international head and neck radiotherapy trials; such as NIMRAD (NIMRAD QA Team, 2014), PATHOS (Owadally et al, 2018) and JAVALIN (Avelumab, 2016). For example, the JAVALIN trial dictates that the PTV must be extracted 3.0 mm from the skin (Avelumab, 2016). This is a similar approach to that used by de Neve et al (2002). This planning method was investigated by Thomas and Hoole (2004). It was found that cropping the PTV back from the patient surface can lead to inadequate CTV coverage when geometric errors are considered.

Studies from non-head and neck sites have been included in this review to determine what planning methods have been used to deal with excessive fluence in the build-up region.

Hong (1999) overcame the problem of increased fluence for breast fixed field IMRT by optimising to a PTV that excluded the build-up region and then extending the fields beyond the skin. This method could be used for fixed field head and neck IMRT plans but is not possible when treating with Volumetric Modulated Arc Therapy (VMAT).

Thilmann et al (2002) first investigated a virtual bolus technique for IMRT breast tangential fields. This study found that a 10 mm thickness of bolus was adequate in eliminating the unintended dose increase in the build-up region. These plans were compared to plans using conventional tangential fields and found to give superior results in plan quality. This study did consider the effect of changes to patient anatomy but did not determine how robust the plan was to these types of changes.

The use of virtual bolus in the planning of breast cancer treated with arc therapy was studied by Tyran et al (2018). In this study plans with and without virtual bolus were compared by evaluating CTV coverage on a CT performed during treatment and as a consequence to modification in the patient's anatomy. The study showed the virtual bolus plan gave an increased CTV coverage compared to the non-virtual bolus plans. Thus demonstrating the benefit of using virtual bolus during VMAT planning to compensate for potential changes in breast shape. This study used patient data to evaluate the effect of patient changes and determined how robust a plan was to these changes.

In total body irradiation (TBI) the CTV is the entire body, including the skin. The PTV therefore extends into the surrounding air. Bardies et al (2017) studied the performance of virtual bolus when planning TBI treatments when treated with tomotherapy. The optimal virtual bolus was determined to compensate for large setup errors without introducing hotspots. Virtual bolus of different densities, thickness and design were tested. PTV coverage in the presence of setup errors and fluence peak at the phantom surface was used to assess the virtual bolus performance. In this study the virtual bolus remains in place for the entire planning process but is not used in treatment. This increased the dose delivered due to the increase in patient thickness. The optimal virtual bolus was found to be 8.0 mm thick with a density of 0.4 kg m^{-3}, this included a PTV expansion of 5.0 mm from the skin surface and an additional 3.0 mm of virtual bolus. This study demonstrates that a virtual bolus planning technique is beneficial for the

specific case of total body irradiation where the target is large and setup errors of up to 10.0 mm are observed.

Thomas and Hoole (2004) studied the virtual bolus planning method for head and neck plans. It was concluded that this method gave the most superior results when considering CTV coverage. This solution is also described in UK and European head and neck radiotherapy trials; such as NIMRAD (NIMRAD QA Team, 2014), PATHOS (Owadally et al, 2018) and "Best of" trial (Clemental at al, 2017). For example, guidance for "Best of" trial does not allow PTV margin reduction in the skin direction without justification.

A more complex solution is described by Nguyen et al (2009). This solution uses a multiple-isocentre CTV based objective function. The aim of the method is to give good CTV coverage for all geometric uncertainties without increasing the skin dose. This complex method requires implementation by commercial treatment planning systems and is likely to increase the optimisation time. This method will not be discussed further.

Comparison of fixed field IMRT plans optimised using the different techniques to compensate for the build-up was compared by Thomas and Hoole (2004). This work was based on fixed field IMRT where individual segments can be viewed and manipulated. There is no literature addressing the best solution for optimising in the build-up region for head and neck plans delivered with VMAT. Table 2.2 summaries the guidance from head and neck trials. This shows that there no international or national consensus on which planning method is the best approach.

Table 2.2. Summary of the planning method used from four head and neck trials

Trial	Solution in trial guidance
NIMRAD	PTV cropped from surface and Virtual bolus
PATHOS	PTV cropped from surface and Virtual bolus
JAVALIN	PTV cropped from surface
Best of	Virtual bolus

2.3. Surface Dosimetry

Section 2.2 assumes accurate calculation of skin dose by the treatment planning system. Surface dose and initial build-up dose is an important measure of skin toxicity. Surface dose measurements are challenging, due to steep dose gradients in the surface area and the absence of electron equilibrium (Kim at al 2012). This literature review aims to determine the accuracy of the Eclipse Acuros XB (AXB) algorithm at calculating surface dose and establish an accurate method of measuring surface dose.

There have been a number of studies comparing the Eclipse Anisotropic Analytical Algorithm (AAA) and AXB to Monte Carlo simulations and measurement, these studies are summarised in table 2.3.

Table 2.3. Summary of studies evaluating the accuracy of treatment planning (TPS) algorithms at the surface and in the build-up region.

Study	Algorithm	Comparison Method	Oblique Incidence/ Treatment site	Difference to TPS
Dogan and Glasgow (2003)	AAA (2.5 mm grid)	Parallel plate chamber in phantom	Oblique incidence and IMRT	25%
Akino et al (2012)	AAA v10.0 (2.5 mm grid)	GafChromic EBT2 Film	Breast FF IMRT	15% - 30%
Kim et al (2012|)	AAA (2.5 mm Grid)	Attix chamber GafChromic EBT2 Film Monte Carlo	Direct incidence	20%
Zhunag and Olch (2014)	AAA (1.0 mm grid)	OSLD dosimeters Parallel plate chamber (Markus) Monte Carlo	IMRT plans	Good agreement
Badkul et al (2015)	AAA (1.0 mm grid)	MOSFETs	Range of clinical plans	Good agreement
Uehare and Tachibana (2016)	AXB	Kodak EBR2 Film	Head and neck FF IMRT	4%
Akbas et al (2017)	AAA (2.5 mm grid)	GafChromic EBT3 Film	Head and neck FF IMRT	
Cao et al (2017)	AAA, AXB, PBC and CCC	GafChromic EBT2 Film Monte Carlo	Oblique incidence	Algorithm dependent
Wang et al (2018)	AAA (2.5 mm grid)	OSLD dosimeters Monte Carlo	3D conformal, FF IMRT and VMAT	4% with extended body contour
Arbor et al (2019)	AAA (1.0 mm dose grid)	GafChromic EBT3 film Monte Carlo	Breast plans	25%
Kesen and Akbas (2021)	AXB	Parallel plate chamber (Markus) GafChromic EBT3 Film	Direct incidence	Good agreement

Akino et al (2012) investigated the accuracy of Eclipse treatment planning system in the build-up region for various breast cancer treatment techniques including IMRT using Gafchromic EBT2 film. This comparison was of Eclipse TPS version 10.0 with AAA. Calculations were performed with a 2.5 mm grid size. This study found that for all techniques the measured dose was 15% to 30% higher than the TPS. This concludes that Eclipse AAA v10.0 does not provide accurate dosimetry at depths less than 6.0 mm. This result was confirmed by Akbas et al (2017). Akbas et al used GafChromic EBT3 film to evaluate the surface dose calculated by Eclipse AAA with a grid size of 2.5 mm for fixed field IMRT plans for head and neck cancer patients. The surface doses were found to be lower in the TPS compared to GafChromic EBT3 film both in IMRT and open field irradiations. The difference was found to be greater for the IMRT fields and concluded to be likely to be due to the use of oblique fields.

Akbas et al confirms the earlier work of Dogan and Glasgow (2003). Dogan and Glasgow studied the effect of IMRT fields on the dose from oblique incident beams. The study showed that IMRT does not contribute to greater skin doses and confirmed that oblique incidence does increase skin dose and moves depth of maximum dose closer to the surface. Comparisons were also made to the planning system and found that doses were overestimated by 25% at the surface and 5% below the surface compared to parallel-plate chamber measurements. Measurements were made in a 30cm x 30cm x 30cm polystyrene phantom for both 0° and 75° incident beams. The increase in surface dose with oblique incident beams and an overestimate of the planning system was also found by Mutic and Low (2000) and Kim et al (2012). Kim et al (2012) assessed the accuracy of surface dose determined by direct measurement (with Attix chamber) and the TPS relative to Monte Carlo calculations. This study showed that the Attix chamber underestimates the surface dose by 2.9%, while EBT2 GafChromic overestimates by 0.9%. The study also showed that Eclipse AAA over estimates the surface dose by up to 20%, and this drops to 2% at depths greater than 2 mm. The study demonstrated the usefulness of GafChromic EBT2 film for measuring surface dose.

Some of the reported difference in surface dose may be explained by the position of the external body contour. Wang et al (2018) showed that the accuracy of skin dose calculated in Eclipse considerably improved by extending the external body contour 1 to 2 cm from the patient's skin. Different extensions beyond the patient's skin was not investigated. The position of the external body contour has not been discussed in any other study.

All of the above studies show differences in the measured dose and the dose calculated by Eclipse AAA dose calculation algorithm at the surface. There are contradictions between studies; some state an over-estimation and others an under-estimation of dose at the surface and within 2.0 mm of the surface. Other studies have shown good agreement between measurement, Monte Carlo simulations and Eclipse AAA. Zhuang and Olch (2014) used optically stimulated luminescent dosimeters (OSLDs) and Eclipse AAA to evaluate the accuracy of skin dose determination. The surface dose for an open 6 MV field was measured using OSLDs and compared to the dose measured with a Markus parallel plate chamber, surface diodes and calculated using Monte Carlo simulations. Three OSLDs were then used to measure the skin doses for IMRT plans where the PTV extended to the surface. These measurements were compared to Eclipse AAA calculations. This showed that OSLDs are accurate dosimeters for measuring skin doses. This study concluded that with accurate commissioning in the build-up region and calculating on a 1 mm dose grid, Eclipse AAA calculates surface dose with a high accuracy. Badkul et al (2015) also investigated the accuracy of Eclipse AAA surface dose for varying dose grids compared to measurements with metal-oxide-semicondutor-field-effect-transistors (MOSFETs) for a range of clinical beams. A body phantom was used to measure at 5 locations for each beam type. These results showed that grid size has a significant impact on calculated surface dose and 1 mm dose grid calculations closely agreed with measurement.

A recent study has evaluated the dose accuracy in the near-surface region for whole breast irradiation (Moncion et al, 2022). This study used radiochromic film to measure doses at 5.0 mm and 10.0 mm depths in a custom made breast phantom. Measured doses were compared to the dose calculated by the TPS for a range of algorithms. It was found that all algorithms calculated near surface dose within an accuracy within 6%. Eclipse AXB was not included in this study and no comparison was made at depths less than 5.0 mm. For head and neck cancer treatment the accuracy of dose calculations at depths less than 5.0 mm is important.

The differences in results seen in table 2.3 may be explained by the conclusions of a study carried out by Court and Tishler (2008). This studied concluded that the steep dose gradient at the surface can make reliable dose calculations difficult. It was found that the interplay between pixel size, pixel location, exact phantom (or patient) location, contour

grid, and dose calculation grid can be expected to have an important effect on the calculated doses.

It is likely the uncertainty in TPS dose at the surface is algorithm dependent. This was investigated by Cao et al (2017). Film measurements and Monte Carlo simulations were compared to four algorithms; Eclipse AXB, Eclipse AAA, Pinnacle Pencil Beam Convolution (PBC) and Raystation Collapsed Cone Convolution (CCC). Comparisons were made for incident angles of 0°, 30° and 60°. The study found that dose calculation in the superficial 2.0 mm varied for each algorithm. AXB performed well for all angles except for a small under-estimation. AAA and PBC showed large discrepancies in calculated dose in the superficial region (less than 2.0 mm) with an incident angle of 30° and 60°. Kesen and Akbas (2021) confirmed the improvement of AXB compared to AAA for superficial calculation but only for an incident angle of 0°. Uehare and Tachibana (2016) used Kodak film to compare to plans calculated with AXB and Adaptive convolve for head and neck IMRT plans. The depth dose profiles were evaluated using EBR2 film sandwiched with solid water. The results showed that AXB over-estimated the dose by 4% for shallow areas ahead of the build-up region.

Many studies have investigated the accuracy of Eclipse AAA for surface dose calculation. Results have not shown consistency between studies; however a range of measurement techniques have been used and evaluated. Studies have shown accurate measurement of dose at the surface with an advanced Markus parallel plate chamber when corrections are made for over-exposure. Other measurement methods such as EBRT2 GafChromic film and detectors such as OSLDs and MOSFITs have also been used successfully to measure surface dose.

A recently available detector called DOSEmappers^{TM} (TRUEinvivo®, Surrey, UK), consisting of Micro Silica bead TLDs have the potential to be good surface dose detectors. Clear Micro Silica Bead TLDs have a linear response to dose, have no angular dependence and response is independent of dose rate (Jafari, 2013). The glass beads show a relativity small energy dependence over the megavoltage range. When normalised to unity for 6MV X-rays, the responses decreases to 0.96 ±0.02 for 15 MV X-rays. (Jafari, 2014). These properties along with the small size (2 mm diameter and 1 mm thickness) make Micro Silica Bead TLDs a suitable detector for measuring doses in high dose gradients and for delivery techniques such as VMAT and non-coplanar beams. Feasibility

studies (Jafari, 2015 and Jafari, 2017) have shown that the Micro Silica Bead TLDs are suitable for clinical plan verification and can be used for postal dosimetry audits. The use of DOSEmappers^{TM} as a surface dose dosimeter have not previously been evaluated.

Studies investigating the accuracy of Eclipse AXB for surface dose and build-up doses have shown that Eclipse can accurately calculate dose in this steep dose gradient region. However, measured doses of the different planning methods used to compensate for excessive fluence in the build-up region have not been studied previously.

2.4 References

Akbas, U. et al. (2017). Surface dose measurement with Gafchromic EBT3 film for intensity modulated radiotherapy technique. *EPJ Web of Conferences*, 154, pp.7–10.

Akino, Y. et al. (2013). Evaluation of superficial dosimetry between treatment planning system and measurement for several breast cancer treatment techniques. *Medical Physics*, 40(1).

Albertsen, P. C. (2010). The Unintended Burden of Increased Prostate Cancer Detection Associated With Prostate Cancer Screening and Diagnosis. *Urology*, *75*(2), 399–405. http://doi.org/10.1016/j.urology.2009.08.078

Arbor, N. et al. (2019). A GATE/Geant4 Monte Carlo toolkit for surface dose calculation in VMAT breast cancer radiotherapy. *Physica Medica*, 61(April), pp.112–117. [online]. Available from: https://doi.org/10.1016/j.ejmp.2019.04.012.

Avelumab (2016) MSB0010718C Study B9991016 Radiation Guidelines for Protocol B9991016 (FINAL)

Badkul, R., Nejaiman, S., Pokhrel, D., Jiang, H. and Kumar, P. (2015), SU-E-T-196: Comparative Analysis of Surface Dose Measurements Using MOSFET Detector and Dose Predicted by Eclipse - AAA with Varying Dose Calculation Grid Size. Med. Phys., 42: 3377-3377.

Barbieri, V., Sanpaolo, P., & Genovesi, D. (2011). Interval between breast-conserving surgery and start of radiation therapy in early-stage breast cancer is not predictive of local recurrence: A single-institution experience. *Clinical Breast Cancer*. http://doi.org/10.1016/j.clbc.2011.03.004

Bardies, M., Simon, L., Moliner, G., Ferrand, R., Izar, F., & Ken, S. (2017). Virtual bolus for total body irradiation treated with helical tomotherapy. *Journal of Applied Clinical Medical Physics*, *16*(6), 164–176. http://doi.org/10.1120/jacmp.v16i6.5580

Bhattacharjee, A., Bhattacharyya, T., Santhosh, S., Kiran, P., Sanudev Sadanandan, V. P., & Geetha, M. (2017). Impact of waiting time for treatment on survival in patients undergoing radiotherapy for head and neck cancer. *Journal of Cancer Policy*, *13*, 1–4. http://doi.org/10.1016/j.jcpo.2017.03.014

Brouha, X.D.R. et al. (2000). Does waiting time for radiotherapy affect local control of T1N0M0 glottic laryngeal carcinoma? *Clinical Otolaryngology and Allied Sciences*, 25(3), pp.215–218.

Cao, Y. et al. (2017). Superficial dose evaluation of four dose calculation algorithms. *Radiation Physics and Chemistry*, 137, pp.23–28. [online]. Available from: http://dx.doi.org/10.1016/j.radphyschem.2016.02.032

Chen, Z., King, W., Pearcey, R., Kerba, M., & Mackillop, W. J. (2008). The relationship between waiting time for radiotherapy and clinical outcomes: A systematic review of the literature. *Radiotherapy and Oncology*, *87*(1), 3–16. http://doi.org/10.1016/j.radonc.2007.11.016

Chevalier, C., Bertaut, A., Quivrin, M., Vulquin, N., Desandes, C., Folia, M., … Maingon, P. (2016). Impact of waiting time on nodal staging in head and neck squamous-cell carcinoma treated with radical intensity modulated radiotherapy. *Clinical and Translational Radiation Oncology*, *1*(December 2013), 27–32. http://doi.org/10.1016/j.ctro.2016.11.002

Clementel, E. and Joachim, G. (2017). Phase III study assessing The "Best of" radiotherapy compared to the "Best of" surgery (trans-oral surgery (TOS)) in patients with T1-T2, NO oropharyngeal carcinoma. RTQA Guidelines – Version 2.0.

Court, L.E. et al. (2008). Experimental evaluation of the accuracy of skin dose calculation for a commercial treatment planning system. *Journal of Applied Clinical Medical Physics*, 9(1), pp.29–35.

DeGraaff, L.H. et al. (2019). The effect of time between diagnosis and initiation of treatment on outcomes in patients with head and neck squamous cell carcinoma. *Oral Oncology*, 96(July), pp.148–152.

Do, V., Gebski, V., & Barton, M. B. (2000). The effect of waiting for radiotherapy for grade III/IV gliomas. *Radiotherapy and Oncology*, *57*(2), 131–136. http://doi.org/10.1016/S0167-8140(00)00257-7

Dogan, N. and Glasgow, G.P. (2003). Surface and build-up region dosimetry for obliquely incident intensity modulated radiotherapy 6 MV x rays. *Medical Physics*, 30(12), pp.3091–3096.

Downing, A., Gilthorpe, M. S., Dodwell, D., Lawrence, G., & Forman, D. (2011). Waiting Times for Radiotherapy after Breast-conserving Surgery and the Association with Survival: A Path Analysis. *Clinical Oncology*. http://doi.org/10.1016/j.clon.2011.02.004

Fortin, A., Bairati, I., Albert, M., Moore, L., Allard, J., & Couture, C. (2002). Effect of treatment delay on outcome of patients with early-stage head-and-neck carcinoma receiving radical radiotherapy. *International Journal of Radiation Oncology Biology Physics*, *52*(4), 929–936. http://doi.org/10.1016/S0360-3016(01)02606-2

Harris, J.P. et al. (2018). Association of survival with shorter time to radiation therapy after surgery for US patients with head and neck cancer. *JAMA Otolaryngology - Head and Neck Surgery*, 144(4), pp.349–359.

Hong, L., Hunt, M., Chui, C., Spirou, S., Forster, K., Lee, H., … McCormick, B. (1999). Intensity-modulated tangential beam irradiation of the intact breast. *International Journal of Radiation Oncology Biology Physics*, *44*(5), 1155–1164. http://doi.org/10.1016/S0360-3016(99)00132-7

Jack, R. H., & Holmberg, L. (2010). Waiting times for radiotherapy after breast cancer: Minimising delay improves outcomes, so investment and planning are needed. *Medical Journal*, *340*(7746), 545–546. http://doi.org/10.1136/bmj.c1007

Jafari, S.M. et al. (2013). Low-cost commercial glass beads as dosimeters in radiotherapy. *Radiation Physics and Chemistry*, 97, pp.95–101. [online]. Available from: http://dx.doi.org/10.1016/j.radphyschem.2013.11.007.

Jafari, S.M. et al. (2014). Energy response of glass bead TLDs irradiated with radiation therapy beams. *Radiation Physics and Chemistry*, 104, pp.208–211. [online]. Available from: http://dx.doi.org/10.1016/j.radphyschem.2014.03.009.

Jafari, S.M. et al. (2015). Feasibility of using glass-bead thermoluminescent dosimeters for radiotherapy treatment plan verification. *British Journal of Radiology*, 88(1055), pp.1–6.

Jafari, S.M. et al. (2017). Feasibility study of silica bead thermoluminescence detectors (TLDs) in an external radiotherapy dosimetry audit programme. *Radiation Physics and Chemistry*, 141(July), pp.251–256. [online]. Available from: http://dx.doi.org/10.1016/j.radphyschem.2017.07.021.

Karlsson, P., Cole, B. F., Colleoni, M., Roncadin, M., Chua, B. H., Murray, E., … Gruber, G. (2011). Timing of radiotherapy and outcome in patients receiving adjuvant endocrine therapy. *International Journal of Radiation Oncology Biology Physics*. http://doi.org/10.1016/j.ijrobp.2010.02.042

Kesen, N. and Akbaş, C. (2021). The investigation of the anisotropic analytical algorithm (Aaa) and the acuros xb (axb) dose calculation algorithms accuracy in surface and buildup region

Kim, J.H., Hill, R. and Kuncic, Z. (2012). Practical considerations for reporting surface dose in external beam radiotherapy: A 6 MV X-ray beam study. *Australasian Physical and Engineering Sciences in Medicine*, 35(3), pp.271–282.

Lee, N., Chuang, C., Quivey, J. M., Phillips, T. L., Akazawa, P., Verhey, L. J., & Xia, P. (2002). Skin toxicity due to intensity-modulated radiotherapy for head-and-neck carcinoma. *International Journal of Radiation Oncology Biology Physics*, *53*(3), 630–637. http://doi.org/10.1016/S0360-3016(02)02756-6

Lehman, M., Jacob, S., Delaney, G., Papadatos, G., Jalaludin, B., Cail, S., … Barton, M. (2004). Waiting times for radiotherapy - A survey of patients' attitudes. *Radiotherapy and Oncology*, *70*(3), 283–289. http://doi.org/10.1016/j.radonc.2004.01.012

León, X., De Vega, M., Orús, C., Morán, J., Vergés, J., & Quer, M. (2003). The effect of waiting time on local control and survival in head and neck carcinoma patients treated with radiotherapy. *Radiotherapy and Oncology*, *66*(3), 277–281. http://doi.org/10.1016/S0167-8140(03)00022-7

Liang, H., Xiang, Y. Q., Lv, X., Xie, C. Q., Cao, S. M., Wang, L., … Xia, W. X. (2017). Survival impact of waiting time for radical radiotherapy in nasopharyngeal

carcinoma: A large institution-based cohort study from an endemic area. *European Journal of Cancer*. http://doi.org/10.1016/j.ejca.2016.12.009

Liao, D.Z. et al. (2019). Association of Delayed Time to Treatment Initiation with Overall Survival and Recurrence among Patients with Head and Neck Squamous Cell Carcinoma in an Underserved Urban Population. *JAMA Otolaryngology - Head and Neck Surgery*, 145(11), pp.1001–1009.

Loureiro, L. V. M., Pontes, L. de B., Callegaro-Filho, D., Koch, L. de O., Weltman, E., Victor, E. da S., … Malheiros, S. M. F. (2015). Waiting time to radiotherapy as a prognostic factor for glioblastoma patients in a scenario of medical disparities. *Arquivos de Neuro-Psiquiatria*, *73*(2), 104–110. http://doi.org/10.1590/0004-282X20140202

Loureiro, L. V. M., Victor, E. D. S., Callegaro-Filho, D., Koch, L. D. O., Pontes, L. D. B., Weltman, E., … Malheiros, S. M. F. (2016). Minimizing the uncertainties regarding the effects of delaying radiotherapy for Glioblastoma: A systematic review and meta-analysis. *Radiotherapy and Oncology*. http://doi.org/10.1016/j.radonc.2015.11.021

Macmillan Cancer Support (2019). Available at: https://community.macmillan.org.uk/cancer-blogs/b/community_news/posts/the-worry-of-waiting (Accessed: January 2019)

Marshak, G., Rakowsky, E., Schachter, J., Shvero, J., Feinmesser, R., Sulkes, A., & Brenner, B. (2004). Is the delay in starting postoperative radiotherapy a key factor in the outcome of advanced (T3 and T4) laryngeal cancer? *Otolaryngology - Head and Neck Surgery*, *131*(4), 489–493. http://doi.org/10.1016/j.otohns.2004.02.042

Moncion, A. et al. (2022). Evaluation of Dose Accuracy in the Near-Surface Region for Whole Breast Irradiation Techniques in a Multi-institutional Consortium. *Practical Radiation Oncology*, 12(4), pp.e317–e328. [online]. Available from: https://doi.org/10.1016/j.prro.2022.01.013.

Morse, E. et al. (2018). National treatment times in oropharyngeal cancer treated with primary radiation or chemoradiation. *Oral Oncology*, 82(February), pp.122–130. [online]. Available from: https://doi.org/10.1016/j.oraloncology.2018.02.010.

Mulcahy, C. M., Parry, D. C., & Glover, T. D. (2010). The "patient Patient": The trauma of waiting and the power of resistance for people living with cancer. *Qualitative Health Research*, *20*(8), 1062–1075. http://doi.org/10.1177/1049732310369139

Mutic, S. and Low, D.A. (2000). Superficial doses from serial tomotherapy delivery. *Medical Physics*, 27(1), pp.163–165.

NHS England and Cancer Research UK (2014) Vision for Radiotherapy 2014 – 2024. Available at: https://news.cancerresearchuk.org/2014/03/03/radiotherapy-our-vision-for-the-next-ten-years/ (Accessed: 20 June 2022)

NHS England (2019) Adult External Beam Radiotherapy Services Delivered as Part of a Radiotherapy Network. Available at: https://www.england.nhs.uk/wp-content/uploads/2019/01/External-Beam-Radiotherapy-Services-Delivered-as-Part-of-a-Radiotherapy-Network-Adults.pdf (Accessed: 20 February 2019)

NIMRAD QA Team (2014). A randomised placebo-controleed trial of synchronous NI-Morazole versus RADiotherapy alone in patients with locally advanced head and neck squamous cell carcinoma not suitable for synchronous chemotherapy or cetuximab. Radiotherapy planning, delivery and QA guidelines, version 1.1.

Nguyen, T. B., Hoole, A. C. F., Burnet, N. G., & Thomas, S. J. (2009). The optimization of intensity modulated radiotherapy in cases where the planning target volume extends into the build-up region. *Physics in Medicine and Biology*, *54*(8), 2511–2525. http://doi.org/10.1088/0031-9155/54/8/017

Owadally, W. et al. (2018). A Phase II / III trial of risk-stratified , reduced intensity adjuvant treatment in patients undergoing transoral surgery for Human Papillomavirus (HPV) - positive oropharyngeal cancer Radiotherapy Outlining , Planning , Delivery and Quality Assurance.

Polesel, J., Furlan, C., Birri, S., Giacomarra, V., Vaccher, E., Grando, G., … Franchin, G. (2017). The impact of time to treatment initiation on survival from head and neck cancer in north-eastern Italy. *Oral Oncology*, *67*, 175–182. http://doi.org/10.1016/j.oraloncology.2017.02.009

Ravnsbæk, A., Marie, H., & Overgaard, J. (2007). Tumor progression in waiting time for radiotherapy in head and neck cancer, *84*, 5–10. http://doi.org/10.1016/j.radonc.2007.04.001

Stordeur, S. et al. (2020). Comorbidity in head and neck cancer: Is it associated with therapeutic delay, post-treatment mortality and survival in a population-based study? *Oral Oncology*, 102(November 2019), p.104561. [online]. Available from: https://doi.org/10.1016/j.oraloncology.2019.104561.

Thilmann, C., Zabel, A., Nill, S., Rhein, B., Hoess, A., Haering, P., … Debus, J. (2002). Intensity-modulated radiotherapy of the female breast. *Medical Dosimetry*, *27*(2), 79–90. http://doi.org/10.1016/S0958-3947(02)00089-4

Thomas, S. J., & Hoole, A. C. F. (2004). The effect of optimization on surface dose in intensity modulated radiotherapy (IMRT). *Physics in Medicine and Biology*, *49*(21), 4919–4928. http://doi.org/10.1088/0031-9155/49/21/005

Waaijer, A., Terhaard, C. H. J., Dehnad, H., Hordijk, G. J., Van Leeuwen, M. S., Raaymakers, C. P. J., & Lagendijk, J. J. W. (2003). Waiting times for radiotherapy: Consequences of volume increase for the TCP in oropharyngeal carcinoma. *Radiotherapy and Oncology*, *66*(3), 271–276. http://doi.org/10.1016/S0167-8140(03)00036-7

Wang, L., Correa, C. R., Hayman, J. A., Zhao, L., Cease, K., Brenner, D., … Kong, F. M. (2009). Time to Treatment in Patients With Stage III Non-Small Cell Lung

Cancer. *International Journal of Radiation Oncology Biology Physics*. http://doi.org/10.1016/j.ijrobp.2008.08.039

Wang, L., Cmelak, A.J. and Ding, G.X. (2018). A simple technique to improve calculated skin dose accuracy in a commercial treatment planning system. *Journal of Applied Clinical Medical Physics*, 19(2), pp.191–197.

Wehming, F. M., Wiese, B., Nakamura, M., Bremer, M., Karstens, J. H., & Meyer, A. (2012). Malignant glioma grade 3 and 4: How relevant is timing of radiotherapy? *Clinical Neurology and Neurosurgery*. http://doi.org/10.1016/j.clineuro.2011.12.024

Zhuang, A.H. and Olch, A.J. (2014). Validation of OSLD and a treatment planning system for surface dose determination in IMRT treatments. *Medical Physics*, 41(8).

Žumer, B. et al. (2020). Impact of delays in radiotherapy of head and neck cancer on outcome. *Radiation Oncology*, 15(1), pp.1–10.

3 Paper A

The Impact of Waiting for Radiotherapy Treatment to Start on Survival and Patient Experience for Head and Neck Cancer at Clatterbridge Cancer Centre

Authors: Julie Kirk[1], Carl Rowbottom[1]

[1] Department of Physics, The Clatterbridge Cancer Centre NHS FT, Liverpool, UK.

Target Journal – Clinical Oncology

Abstract

Purpose: The impact of waiting for radiotherapy to start has on a patient can be split into two categories; these being the effect on treatment outcome and patient experience including well-being. The purpose of this study was to determine the local wait time that has a disadvantage on patient survival and quality of life.

Method: Data from 819 head and neck cancer patients treated from January 2017 to December 2019 was obtained from Aria. The time to treatment start (TTS) was calculated as the number of days between decision to treat date and the date of first treatment. TTS was categorised into 3 groups: 0 to < 15 days, 15 to 29 days, and ≥ 30 days. The overall survival probabilities were estimated from Kaplan-Meier analysis. A log-rank test was used to assess survival difference according to TTS. Hazard ratios (HRs) of death, and corresponding 95% confidence intervals (CIs) were estimated using Cox regression models. Log rank tests were also used to assess survival differences according to age, sex and diagnosis and hazard ratios of death were estimated using Cox regression.

Data relating to patient experience and well-being was collected via a questionnaire. The questionnaire was distributed to 75 head and neck cancer patients. A Grounded theory method of analysis was used to establish a hypotheses from the returned data.

Results: A TTS greater than 30 days was found to be associated with a significant increase in death (HR = 2.545; 95% CI 1.131 – 5.727) when compared to a TTS < 15 days. Age and diagnosis were also found to be associated to overall survival.

Responses to the patient experience questionnaire was obtained from 22 patients. Waiting for radiotherapy treatment to start was considered important to eight patients. 55% of patients reported thinking about the treatment often in this time. Patients reported concerns of treatment outcome, side effects, employment and risk of cancer spreading. This affected patient's quality of life leading to anxiety, worry and effects on relationships and sleep. No correlation were found between the importance of reducing wait times, concerns or effect on daily life and the actual time a patient waited.

Conclusion: A TTS that exceeds 30 days was found as being significant in reducing survival. Focus should therefore be on ensuring all patients are treated within a TTS of 30 days. A patient questionnaire studying the effect of waiting for radiotherapy treatment to start has on patient's quality of life supports this conclusion.

3.1. Introduction

The impact of waiting for radiotherapy to start has on a patient can be split into two categories; these being the effect on treatment outcome and patient experience including well-being. A joint report by NHS England and Cancer Research UK in 2014 set a ten year vision for radiotherapy in the UK. One of the aims set out to improve survival and patient experience was to reduce waiting times from diagnosis to treatment (NHS England and Cancer Research UK, 2014). In additional to this report; radiotherapy specifications have been published by NHS England. External beam radiotherapy services delivered as part of a radiotherapy network state '*providers should aim to treat category 1 Service Users within seventeen days from decision to treat with radiotherapy to commencement*' (NHS England, 2019). Fourteen days was recommended by Joint Collegiate Council for Oncology (JCCO, 1993), seventeen days allows for an additional weekend. Reducing the time waiting for radiotherapy is thought to be an advantage; however, neither of these reports has presented evidence to support these recommendations.

There have been a number of studies on how time to treatment initiation (TTI) impacts survival for head and neck cancer patients. The TTI is the time between patient diagnosis and start of radiotherapy treatment. Studies by Chevalier et al (2016), Leon et al (2003) and DeGraff et al (2019) found that TTI did not have a significant impact on patient outcome. These studies were considered to confirm the findings of earlier studies, such as Brouha et al (2000). Leon concluded that outcomes were not affected by delays in treatment initiation and that this should be used to alleviate patient anxiety. Schoonbeel et al (2022) studied the effect a delay to primary treatment initiation had on adverse effects and recurrence. It was found a delay was significantly associated with recurrence for surgery patients but no significant association was found for radiotherapy patients. This is contradicted by the finding of others, such as Fortin et al (2002) and Polesal et al (2017). Both of these large sample sized studies found delaying radiotherapy had a deleterious effect and radiotherapy should be started as soon as possible. For Fortin et al this was within 20-30 days after evaluation by an oncologist and Polesal et al within 45 days of diagnosis. It was also concluded by Liao et al (2019), independent of other relevant factors, that patients with a TTI exceeding 60 days had poorer survival and a greater risk of recurrence. These studies do not reflect the seventeen day time frame recommended in the Radiotherapy service specifications (NHS England, 2019). This

study aims to evaluate the impact of time between decision to treat with radiotherapy and treatment start (TTS) has on survival. This differs from previous studies; TTS will be shorter than TTI and has the advantage of matching the time set in the radiotherapy service specifications.

Jack (2010) and Mulcahy et al (2010) demonstrated that increased waiting times for radiotherapy are highly likely to lead to stress, anxiety and depression for patients. There are limited qualitative studies; this study therefore aims to determine how important waiting for radiotherapy treatment is to head and neck cancer patients and how waiting for radiotherapy treatment to start affects the patient's quality of life.

3.2. Materials and Method

3.2.1 Impact of TTS on Survival

3.2.1.1 Study Population

The Clatterbridge Cancer Centre serves a population of 2.4 million people across Cheshire, Merseyside and the surrounding areas, including the Isle of Man. Radiotherapy treatment is provided to head and neck cancer patients through the record and verify system Aria (Varian, Palo Alto, CA). Aria is used to map the patient's radiotherapy carepath from pre-treatment imaging through to the end of treatment. Aria is not an electronic patient record (EPR) system but does hold information such as diagnosis and key dates such as diagnosis date and decision to treat date. This data is automatically transferred from the EPR system to Aria via an integration engine.

Aria was used to report on all patients that had a plan name containing H+N, NH or H&N and started treatment between 1st January 2017 and 31st December 2019. Patients that were treated for a palliative intent, lymphoma, sarcoma or a skin cancer were removed from the study. Patients that did not complete the full course of radiotherapy were also removed from the study. This left a total of 819 patients available for the analysis.

Aria was used to obtain the following information: date of birth (DoB), sex, diagnosis, date of diagnosis, date of decision to treat with radiotherapy (D2T) and date of first radiotherapy treatment. The decision to treat date is the date the patient was seen by a clinical oncologist and actioned for radiotherapy treatment using an electronic action sheet (EAS). Completion of the EAS starts the radiotherapy pre-treatment process.

Patient information such as TNM staging, comorbidities and the inclusion of other treatments such as chemotherapy and surgery are not available in Aria and have therefore not been included in this study.

3.2.1.2 Statistical Analysis

All statistical analysis performed in this study used IBM SPSS Statistics v. 28 (IBM, Armonk, NY, USA). A similar statistical analysis as that used by Polesel et al (2017) and Liao et al (2019) has been followed in this study. Time elapsed (days) since date of decision to treat with radiotherapy (D2T) to the date of death, or to the follow-up date of 1st February 2022, whichever came first, was calculated. The time to treatment start (TTS) was calculated as the number of days between decision to treat date and date of first treatment. TTS was categorised into three groups: 0 to < 15 days, 15 days to 29 days, and ≥ 30 days. The overall survival probabilities were estimated by Kaplan-Meier analysis. A log-rank test was used to assess survival difference according to TTS. Hazard ratios (HRs) of death, and corresponding 95% confidence intervals (CIs) were estimated using Cox regression models. The TTS hazard ratios were also estimated when adjusted for age.

The time to treat initiation (TTI) is the number of days between diagnosis date and date of the first treatment. This time has not been analysed in this study as it does not match the time set in the radiotherapy service specifications. Studying TTS has the advantage that it can be controlled by the processes within a radiotherapy department. Process redesign through a quality improvement project could be used to reduce the TTS for head and neck cancer patients if it was found to impact overall survival.

Log rank tests were also used to assess survival differences according to age, sex and diagnosis. Hazard ratios of death were estimated using Cox regression models. These categorises and corresponding demographics are shown in table A1. SPSS only allows a maximum of 8 categories. Diagnosis was therefore grouped as shown in table A1.

Table A1. Demographics of data set

Variable	Patients (N= 819)
TTS (Days)	
<15	35 (4.3%)
15 to 29	696 (85%)
≥ 30	88 (10.7%)
Age (Years)	
<50	100 (12.2%)
50 to 64	389 (47.5%)
65 to 74	239 (29.2%)
≥75	91 (11.1%)
Sex	
Female	225 (27.5%)
Male	594 (72.5%)
Diagnosis	
Floor of mouth	27 (3.3%)
Glottis*	114 (13.9%)
Nasopharynx	27 (3.3%)
Parotid	25 (3.1%)
Sinus**	38 (4.6%)
Tongue***	211 (25.8%)
Tonsil	218 (26.6%)
Other****	159 (19.4%)

** includes Glottis, Supraglottis and Larynx*
*** includes Pyriform Sinus, Maxillary Sinus and Nasal Cavity*
**** includes base of tongue and boarder of tongue*
***** includes Oropharynx, Hypopharynx, Submandibular gland, Thyroid, unknown primary, Uvula and Tonsillar fossa*

Other covariates, such as comorbidities and TNM staging have not been included in this study.

3.2.2 Impact of TTS on Patient Experience

3.2.2.1 Questionnaire Design

The Health Foundation published guidance in 2013 in how to measure patient experience (de Silva, 2013). The guidance presents evidence in approaches to measure patient and carer experiences of healthcare. The evidence base described cannot prescribe the best approaches, but it does highlight some of the key learning points to consider. The aim of the questionnaire in this study was to understand the time head and neck cancer patients were willing to wait for radiotherapy treatment and how waiting for radiotherapy

treatment to start affected the patient's quality of life. The questionnaire was designed with assistance of patient representatives that are part of this institution's Patient Experience and Inclusion Group. The questionnaire used open and closed ended questions. Some key questions were repeated in different formats to ensure understanding and to evaluate consistency of the answers provided.

An option was added for the patient to include their name. This was optional as it was thought that it may reduce a patient's willingness to complete the questionnaire. Having the patient's name added to the analysis as wait times estimated by the patient could be compared to the actual wait times (TTS).

The questionnaire is shown in Appendix C.

3.2.2.2 Study Population

The questionnaire was given to all radial head and neck patients until 75 questionnaires had been distributed. Ashley et al (2012) studied when best to approach cancer patients to take part in improvement studies. It was reported that this is best done when patients are settled on treatment provided they are coping physically and emotionally. Questionnaires were therefore given to patients when they were in week two or three of treatment. At this point the patients have settled into their treatment and before they may start to struggle to cope physically with any treatment side effects.

3.2.2.3 Analysis

A Grounded theory method of analysis has been used in this study. In grounded theory the analysis and development of theories happens after the data has been collected (Statistics How To). It was first introduced by Glaser and Strauss in 1967. Grounded theory is an inductive process of identifying analytical categories as they emerge from the data (Glaser and Strauss, 1967). In this process data is read and reread to identify themes and categories. Grounded theory relies on a constant comparison, in which each item is checked or compared with the rest of the data. Once categorised it should then be possible to move towards hypotheses or propositions about the data.

3.3. Results

3.3.1 Impact of Time to Treatment Start (TTS) on Survival

Overall, 819 head and neck cancer patients were identified. The majority of cases (89.3%) were treated with a curative intent within 30 days of decision to treat. Six of the 819 patient waited more than 50 days between decision to treat and treatment. The average TTS was 23.2 days (7.82 days), median 20 days and interquartile range Q1 – Q3: 19 days – 26 days. The minimum TTS was 8 days and the maximum 113 days. TTS was similar according to age, sex and diagnosis.

Overall survival decreased with increasing TTS is shown in figure A1. Compared to TTS < 15 days, the corresponding unadjusted hazard ratios (HRs) of death were 1.661 (95% CI: 0.783 - 3.523) for 15 to 29 days and 2.070 (95% CI: 0.923 – 4.644) for ≥ 30 days. When adjusted for age the HRs increased as shown in table A2. Only a TTS ≥ 30 days is associated with a significant increase of death (HR = 2.545; 95% CI 1.131 – 5.727). TTS in the group 15 days to 29 days do show an increased HR compared to < 15 days; however the 95% confidence intervals drop below 1.0 so are therefore considered insignificant.

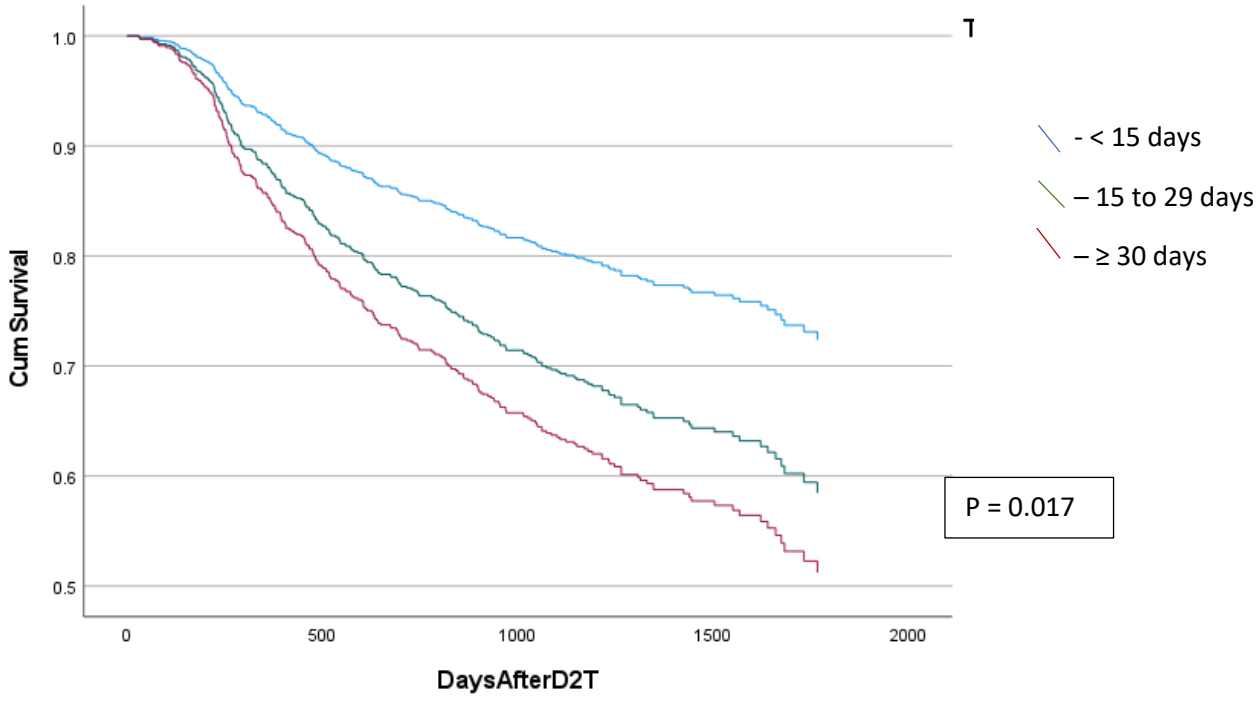

Figure A1. Overall survival according to time to treatment to start

Table A2 shows the HRs of death for selected covariates of age, sex and diagnosis. Age is associated with a significant increase of death. Compared to an age of < 50 years the HRs of death were 1.779 (95% CI: 1.097 – 2.884) for age group of 50 to 64 years, 2.243 (95% CI: 1.336 – 2.684) for group 65 to 74 years and 3.749 (95% CI: 2.203 – 6.379) for ≥ 75 years. This is also shown in figure A2. The HR for males compared to females was insignificant however there were 594 males in the study compared to just 225 females. When compared to a diagnosis of the Floor of Mouth; tongue and tonsil diagnoses had a significant reduction in the HR. HRs for each diagnosis are shown in table A2.

Table A2 Hazard ratio(HR) of death and 95% confidence intervals (CI) according to time to treatment start (TTS), age, sex and diagnosis

	Patients n	**Deaths n**	**Deaths %**	**Univariate HR (95% CI)**	**HR adjusted for age (95% CI)**
TTS (Days)					
<15	35	7	20	Reference	Reference
15 to 29	696	233	33.5	1.661 (0.783-3.523)	1.827 (0.860 - 3.878)
≥ 30	88	37	52	2.070 (0.923 – 4.644)	2.545 (1.131 – 5.727)
Age (Years)					
<50	100	19	19	Reference	
50 to 64	389	122	31.4	1.779 (1.097 - 2.884)	
65 to 74	239	88	36.8	2.243 (1.366 – 2.684)	
≥75	91	48	52.7	3.749(2.203 – 6.379)	
Sex					
Female	225	68	30.2	Reference	
Male	594	209	35.2	1.215 (0.924 – 1.598)	
Diagnosis					
Floor of mouth	27	15	55.6	Reference	
Glottis	114	46	40.4	0.702 (0.392 – 1.258)	
Nasopharynx	27	10	37.0	0.561 (0.252 – 1.249)	
Parotid	25	10	40.0	0.651 (0.292 – 1.449)	
Sinus	38	17	44.7	0.894 (0.447 – 1.791)	
Tongue	211	65	30.8	0.486 (0.277 – 0.853)	
Tonsil	218	51	23.4	0.346 (0.194 – 0.615)	
Other	159	63	39.6	0.667 (0.380 – 1.171)	

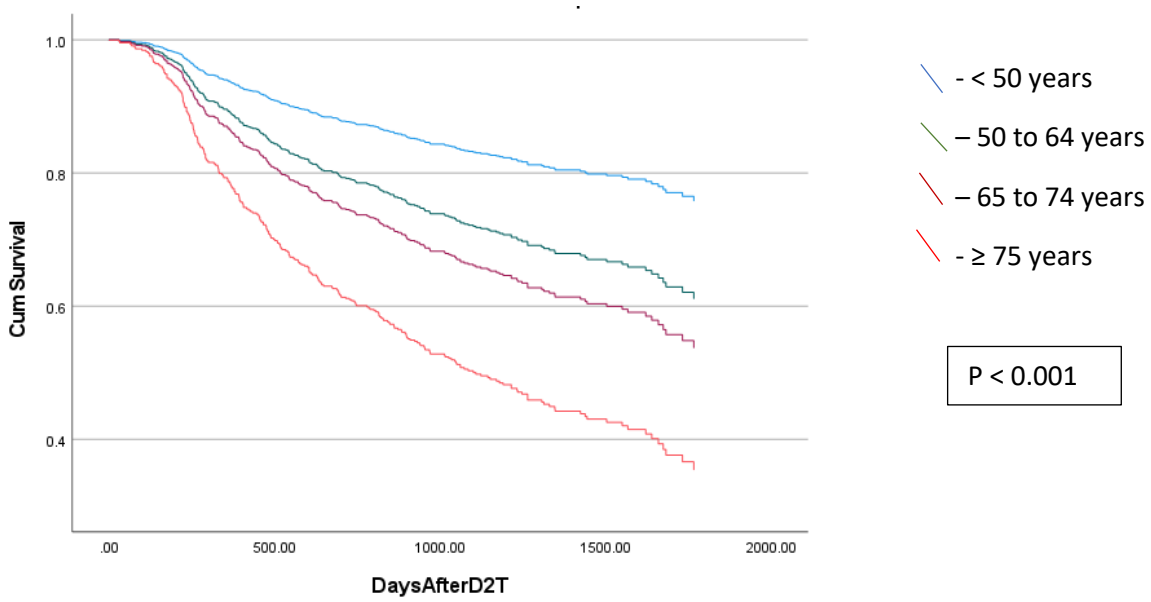

Figure A2. Overall survival according to patient age at decision to treat date.

3.3.2 Impact of TTS on Patient Experience

Of the 75 questionnaires distributed; responses from 22 patients were returned. Seventeen of these patients gave their name and therefore actual wait times could be extracted from ARIA. The patient estimated TTS verses the actual TTS is plotted in the figure A3.

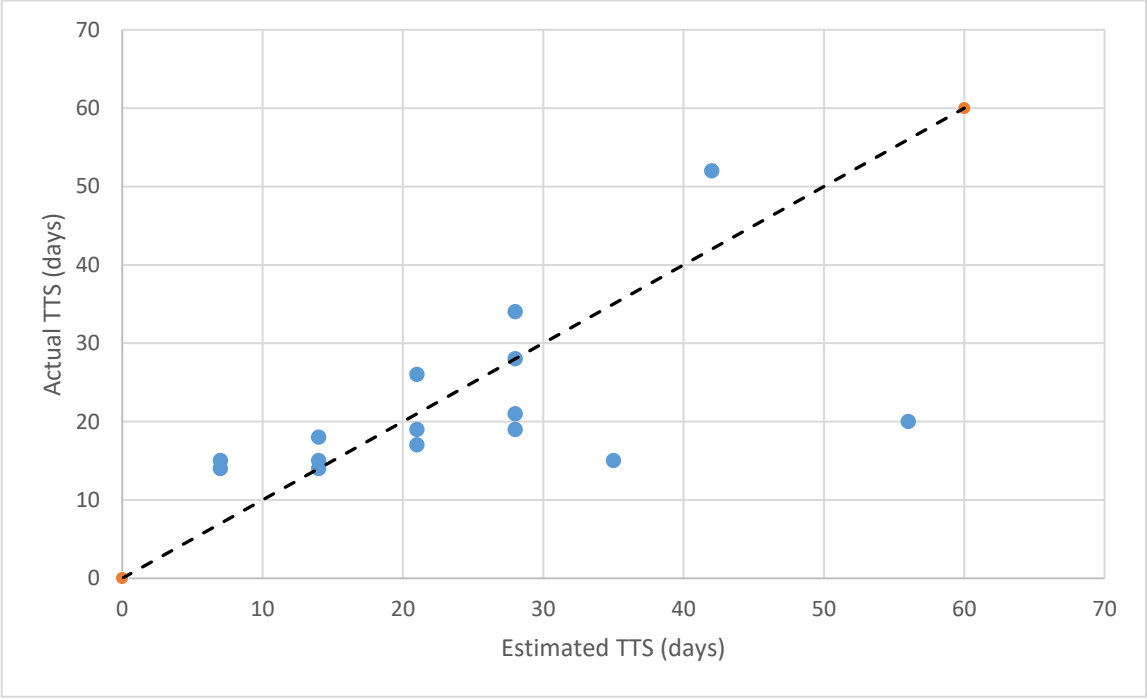

Figure A3. Patient estimated TTS and actual TTS. Dashed line represents estimated TTS equal to actual TTS.

The average TTS times estimated by patients was 25.4 days (12.4 days). A large range in answers was given from 7 days to 56 days. Patients 12 and 22 reported waiting significantly longer (≥ 20 days) than the actual wait time, this could have been a miss understanding of the question. Without a discussion with the patients it is difficult to establish if this was the case. The remaining patients who gave their name all estimated the wait time within ± 10 days of the actual wait time.

Some patients TTS was affected by personal circumstances. Patient 7 reported being out of the country and patient 9 was having care in another hospital. Patient 11 stated '*I wanted to start as quickly as possible but appreciate further tests and scans had to be performed*'.

Two patients estimated they waited 7 days, in both cases this was an under-estimate of the waiting time as the actual time was 14 days and 15 days.

Questions 2, 3 and 5 were all aimed to establish the importance to head and neck patients of when treatment starts. 20 of the 22 patients reported they were satisfied or very satisfied with the time they had to wait for treatment to start. However 17 patients stated they would have been ready to start treatment sooner and 9 patients were prepared to travel if they could have started treatment sooner. One patient who stated they were prepared to travel to start sooner, contradicted this answer by stating they would have not been ready to start sooner. One patient was traveling from the Isle of Man and therefore was unsure in answering the question with regard to travel time as travel time was already high.

Table A3 shows the category of patients that reported they would have been ready to start treatment sooner and were prepared to travel to start sooner. This patient category gives an indication of which patients considered a reduction in TTS important.

Table A3. Category of patients who reported they would have been ready to start treatment sooner and were prepared to travel to start sooner. Question 2. Were you satisfied with the timescales from consultation with your radiotherapy doctor to the start of your radiotherapy treatment? Very satisfied scores 5, very dissatisfied scores 0. Question 6. If you could have started treatment sooner in another hospital how far would you have been prepared to travel?

Patient No.	Estimated wait time (days)	Actual wait time (days)	Qu2. How satisfied with timescales?	Qu. 6 Travel Time (mins)
2	21		2	30
4	42	52	4	120
5	7	15	5	60
6	14	14	5	60
7		39	4	60
11	56	20	5	30
13			5	60
14	28	34	3	120

Table A4 shows the link between how often a patient thinks about starting treatment during the TTS time and the estimated and actual TTS times. Statistical analysis of this data shows there is no correlation between TTS and thinking about treatment. Twelve patients (55%) reported thinking about their treatment often, with a score of 8 or greater.

Table A4. Link between how often a patient thinks about start treatment and estimated and actual TTS. Question 11. During this time on an average day how often did you think about starting treatment? 0 being none of the time and 10 being all of the time.

Patient No.	Qu. 11 How often think about starting trt	Estimated TTS	Actual TTS
1	8	21	19
2	10	21	
3	10	28	
4	10	42	52
5	4	7	15
6	10	14	14
7	2		39
8	0	14	18
9	0		19
10	8	28	19
11	8	56	20
12	3	35	15
13	10		
14	4	28	34
15	10	14	15
16	10	28	21
17	10	21	26
18	0	28	28
19	0	7	14
20	8	21	17
21	5	28	
22	4	42	

Of the 22 patients, eight had concerns regarding treatment outcome and five had concerns relating to treatment side effects while waiting for radiotherapy to start. Others reported concerns around cost of travel, employment, work, financial, '*worry cancer is getting worse and spreading*' and '*fear of treatment mask*'. A number of patients reported how this affected their daily life during this time '*unable to perform simple task as worrying all the time*', '*general worry, sleepless and extra epileptic fits*', '*felt scared and upset*', '*Just general anxiety*', '*made me very anxious daily*'. Many patients reported that they felt their daily life was not affected or did not answer the question. To determine if the category of patients identified in table A3 have a greater concern than the rest of the patient cohort the scoring of question 11 and statements from questions 12 and 13 are shown in table A5. This shows that 62% of this category of patients reported thinking about their treatment often, with a score of 8 or greater.

Table A5. Quality of life measures for patient category who consider starting radiotherapy treatment sooner important.

Patient No.	Qu. 11 How often think about starting trt	Qu.12 Patient concerns	Qu. 13 Effect on daily life
2	10	Very worried	Worried all the time
4	10	Cost travel, employment	Created stress
5	4	Treatment outcome	
6	10	Side effects of treatment	Worry and sleepless
7	2	Treatment outcome	Relationships
11	8	Treatment outcome and side effects	General anxiety
13	10	Treatment outcome	Stress
14	4	Treatment outcome	

All patients reported that the time between visits was explained to them and that they were told when the treatment was going to start. Two patients stated that the treatment start date changed and were told why the change was required.

3.4. Discussion

3.4.1 Impact of TTS on Survival

The results of this study confirmed a reduction in overall survival when TTS exceeds 30 days, this is independent of other relevant factors. This study has explored the time between decision to treat with radiotherapy and the start of treatment. The timing was also studied by Fortin et al (2002); it was found that a delay of more than 40 days was significantly associated with an increased risk of local and neck failure and poorer survival relative to patients treated in less than 30 days or between 31 and 40 days. A subgroup of patients with T2N0 disease a delay of more than 30 days was associated with poorer outcome. Fortin et al therefore concluded that treatment should start within 30 days of oncologist evaluation. The majority of other studies have determined the impact TTI has on survival. TTI is the time between diagnosis and the initiation of treatment, therefore the TTI times that impact survival are higher than reported in this study and by Fortin et al. Table A6 shows the studies that found time to treatment had a disadvantage for patient survival. The time each study found to significantly impact survival is reported.

Table A6. Comparison of head and neck studies where time to treatment had a disadvantage on patient survival.

Study	Time interval studied	Time to impact survival
Fortin et al (2002)	TTS	30 days
Liang et al (2016)	TTI	45 days
Bhattacharjee et al (2017)	TTI	45 days
Polesal et al (2017)	TTI	45 days
Harris et al (2018)	TTI	50 days
Liao et al (2019)	TTI	60 days
This study	TTS	30 days

A TTS of more than 30 days has been reported in this study as resulting in a significant reduction in overall survival. A TTS of 30 days is much higher than the guidance issued by NHS England in 2019 that '*provider should aim to treat category 1 Service Users within seventeen days from decision to treat with radiotherapy to commencement*'.

This study has not investigated the reason for a delayed start to treatment. In some cases it is likely that a delay may be a result of other co-morbidities or a poor performance statues. It is likely that co-morbidities affected a large proportion of the patient group, Fazel et al (2020) examined 643 head and neck patient files and found that 79.6% had co-morbidities. Co-morbidities are likely to impact overall survival and not including them in this study is a limitation.

In this study age and diagnosis were found to be significant covariates. As a patient age increases the hazard ratio of death significantly increases. Tongue and tonsil diagnoses were found to have a significant reduction in the HR compared to other head and neck diagnoses.

The data used in this analysis of survival and the patient questionnaires were carried out at very different times. The survival data was from patients treated between January 2017 and December 2019. These patients were treated before radiotherapy specifications were published by NHS England in 2019, with a guidance of a TTS of seventeen days. This data was also for patients treated before the COVID pandemic and before the opening of a new cancer centre. To determine if these factors have affected wait times the analysis

would need to be repeated with more recent data. Responses from the questionnaire carried out in late 2021 into early 2022 have an average wait time of 22.6 days (10.4 days) compared to 23.2 days (7.82 days) in the study presented. The TTS time determined from the questionnaire is only an average from 17 patients but does show that TTS times are similar to that from 2017 to 2019. It may be that the publishing of radiotherapy specifications has not had an impact on TTS time in the local setting. The data from the questionnaire shows that 3 patients had a TTS ≥ 30 days and that large variations in TTS are still present.

3.4.2. Impact of TTS on Patient Experience

Using Grounded theory a category of patients has been identified where a reduction in TTS is considered to be important. This group of patients have stated that they would have been ready to start treatment sooner and were prepared to travel to start treatment sooner. Table A3 shows there is a large variation in the patient estimated wait time and actual wait time for this small patient group. The range of these wait times covers the range seen in the full patient group. It may have been expected that patients who have waited a longer than average time would have been less satisfied with waiting and would have been prepared to travel. The actual wait time and the time the patient estimated they waited does not correlate to importance of starting treatment sooner. In the patient category shown in table A3, 62% reported thinking about starting radiotherapy often (scoring 8 or more), compared to 55% of the full patient cohort. Considering the small patient numbers this difference is not considered significant. The patient concerns reported and the effect waiting has on a patients daily life is no different from the full patient cohort. It can therefore be concluded from this category of patients that there is no link between importance of starting treatment sooner, estimated TTS times and how the patient is affected in this time.

Table A4 shows there is no correlation between estimated and actual TTS and how often a patient thinks about starting radiotherapy during this time. Four patients estimated having a TTS greater than 30 days, two of these patients reported thinking about starting treatment often (score 8 or higher) and stated that concerns caused stress and anxiety that affected their daily life. Two of these patients scored less than five and stated they did not have any concerns. It is therefore not possible to identify a TTS time that begins

having a negative impact on a patient's quality of life. From this data it has been hypothesised that the effect of waiting for radiotherapy treatment to start has on a patient's quality of life is patient dependent and not time dependent.

Only one patient stated '*worry cancer is getting worse and spreading*'. The concerns from the majority of patients was treatment outcome and treatment side effects. Although from a relatively small sample size, the questionnaire highlights that outcome and side effects are more likely to be important to patients than waiting for treatment to start.

3.5. Conclusion

The impact of waiting for radiotherapy to start has on patient overall survival has been found in this study to be significant when the time exceeds 30 days. The patient responses to a quality of life questionnaire supports this conclusion. This shows that reducing the wait time to less than 30 days improves overall survival and is likely to have a positive impact on a patient's quality of life.

In both the larger patient cohort used for survival analysis and the smaller cohort reporting patient experience a large range of TTS was found. Results show that 10.7% of head and neck cancer patients waited more than 30 days for radiotherapy treatment to start. Based on patient feedback and overall survival data; it is clear that this is an area for improvement.

Considering both impact on patient survival and patient's quality of life it has been concluded that there should be a greater focus on ensuring all head and neck cancer patients are treated within a TTS of 30 days.

3.6.Acknowledgements

The authors wish to thank Jennifer Cadwallader for her assistance with questionnaire distribution and collection. Thanks also to The Clatterbridge Cancer Centre's Patient Experience and Inclusion group for their contributions in developing the patient questionnaire.

3.7. Author Contributions

Julie Kirk contributed to study design, data collection, analysis and interpretation, and drafted the manuscript. Carl Rowbottom contributed to study design, data collection, study supervision, and critical revision of the manuscript. All authors discussed the results and gave final approval of the submitted article.

3.8. References

Ashley L, Jones H, Velikova G, Wright P. Cancer patients' and clinicians' opinions on the best time in secondary care to approach patients for recruitment to longitudinal questionnaire-based research. Support Care Cancer 2012; 20(12): 3365- 3372.

Bhattacharjee, A., Bhattacharyya, T., Santhosh, S., Kiran, P., Sanudev Sadanandan, V. P., & Geetha, M. (2017). Impact of waiting time for treatment on survival in patients undergoing radiotherapy for head and neck cancer. *Journal of Cancer Policy*, *13*, 1–4. http://doi.org/10.1016/j.jcpo.2017.03.014

Brouha, X.D.R. et al. (2000). Does waiting time for radiotherapy affect local control of T1N0M0 glottic laryngeal carcinoma? *Clinical Otolaryngology and Allied Sciences*, 25(3), pp.215–218.

Chevalier, C., Bertaut, A., Quivrin, M., Vulquin, N., Desandes, C., Folia, M., Maingon, P. (2016). Impact of waiting time on nodal staging in head and neck squamous-cell carcinoma treated with radical intensity modulated radiotherapy. *Clinical and Translational Radiation Oncology*, *1*(December 2013), 27–32. http://doi.org/10.1016/j.ctro.2016.11.002

DeGraaff, L.H. et al. (2019). The effect of time between diagnosis and initiation of treatment on outcomes in patients with head and neck squamous cell carcinoma. *Oral Oncology*, 96(July), pp.148–152.

De Silva. (2013). Measuring the patient experience. *Nurse Researcher*, 19(1), pp.25–28.

Fazel, A. et al. (2020). The Influence of Smoking and Co-morbidity on Dose Achievement in Primary or Adjuvant Radio(Chemo)Therapy in Head and Neck Squamous Cell Carcinoma (HNSCC). *Frontiers in Oncology*, 10(March).

Fortin, A., Bairati, I., Albert, M., Moore, L., Allard, J., & Couture, C. (2002). Effect of treatment delay on outcome of patients with early-stage head-and-neck carcinoma receiving radical radiotherapy. *International Journal of Radiation Oncology Biology Physics*, *52*(4), 929–936. http://doi.org/10.1016/S0360-3016(01)02606-2

Glaser, B., & Strauss, A. (1967). The Discovery of Grounded Theory: Strategies for Qualitative Research. Mill Valley, CA: Sociology Press.

Jack, R. H., & Holmberg, L. (2010). Waiting times for radiotherapy after breast cancer: Minimising delay improves outcomes, so investment and planning are needed. *Medical Journal*, *340*(7746), 545–546. http://doi.org/10.1136/bmj.c1007

León, X., De Vega, M., Orús, C., Morán, J., Vergés, J., & Quer, M. (2003). The effect of waiting time on local control and survival in head and neck carcinoma patients treated with radiotherapy. *Radiotherapy and Oncology*, *66*(3), 277–281. http://doi.org/10.1016/S0167-8140(03)00022-7

Liao, D.Z. et al. (2019). Association of Delayed Time to Treatment Initiation with Overall Survival and Recurrence among Patients with Head and Neck Squamous Cell Carcinoma in an Underserved Urban Population. *JAMA Otolaryngology - Head and Neck Surgery*, 145(11), pp.1001–1009.

Mulcahy, C. M., Parry, D. C., & Glover, T. D. (2010). The "patient Patient": The trauma of waiting and the power of resistance for people living with cancer. *Qualitative Health Research*, *20*(8), 1062–1075. http://doi.org/10.1177/1049732310369139

NHS England (2019) Adult External Beam Radiotherapy Services Delivered as Part of a Radiotherapy Network. Available at: https://www.england.nhs.uk/wp-content/uploads/2019/01/External-Beam-Radiotherapy-Services-Delivered-as-Part-of-a-Radiotherapy-Network-Adults.pdf (Accessed: 20 February 2019)

Polesel, J., Furlan, C., Birri, S., Giacomarra, V., Vaccher, E., Grando, G., Franchin, G. (2017). The impact of time to treatment initiation on survival from head and neck cancer in north-eastern Italy. *Oral Oncology*, *67*, 175–182. http://doi.org/10.1016/j.oraloncology.2017.02.009

Schoonbeek, R.C. et al. (2022). The effect of delayed treatment initiation on adverse events and recurrence in older head and neck cancer patients. *Radiotherapy and Oncology*, 173, pp.154–162. [online]. Available from: https://doi.org/10.1016/j.radonc.2022.06.001.

Statistics How To. Grounded Theory: Simple Definition and Examples. Available at https://www.statisticshowto.com/grounded-theory/

4. Paper B

Evaluation of Planning Methods Used to Compensate for Increased Fluence at the Surface for Inverse Planned Head and Neck Cancer Treatment

Authors: Julie Kirk[1], Carl Rowbottom[1]

[1] Department of Physics, The Clatterbridge Cancer Centre NHS FT, Liverpool, UK.

Target Journal – The Journal of Applied Clinical Medical Physics

Abstract

Purpose: In radiotherapy of the head and neck it is common for the clinical target volume (CTV) to extend to the patient's skin. Adding a margin for set-up uncertainty and delivery creates a planning target volume (PTV) that extends beyond the patient surface. For inverse planning this results in excessive fluence being delivered to the build-up region and therefore the skin. This study evaluates four different planning methods used to compensate for excessive fluence in the build-up region when planning head and neck cancer treatments using volumetric modulated arc therapy (VMAT). The aim of the study is to determine which planning method gives superior plan quality when considering CTV coverage, skin dose and plan robustness.

Method: Ten head and neck cancer patients with a CTV contoured to the skin surface were planned using four different planning methods. The planning methods compared were cropping the optimisation planning target volume (PTV) back from the skin surface by 5.0 mm, 3.0 mm and 0.0 mm and a virtual bolus method. For each planning method the increased fluence at the skin surface was analysed. The CTV coverage and skin doses were compared. Plan robustness was evaluated by applying an isocentre shift of ±3.0 mm in the principal axes. The effect this shift has on CTV coverage and skin dose was evaluated for each planning method.

Results: The planning method of cropping the PTV 0.0 mm from the skin surface results in an increased fluence in the build-up region. Cropping the optimisation PTV reduced CTV coverage. The average volume of CTV receiving 98% of the prescription dose ($D_{98\%}$) was 89.6% when cropping 5.0 mm, 91.6% when cropped by 3.0 mm, 93.5% when cropping 0.0 mm and 93.4% for the virtual bolus plan. Introducing a plan uncertainty affects CTV coverage the most when using the planning method of cropping 5.0 mm. The maximum reduction in $D_{98\%}$ averaged over the ten patients was 4.2% when cropping 5.0 mm, 2.3% when cropped by 3.0 mm, 0.9% when cropping 0.0 mm and 0.7% for the virtual bolus plan. Cropping the optimisation PTV from the skin surface reduces the skin dose. When plan uncertainties are considered the planning methods of cropping 5.0 mm, 3.0 mm and the virtual bolus method all have the same average skin dose within ±0.3%.

Conclusion: This study shows that a virtual bolus planning method achieves no increased fluence at the patient's surface, improves CTV coverage and is the most robust to changes in setup and patient anatomy.

4.1. Introduction

In head and neck radiotherapy tumour control is achieved by irradiating clinical target volumes (CTVs) to a prescribed dose. CTVs for head and neck cancers are complex and individual to each patient. In many head and neck patients the CTV can extend to the patient's skin. When a margin is added for uncertainties in set-up and delivery a planning target volume (PTV) that extends beyond the patient surface is created. It is valid to have a PTV that extends beyond the surface of the patient as it is likely the CTV will fall into this volume throughout the treatment course. When creating a non-inverse plan the PTV coverage outside of the patient is achieved by simply extending the treatment fields out of the body to cover the PTV. This ensures CTV coverage for all uncertainties. In inverse planning; dose objectives are added to structures to achieve target coverage, to reduce dose to normal tissues and to avoid hotspots. Coverage of the PTV is achieved by adding a minimum dose objective to the PTV. The treatment planning system (TPS) optimises the plan with the aim to achieve this minimum dose objective. In 2004, Thomas and Hoole demonstrated that PTV based optimisation removes low doses within the PTV, even when caused by the build-up region. This results in excessive fluence being delivered to the build-up region and therefore the skin. This can result in acute skin toxicity as seen by Lee et al (2002). Since the introduction of inverse planning a number of solutions have been considered to compensate for this problem.

One solution is to consider the skin as a sensitive structure and remove the structure from the PTV when optimising IMRT plans. This method was introduced by Lee et al (2002) and later investigated by Thomas and Hoole (2004). Thomas and Hoole (2004) found that geometric errors lead to inadequate CTV coverage when using this method. This can be considered to be equivalent to cropping the PTV back from the skin surface; a solution that is described in a number of UK and international head and neck radiotherapy trials; such as NIMRAD (NIMRAD QA Team, 2014), PATHOS (Owadally et al, 2018) and JAVALIN (Avelumab, 2016).

A virtual bolus method was first investigated by Thilmann et al (2002) for breast treatments using tangential fields. In this solution bolus is added to the patient's surface for optimisation only. The bolus is removed for the final dose calculation and not used for treatment. Thomas and Hoole (2004) found that this method gave the most superior results when considering CTV coverage for head and neck plans. The use of virtual bolus in the planning of breast cancer treated with arc therapy was studied by Tyran et al (2018). In this study, plans (RayStation v5.0) with and without virtual bolus were compared by evaluating CTV coverage on a CT performed during treatment and as a consequence of modification in the patient's anatomy. The study showed the virtual bolus plan gave an increased CTV coverage compared to the non-virtual bolus plan. This demonstrates the benefit of using the virtual bolus during inverse planning to compensate for potential changes in breast shape. This solution is also described in UK and European head and neck radiotherapy trials; such as NIMRAD (NIMRAD QA Team, 2014), PATHOS (Owadally et al, 2018) and "Best of" trial (Clemental at al, 2017).

Due to the variation in guidance given in head and neck radiotherapy trials a survey of UK radiotherapy centres was carried out as part of this study. This showed that 18 of the 22 centres that responded did not use the virtual bolus planning method. The survey also showed 21 of the 22 centres used the technique of cropping the PTV in from the patient surface. The amount the PTV was cropped from the surface varied between 3.0 mm and 6.0 mm.

The results from this survey and the guidance for head and neck radiotherapy trials shows there is no consensus in what planning method gives the best solution for optimising in the build-up region for head and neck plans.

In this paper, the different planning methods to compensate for the excessive fluence in the build-up region while achieving an acceptable plan for all set-up uncertainties are compared. The method that gives superior plan quality when considering CTV coverage and skin dose is determined.

4.2. Methods and materials

Computer tomography (CT) images of ten head and neck patients were acquired in head-gantry, supine position. At the time of acquiring the CT images all patients had been immobilised in a 5 fixation point thermoplastic mask, supported by a headrest and vac bag. The gross tumour volume (GTV) and clinical target volumes (CTVs) were defined and contoured by a radiation oncologist. Each patient had two CTVs; a high dose CTV which was irradiated to highest prescribed dose and a low dose or prophylactic CTV. All selected patients had the high dose CTV contoured to the skin surface. Organs at risk (OARs) were automatically contoured by Mirada DLCExpert 2.6.2 (Mirada, Oxford, UK), followed by modification, if required and approval by a radiation oncologist. Treatment plans were created using Eclipse 15.6 (Varian, Palo Alto, CA) treatment planning system on a Varian Truebeam linac. In brief, two complementary 6MV coplanar volumetric modulated arc therapy (VMAT) arcs (one counter clockwise, one clockwise) were used. Each arc had a collimator rotation of 30° and 330° respectively.

Optimisation was performed with the Photon Optimiser Algorithm (PRO) v15.6. The optimisation is based on dose-volume objectives that the user sets for each target and organ at risk (OAR). The PRO algorithm allows the user to a set a monitor unit (MU) objective, this objective limits the total number of MUs in a plan. Limiting the MUs can increase the size of multi-leave collimator (MLC) apertures. This is considered important in IMRT plans as small MLC apertures may be associated with dosimetric errors between the calculated and delivered dose (Jolly et al, 2011). For each plan a MU objective was set to 250 times the daily prescribed dose (Gy) with the aim to avoid over modulation and therefore avoid the optimiser creating small, complex segments. Another parameter that can be set in the PRO algorithm is the Normal Tissue Objective (NTO). The NTO defines how the dose falls off outside the PTVs by limiting the dose level and preventing hotspots in healthy tissue (Varian Medical Systems, 2015). In this study a standard set of NTO parameters were created and remained the same for each planning method. Throughout optimisation the PRO algorithm uses a Multi-Resolution Dose Calculation (MRDC) algorithm for fast dose estimation. For all optimisations the Automatic Intermediate Dose function was utilised. This function compensates for differences in dose calculated with the MRDC algorithm and the final dose calculation algorithm. For all calculation throughout the optimisation a grid resolution of 2.5 mm was used.

The final dose calculation was performed with AcurosXB 15.6, with a grid size of 1.0 mm. Badkul et al (2015) and Zhuang and Olch (2014) showed for Eclipse Anisotropic Analytical Algorithm (AAA) that grid size has a significant impact on the surface dose calculated. Both groups state that 1.0 mm dose grid calculations closely agree with measurement and gives a high accuracy in surface dose. This study compares the skin dose for different planning methods therefore a high accuracy in surface dose calculation is needed. A different Eclipse algorithm is used in this study compared to that of Badkul et al (2015) and Zhuang and Olch (2014). However; a 1.0 mm dose grid is likely to give a higher accuracy compared to the standard 2.5 mm dose grid.

For each dataset four plans were created. These plans included cropping the PTVs back from the skin surface by varying amounts and using virtual bolus in the optimisation. The creation of these plans is described below and summarised in table B1.

4.2.1 Initial Plan Creation

PTVs were created from the high dose CTV and the low dose CTV with a margin of 5.0 mm in all directions. This margin is used by the local institution and reflects the geometric accuracy of the immobilisation system. Additional PTVs were created for optimisation by cropping the PTVs 5.0 mm internal from the skin surface. This has the effect of creating a negative CTV to PTV margin when the CTV is contoured to the skin surface. Planning Organs at Risk Volumes (PRVs) were created for all serial structures. A margin of 3.0 mm was applied to the Spinal Cord, Brainstem and Mandible.

An additional structure was created to compare doses to the skin, this structure has not been used in any optimisation. The skin structure is a 2.0 mm thick shell around the patient with the outer surface consistent with the surface of the patient. The dermis layer of the skin is between 0.05 mm and 1.5 mm, depending on the anatomic location (Cao et. al. 2017). A skin thickness of 2.0 mm was used by Court et al (2008) and Chow and Grigorov (2007) in similar practical work. Clinical trial protocols such as Keynote-867 (Sharp and Dohme, 2021) and Saron (University College London, 2020) define the skin as a 5.0 mm ring contour. In this study the skin structure is overlapping the CTV. When reporting maximum doses the thicker the ring the more likely this structure will not represent the actual dose to the skin, therefore a 2.0 mm ring is more appropriate.

An external body contour used by Eclipse to calculate the dose distribution was extended to include the patient's thermoplastic mask and an additional 5.0 mm in the region of the PTVs (Wang et al, 2018).

Clinically acceptable plans were produced for each dataset. Each of these plans were individually optimised, planning aims were prioritised in the following order:

- Meet all mandatory constraints (spinal cord, brainstem, mandible)
- High dose PTV coverage
- Low dose PTV coverage
- Non-critical OAR constraints (e.g. parotids, larynx, oral cavity)
- Other non-specified normal tissue

All plans were deemed optimal by two experienced planners. Plans were normalised to the median dose of the high dose PTV that had been cropped back 5.0 mm (ICRU 83, Deluca, 2019).

Eclipse has a function where objectives used in an optimisation can be saved as a template. This template can then be loaded for subsequent plans. For each dataset the optimisation objectives were saved as a template once an optimal plan had been achieved. Optimisations on each dataset used the saved templates and therefore had the same optimisation objectives as the initial plan.

4.2.2 Creation of Plans with PTV Cropped Back from Skin Surface

Additional optimisation PTVs were created for each dataset by cropping the PTV 3.0 mm and 0.0 mm from the skin surface. Plans were created for each of these optimisation PTVs using identical field arrangements and optimisation objectives as the initial plan. All plans were normalised to the median dose of the high dose PTV that had been used in optimisation, e.g. PTV cropped 3.0 mm or 0.0 mm from the skin surface.

4.2.3 Creation of Virtual Bolus Plan

Plans were created for each dataset using the PTV cropped 0.0 mm from the skin surface. These plans were optimised with a bolus structure in place. The bolus structure is a structure that has been created by margining 5.0 mm from the optimisation PTV and avoiding the inside of the patient external contour. The bolus structure is assigned a material of water. An identical field arrangement and optimisation objectives to initial plan were used. The bolus structure was removed for the final dose calculation. Plans were normalised to the median dose of the high dose PTV that had been cropped back to the skin surface.

Table B1. Summary of four planning methods used in this study

Plan Name	**Optimisation PTV**	**Plan Normalisation**
Crop_5.0mm	PTV_Crop5.0mm – PTV cropped 5.0 mm from the skin surface	Median dose to PTV_Crop5.0mm
Crop_3.0mm	PTV_Crop3.0mm – PTV cropped 3.0 mm from the skin surface	Median dose to PTV_Crop3.0mm
Crop_0.0mm	PTV_Crop0.0mm – PTV cropped 0.0 mm from the skin surface	Median dose to PTV_Crop0.0mm
Virtual Bolus	PTV_Crop0.0mm – PTV cropped 0.0 mm from the skin surface	Median dose to PTV_Crop0.0mm

4.2.4 Plan uncertainty

For each plan in each dataset the plan uncertainty doses were calculated using the Eclipse plan uncertainty tool (Varian Medical Systems, 2017). This tool has been used to evaluate plan robustness to shifts in treatment isocentre position. This estimates how the differences in planned patient setup and treated patient setup affect the dose distribution and therefore dose to targets and OARs (Varian Medical Systems, 2017). The plan uncertainty tool recalculates the original plan with the isocentre shifted by a defined amount in the X, Y or Z directions. In this study a shift of 3.0 mm has been applied left, right, anterior, posterior, superior and inferior to produce six plan uncertainty distributions. A shift of 3.0 mm has been used as this represents the local cone beam CT (CBCT) imaging tolerance across the length of the treatment volume. Although this method of calculating the plan uncertainty shifts the isocentre by 3.0 mm; at the surface

it also represents a change in the patient's external contour in a given direction. For example if the CTV is to the patient's skin surface on the right of a patient; an isocentre shift to the patients left is equivalent to an increase in the external contour on the right. Provided the CTV is still to the patient's skin surface the plan uncertainty distribution will show now the CTV coverage has changed with either a setup uncertainty or change in the external contour at the surface.

4.2.5 Fluence check

Optimising with a PTV to or beyond the skin surface results in excessive fluence being delivered to the skin surface (Thomas and Hoole, 2004). It is therefore vital to determine if any and which of the planning methods gives excessive fluence at the skin surface. If excessive fluence is present this will be visible in the dose distribution when the plan is recalculated with a bolus structure added over the PTV. All plans for each dataset were recalculated (maintaining planned monitor units) with a bolus structure that is margined 5.0 mm from the PTV cropped 0.0 mm from the patients surface and avoiding the inside of the external patient contour, as shown in figure B1. An increase fluence at the surface will give hotspots within the patient. The dose to 1 cc of the entire body (D_{1cc}) has been compared between planning methods.

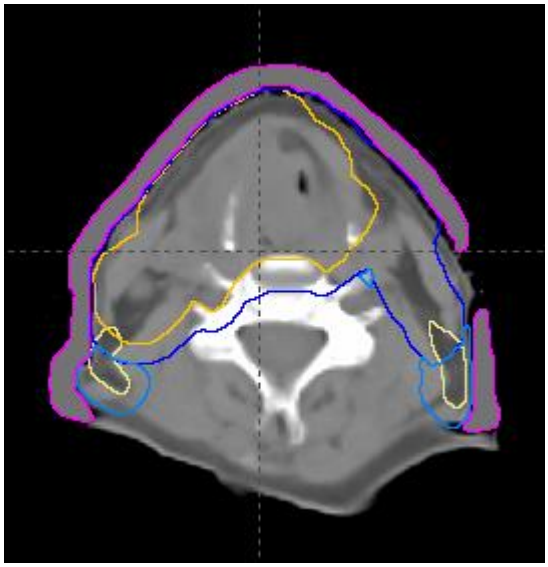

Figure B1. Bolus structure added to check for excessive fluence at the skin surface.

4.2.6 Plan evaluation

For each planning method the dose to 98% of the high dose CTV (CTV_High) and the low dose CTV (CTV_Low) as a percentage of the prescription dose ($D_{98\%}$) has been calculated and compared. Plans have been evaluated by calculating the CTV $D_{98\%}$ for the range of plan uncertainties. The purpose of the CTV to PTV margin is to ensure the prescribed dose is delivered to the CTV (ICRU 62, Lanberg (2001)). A good plan is defined as giving a clinically acceptable coverage of the CTV when shifted by a distance equal to the CTV to PTV margin in any direction (ICRU 62, Lanberg (2001)). In this study the isocentre has been shifted by a distance less than the CTV to PTV margin. This shift should therefore give good CTV coverage as the extremes have not been reached. The standard deviation for CTV $D_{98\%}$ has been calculated for each planning method across the six plan uncertainties. The standard deviation gives an indication of how robust the plan is to changes in setup and to changes in patient anatomy.

To evaluate the dose to the skin the dose to 1.0 cc and 0.1 cc has been determined as a percentage of the prescription dose.

4.3. Results

4.3.1 Fluence check

Plans that have been optimised with virtual bolus do not have an increased fluence at the skin surface. When these plans are recalculated with virtual bolus in-situ the dose to 1.0 cc of the body decreases by an average of 0.4%. Visual inspection of plans from all the datasets also shows no increase in dose at the patient surface. For each planning method the percentage of the prescription dose to 1 cc of the body have been compared to the virtual bolus plan. Figure B2 shows the change in body doses for each planning method where the PTVs have been cropped from the skin surface. The average increase in dose from the virtual bolus plan being 0.09% (0.004%), 0.37% (0.005%) and 2.10% (0.011%) for the PTV crop 5.0 mm, PTV crop 3.0 mm and PTV crop 0.0 mm plans respectively.

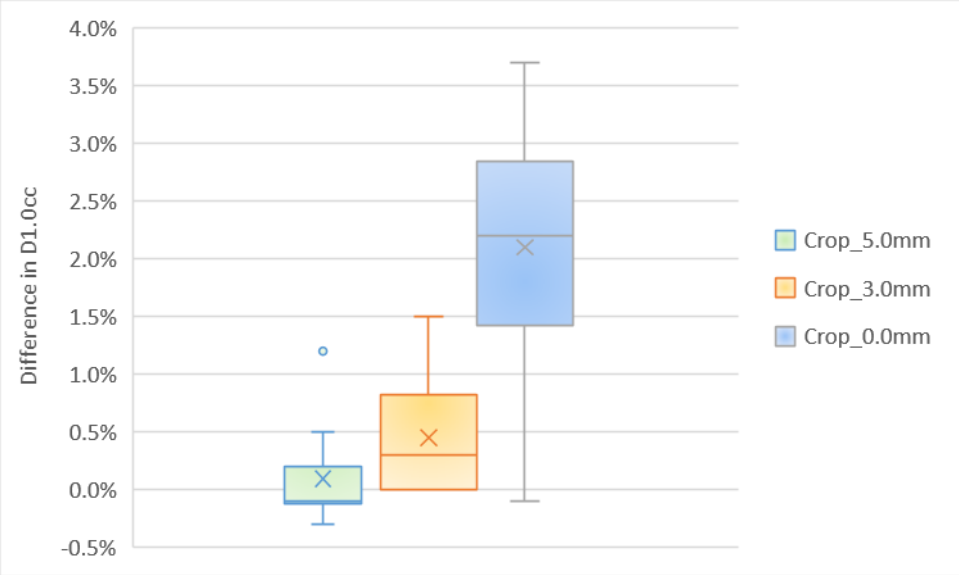

Figure B2. Box plot showing the body dose for the planning methods of cropping the PTV from the skin surface when plans have been recalculated with virtual bolus in situ. The percentage difference from the virtual bolus planning method is shown.

The plot shows when plans are recalculated with bolus the increase in dose is dependent on the amount the PTV is cropped back from the skin surface. As the amount the PTV is cropped back decreases the maximum dose within the body increases.

4.3.3 CTV Coverage

For each plan the $D_{98\%}$ for each CTV has been calculated. To determine how the $D_{98\%}$ is effected by the planning method of cropping the PTV back from the patient's surface or optimising with virtual bolus, the $D_{98\%}$ for each CTV has been compared. The box plot in Figure B3 shows the high dose CTV $D_{98\%}$ for each planning method.

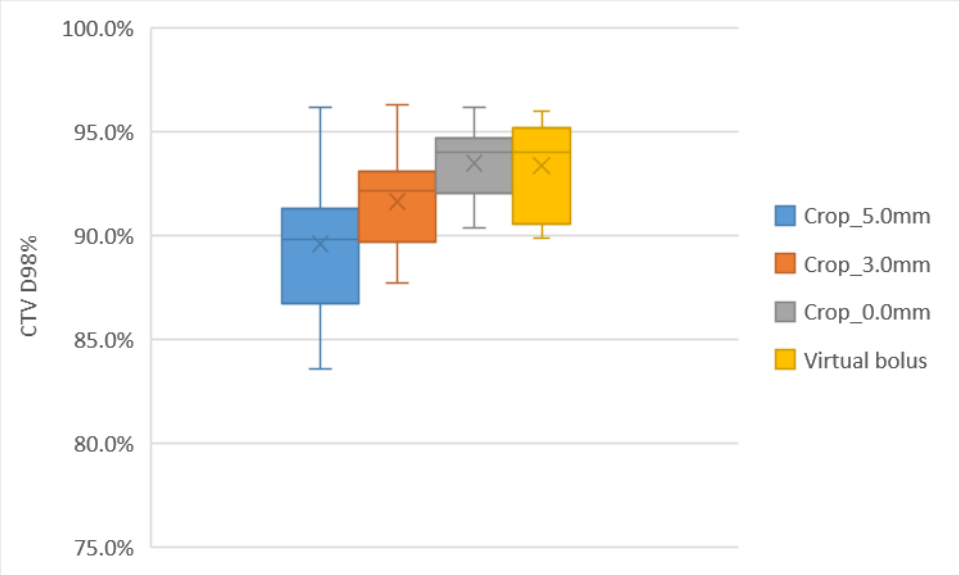

Figure B3. Box plot showing the $D_{98\%}$ *for the high dose CTV for each planning method*

As the amount the PTV is cropped back from the skin surface reduces the $D_{98\%}$ increases. For the virtual bolus planning method the average $D_{98\%}$ is the same as cropping 0.0 mm from the patient surface. This is an increase of 3.8% in the $D_{98\%}$ compared to cropping the PTV back 5.0 mm from the patient surface. For the low dose CTV the difference in the $D_{98\%}$ between planning methods is reduced but follows the same pattern as the high dose CTV, as shown in table B2.

Table B2. Average $D_{98\%}$ *for each planning method*

Planning Method	**CTV_High**	**CTV_Low**
PTV crop 5.0 mm	89.6% (3.4%)	96.0% (1.7%)
PTV crop 3.0 mm	91.6% (2.4%)	97.7% (0.8%)
PTV crop 0.0 mm	93.5% (1.7%)	98.2% (0.6%)
Virtual bolus	93.4% (2.1%)	97.9% (0.5%)

The planning method of cropping the PTV 5.0 mm from the skin surface gives on average a CTV $D_{98\%}$ of 89.6%. Figure 3 shows for an individual case the $D_{98\%}$ for the high dose CTV dropped to 83.6%. For this individual case cropping 3.0 mm and 0.0 mm will increase the $D_{98\%}$ to 87.2% and 92.0% respectively. Planning with virtual bolus improved the CTV coverage from the 5.0 mm cropped plan with a $D_{98\%}$ of 89.4%.

4.3.4 Maximum Skin Dose

The maximum dose to 1.0 cc and 0.1 cc of the skin has been determined for each plan. This has then been averaged across the 10 datasets and is shown in table B3.

Table B3. Skin dose for each planning method averaged across the 10 data sets.

Planning Method	Average dose to 1.0cc skin	Average dose to 0.1cc skin
PTV crop 5.0 mm	93.9% (1.7%)	97.3% (1.6%)
PTV crop 3.0 mm	95.4% (2.1%)	98.4% (1.5%)
PTV crop 0.0 mm	98.4% (2.1%)	101.4% (1.6%)
Virtual bolus	97.3% (2.2%)	99.8% (2.1%)

The skin dose increases as the amount the PTV is cropped from the surface reduces; with cropping the PTV to surface giving the highest skin dose.

4.3.5 Plan Uncertainty

4.3.5.1 CTV Coverage

The average and standard deviation of the high dose CTV $D_{98\%}$ has been calculated across the 6 plan uncertainties. As described in the method section plan uncertainties are determined by applying a 3.0 mm isocentre shift in each of the 6 cardinal directions.

The difference in the average $D_{98\%}$ for the high dose CTV across the 6 plan uncertainties compared to the $D_{98\%}$ for the non-shifted plan is shown in table B4. For all planning methods the introduction of plan uncertainty on average reduces the $D_{98\%}$ from the non-shifted plan. The reduction in the $D_{98\%}$ increases as the amount the PTV is cropped back from the skin surface increases. In all cases, with two exceptions, the average difference from the non-shifted plan is less than 1%. This suggesting that if all plan uncertainties are random then the delivered CTV $D_{98\%}$ will be as the calculated (non-shifted) ±1% for all planning methods.

Table B4. Difference in the averaged CTV $D_{98\%}$ across the plan uncertainties compared to the $D_{98\%}$ for the non-shifted plan.

Planning Method	1	2	3	4	5	6	7	8	9	10	Av
PTV crop 5.0 mm	-0.9%	-0.5%	-0.5%	-0.7%	-0.3%	-1.2%	-0.9%	-0.3%	-0.6%	-0.1%	-0.6%
PTV crop 3.0 mm	-0.6%	-0.4%	-0.5%	-0.4%	-0.1%	-1.1%	-0.3%	-0.2%	-0.1%	-0.1%	-0.4%
PTV crop 0.0 mm	-0.2%	-0.1%	-0.2%	-0.3%	-0.1%	-0.3%	-0.1%	-0.2%	0.0%	0.0%	-0.2%
Virtual Bolus	-0.2%	0.0%	-0.1%	-0.2%	0.0%	-0.4%	0.0%	-0.1%	-0.2%	-0.2%	-0.2%

The standard deviation for CTV $D_{98\%}$ has been calculated for each planning method across the 6 plan uncertainties. Table B5 shows the standard deviation for each planning method for each dataset.

Table B5. The standard deviation for CTV $D_{98\%}$ for each planning method across the 6 plan uncertainties.

Planning Method	1	2	3	4	5	6	7	8	9	10	Av
PTV crop 5.0 mm	2.8%	2.7%	2.3%	2.5%	0.6%	3.6%	3.2%	1.8%	2.5%	0.7%	2.3%
PTV crop 3.0 mm	1.5%	1.4%	1.9%	1.0%	0.3%	2.2%	1.2%	1.1%	1.1%	0.3%	1.2%
PTV crop 0.0 mm	0.1%	0.6%	1.1%	0.6%	0.2%	0.5%	0.5%	1.3%	0.7%	0.0%	0.6%
Virtual Bolus	0.3%	0.2%	0.4%	0.4%	0.2%	0.5%	0.6%	0.4%	0.3%	0.2%	0.3%

This data shows that the virtual bolus planning method gives the least variation in CTV $D_{98\%}$ when a plan uncertainty of 3.0 mm is applied. The variation in CTV $D_{98\%}$ increases as the amount the PTV is cropped back from the surface increases. The standard deviation does not give an indication of the direction of change. An increase in the $D_{98\%}$ would benefit the distribution however a reduction in $D_{98\%}$ would indicate further compromise to the CTV and therefore likely to reduce the tumour control probability. The greatest reduction in the $D_{98\%}$ from the non-shifted plan for each planning method is shown in figure B4.

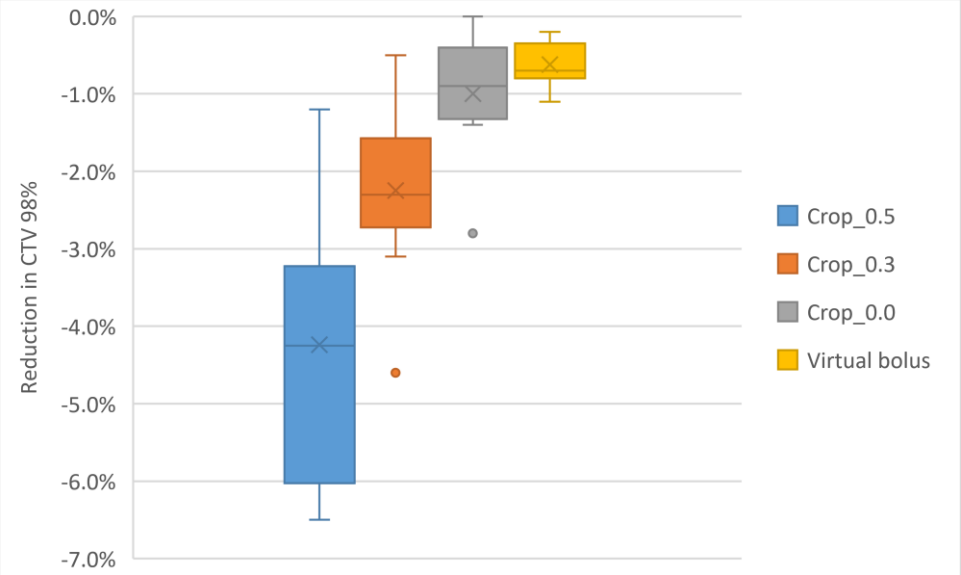

Figure B4. Box plot showing the greatest reduction in high dose CTV $D_{98\%}$ *resulting from an isocentre shift of 3.0 mm.*

The plot shows the virtual bolus plans have an average reduction in $D_{98\%}$ of 0.6%. The reduction in $D_{98\%}$ increases as the amount the PTV is cropped back from the surface increases. The planning method of cropping the PTV back from the skin surface by 5.0 mm gives the greatest reduction in $D_{98\%}$.

4.3.5.2 Skin Dose

The plan uncertainty calculations show changes in skin dose when 3.0 mm shifts are applied. Table B6 shows that the greatest increase in skin dose is for plans that have the PTV cropped back 5.0 mm from the skin surface. Applying an isocentre shift to the virtual bolus plans increases the skin dose by an average of 0.3%.

Table B6. Maximum increase in skin $D_{0.1cc}$ for each plan due to 3.0 mm shift in isocentre position. Red showing an increase greater than 2.0% and yellow greater than 1.0%

Planning Method	1	2	3	4	5	6	7	8	9	10	Av
PTV crop 5.0 mm	1.5%	1.8%	1.4%	1.5%	0.6%	3.3%	1.3%	1.4%	1.8%	1.4%	1.6%
PTV crop 3.0 mm	0.5%	0.5%	1.6%	0.9%	0.6%	3.2%	0.5%	1.1%	0.8%	0.8%	1.1%
PTV crop 0.0 mm	0.9%	0.2%	0.9%	0.0%	0.5%	0.5%	0.2%	1.2%	0.3%	0.8%	0.6%
Virtual Bolus	0.3%	0.2%	0.0%	0.0%	0.8%	0.0%	0.6%	0.6%	0.4%	0.4%	0.3%

The maximum skin dose for each planning method can be determined by adding the maximum increase in dose (table B6) to the skin dose calculated from the non-shifted plans (table B3). The planning methods of using virtual bolus and cropping the PTV 3.0 mm and 5.0 mm have an average maximum skin dose of 99.8% ±0.3%. The planning method of cropping PTV 0.0 mm has an average maximum skin dose of 102.0%

4.4. Discussion

4.4.1 Increase in Fluence

Inverse planning can result in solutions that give higher fluence to tangential beam segments near the skin surface, in an attempt to counter the low dose in the build-up region (Thomas and Hoole, 2004). Thomas and Hoole (2004) demonstrated that hot-spots of 126% can be delivered to the skin by plans where PTV is to the skin surface. The increased fluence in the build-up region has not previously been validated using modern optimisation algorithms, such as the PRO algorithm used in this study.

The planning methods selected in this study aim to avoid an increase in fluence at the skin surface and have been tested previously by Thomas and Hoole (2004) and Thilmann et al (2002). These studies along with Ezzell et al (2003) cropped PTVs back by 5.0 mm and 6.0 mm from the skin respectively. Thilmann et al (2002) and Tyran et al (2018) investigated the virtual bolus method for the planning of breast IMRT.

Before comparing these different planning methods the increase in fluence for each planning method has been evaluated.

Recalculating the plans with bolus shows that an increase in fluence at the skin surface is evident for some of the planning methods. It has been shown that optimising with the virtual bolus does not give an increased fluence. Figure B2 shows the results from the planning methods of cropping PTVs from the patient surface. It can be seen that as the amount of cropping back from the surface reduces, the maximum dose within the body increases when recalculated with bolus. Cropping the PTV to the patient surface shows an increase in hotspots within the body.

This can also be seen when reviewing the isodoses for plans that have been recalculated with the bolus added. Images in figure B5 and figure B6 show the resultant isodoses from two datasets. The 107%, 105%, 100% and 95% isodoses are shown for the plans when PTV has been cropped to the skin surface [A], 3.0 mm from the skin surface [B], 5.0 mm from the skin surface [C] and planned with virtual bolus [D]. Similar isodoses have been observed on all datasets in this study.

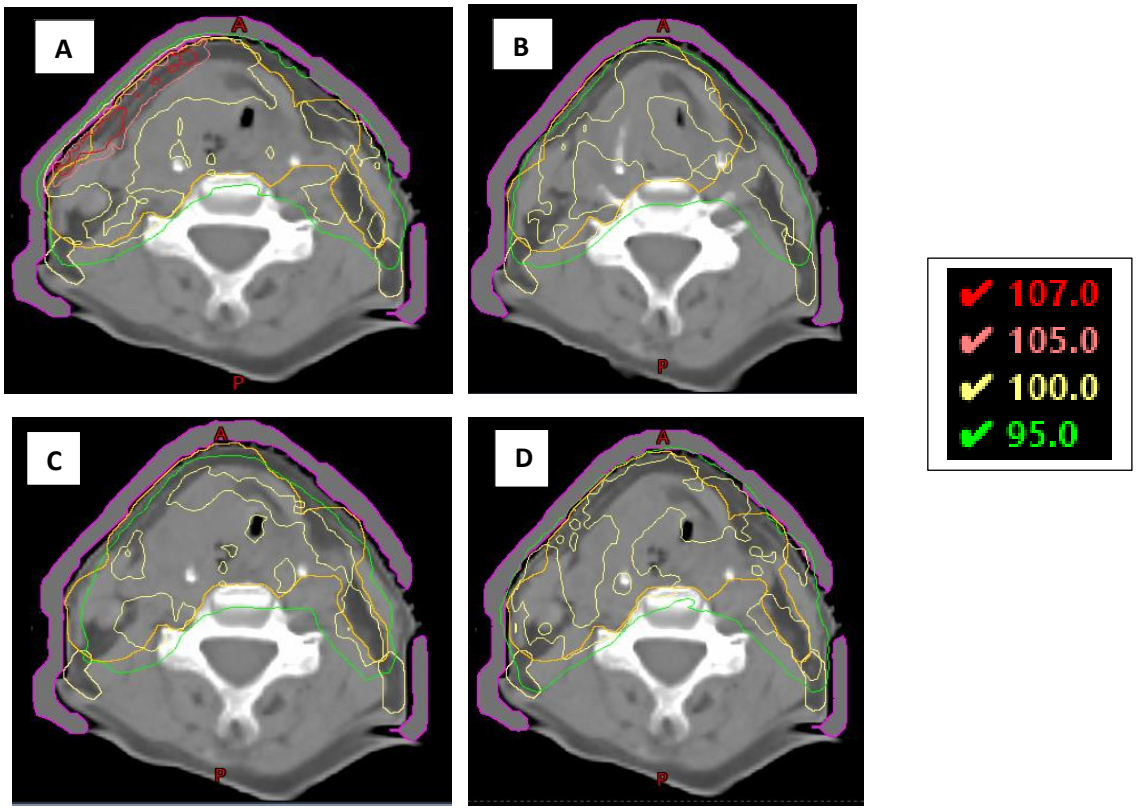

Figure B5. Dose distribution for four different planning methods when recalculated with virtual bolus in situ.

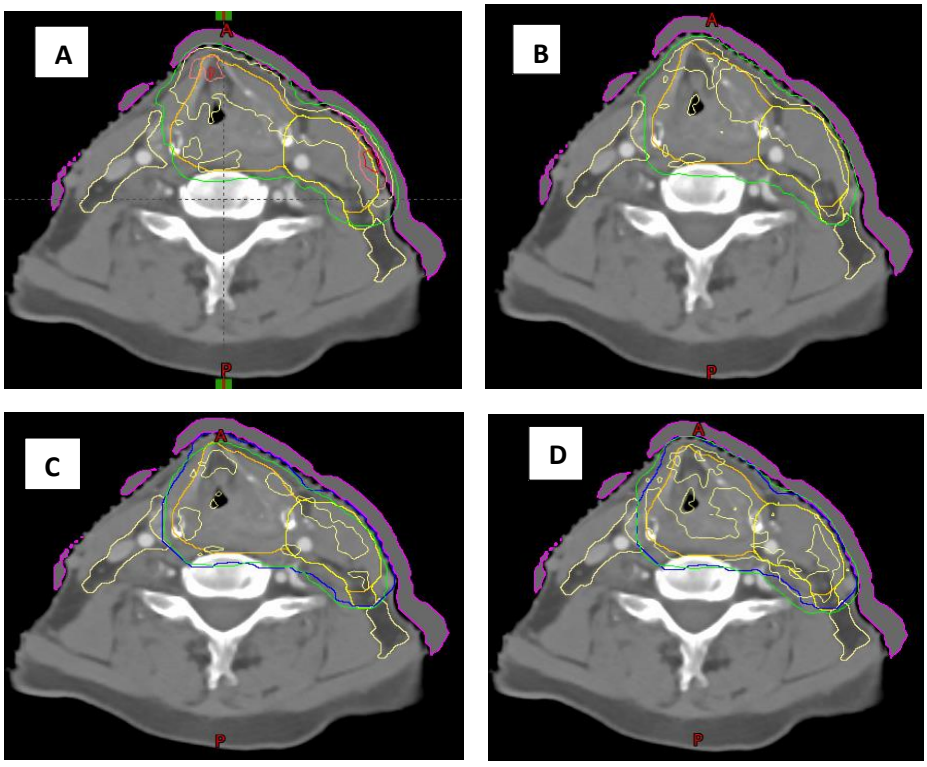

Figure B6. Dose distribution for four different planning methods when recalculated with virtual bolus in situ.

The increase in skin dose observed when bolus is added is significantly lower than that reported by Thomas and Hoole (2004). Thomas and Hoole (2004) used Xio v4.02 (Computerised Medical Systems, St Louis) to produce IMRT plans with five segmented step-and-shoot fields. There have been many changes to inverse planning and IMRT delivery since 2004. These changes are likely to have smoothed the fluence of IMRT and VMAT fields and therefore reduce spikes in fluence at the patient's surface.

Results from the fluence check show that in all cases the plans with PTV cropped to the skin surface have an increased fluence at the surface. Plans with the PTV cropped back 3.0 mm also give a slight increase in dose within the body contour, however this is not evident when reviewing the isodoses of the plan. Plans with the PTV cropped back 5.0 mm do not show any increase in body dose and therefore it is assumed do not have an increased fluence in the build-up region.

An increased fluence in the buildup region could result in higher doses at the skin surface with small changes in position or patient anatomy. An increased fluence must therefore be avoided to keep the dose to the skin within the prescription dose and therefore avoiding acute skin toxicity.

4.4.2 High Dose CTV Coverage

Figure B3 and table B2 show that cropping the PTV back from the patient surface for optimisation results in a reduced CTV coverage compared to using the virtual bolus method.

CTV coverage is not expected in the build-up region. Cropping the target optimisation structure in from the patient's skin and therefore in from the CTV; is effectively giving a negative CTV to PTV margin. Assuming the CTV is up to the patient's skin the virtual bolus planning method and cropping the PTV to the patient's skin gives a 0.0 mm CTV to PTV margin. The virtual bolus planning method has shown not to increase the fluence and give the highest CTV coverage (excluding the planning method of cropping to the patient's skin, which gives an increase in fluence). Cropping the PTV back 5.0 mm reduces the CTV $D_{98\%}$ to 89.6% of the prescription dose. As the amount the PTV is cropped back from the skin surface reduces the CTV $D_{98\%}$ increases as a result of optimising to a target that includes more of the CTV.

Plan uncertainty results in table B5 and figure B4 demonstrate how the negative CTV to PTV margin results in a plan that is less robust to systematic changes in setup and anatomy. For head and neck patients, changes in the patient's anatomy are likely to be systematic, for example patient weight loss or gain or tumour growth. Cropping the PTV 5.0 mm back from the patient surface could result in a 4.2% reduction in the CTV $D_{98\%}$ with just a 3.0 mm anatomy change or systematic setup shift. This results in a further reduction in the CTV coverage than reported in the un-shifted, intended plan. All the planning methods are subject to a change in the CTV $D_{98\%}$ when applying an isocentre shift, this is due to the 0.0 mm or negative CTV to PTV margin in the direction of the skin. Some shifts increase the CTV $D_{98\%}$ and are likely to improve the tumour control probability. Other shifts reduce the CTV $D_{98\%}$, compromising the CTV further. Any changes in setup or anatomy are unknown prior to treatment therefore plans need to be robust to changes or shifts in any direction. Table B5 shows the CTV $D_{98\%}$ standard deviation for the six plan uncertainties (isocentre shifts). The standard deviation reduces as the amount the PTV is cropped back reduces. This is expected; as the negative margin reduces the plan becomes more robust to isocentre shifts. The standard deviation is 0.3% (averaged across the datasets) for the virtual bolus planning method, showing that this planning method is the most robust to isocentre changes and therefore setup uncertainties and anatomy changes. This planning method also gives the lowest reduction in the CTV $D_{98\%}$ as shown in figure B4.

The virtual bolus planning method and cropping the PTV to the patient's skin produces plans with the best CTV coverage and the most robust plans when compared to the planning method of cropping the PTV from the patient surface. The cropping method of planning removes increased fluence at the patient's surface but reduces the CTV coverage and makes the plan less robust to changes in anatomy and setup uncertainties.

4.4.3 Maximum Skin Dose

To compare plans the skin is assumed to be a 2.0 mm ring internal to the patient surface. Maximum doses to 0.1 cc and 1.0 cc of the skin structure have been reported and compared between plans. The absolute dose to the skin and in the build-up region have not been verified for this algorithm and cannot be assumed to accurate.

When comparing plans that have not had an isocentre shift applied, the maximum skin dose reduces by approximately 1% for every 1.0 mm the PTV is cropped back from the surface. Cropping the PTV to the patient surface gave the highest skin dose (average $D_{0.1cc}$ of 101.4%). The virtual bolus plan gave a higher skin dose than cropping the PTV 3.0 mm or 5.0 mm from the skin surface. In some cases for the virtual bolus planning method and the method of cropping the PTV to 0.0 mm, the maximum skin doses were greater than 100%. These plans have not been optimised with a skin objective, only the maximum PTV objective is preventing hotspots within this volume.

When an isocentre shift is introduced the maximum skin dose increases by a greater amount as the amount the PTV is cropped back from the surface increases. The average maximum skin dose for the planning methods of cropping 5.0 mm, 3.0 mm, and the virtual bolus method are within 0.3% of each other. It is therefore concluded that the planning methods of cropping 5.0 mm, 3.0 mm, and the virtual bolus method give the same skin dose when plan uncertainties are considered.

The greater changes seen in skin dose when cropping the PTV back from the skin surface also gives an indication of plan robustness, confirming the results of changes to CTV coverage with plan uncertainty.

Thomas and Hoole (2004) results show an increase in maximum skin dose when uncertainty shifts are applied. The maximum dose to the skin increased to 126% from 115% when a 10.0 mm shift was applied to a plan that had been optimised with the PTV to the patient's skin. A skin dose as high as 126% is not seen in the plans in this study. Changes to inverse planning and IMRT delivery have improved the fluence at the patient's surface. This removes the need to crop the PTV back from the patient's surface as much as 5.0 mm and makes optimised plans more robust to changes in setup and anatomy.

4.5. Conclusion

The fluence check results and maximum skin doses with uncertainty shifts applied show that cropping the PTV to the patient surface does give a spike in fluence when optimising with Eclipse PRO algorithm V15.6. The fluence check results show the need to crop the optimisation PTV back from the surface as much as 5.0 mm has reduced with up-to-date optimisation algorithms and delivery methods. A spike in fluence is not evident when the optimisation PTV is 3.0 mm or more from the skin surface.

Reducing the amount the optimisation PTV is cropped back or using a virtual bolus planning method ensures the plan is more robust to changes in patient setup or anatomy. Increasing the amount an optimisation PTV is cropped back from the surface; increases the compromise to CTV coverage and reduces the plan robustness.

The planning method that achieves no increased fluence at the patient's surface, improves CTV coverage and is the most robust to changes in setup and anatomy is the virtual bolus planning method. The maximum skin dose for this method compared to the cropping PTV 5.0 mm back from the skin surface does not increase when plan uncertainties are taken into account.

If a planning method of cropping the PTV from the skin surface is used the amount the PTV needs to be cropped back from the surface can be reduced to 3.0 mm. Compared to cropping the PTV 5.0 mm back, this improves CTV coverage and makes the plan more robust to changes in setup and anatomy. This was also stated by Court and Tishler (2006). Court and Tishler concluded that the PTV should not be pulled back more than 3.0 mm from the skin surface, and setup uncertainty should be kept below 3.0 mm. UK and international trials recommend cropping the PTV back up to 5.0 mm from the skin surface. Survey results also show it is common UK practise to crop the PTV back from the skin surface by as much as 6.0 mm. This study shows that this will reduce CTV coverage and reduce the plans robustness to changes in setup and anatomy compared to cropping the PTV 3.0 mm or using the virtual bolus planning method.

It is therefore recommended that if the CTV is within 3.0 mm of the patient surface a virtual bolus planning method is be used. It is also recommended that if the PTV is cropped back from the patient surface, then the PTV should be cropped back by 3.0 mm.

4.6 Author Contributions

Julie Kirk contributed to study design, data collection, analysis and interpretation, and drafted the manuscript. Carl Rowbottom contributed to study design, study supervision, and critical revision of the manuscript.

4.7. References

Avelumab (2016) MSB0010718C Study B9991016 Radiation Guidelines for Protocol B9991016 (FINAL)

Badkul, R., Nejaiman, S., Pokhrel, D., Jiang, H. and Kumar, P. (2015), SU-E-T-196: Comparative Analysis of Surface Dose Measurements Using MOSFET Detector and Dose Predicted by Eclipse - AAA with Varying Dose Calculation Grid Size. Med. Phys., 42: 3377-3377.

Cao, Y. et al. (2017). Superficial dose evaluation of four dose calculation algorithms. *Radiation Physics and Chemistry*, 137, pp.23–28. [online]. Available from: http://dx.doi.org/10.1016/j.radphyschem.2016.02.032.

Chow, J.C.L. and Grigorov, G.N. (2008). Surface dosimetry for oblique tangential photon beams: A Monte Carlo simulation study. *Medical Physics*, 35(1), pp.70–76.

Clementel, E. and Joachim, G. (2017). Phase III study assessing The "Best of" radiotherapy compared to the "Best of" surgery (trans-oral surgery (TOS)) in patients with T1-T2, NO oropharyngeal carcinoma. RTQA Guidelines – Version 2.0.

Court, L.E. et al. (2008). Experimental evaluation of the accuracy of skin dose calculation for a commercial treatment planning system. *Journal of Applied Clinical Medical Physics*, 9(1), pp.29–35.

Court, L. and Tishler, R. (2006), SU-FF-T-88: An Experimental Evaluation of the Impact of Setup Uncertainty On Dose Near the Surface for IMRT Plans Where the Skin Is Considered a Sensitive Structure and Is Excluded From the PTV. Med. Phys., 33: 2069-2069.

Deluca, P.M. (2019). International Commission on Radiation Units and Measurements. ICRU Report83. Prescribing, Recording, and Reporting Photon-Beam Intensity-Modulated radiation therapy (IMRT). Journal of ICRU Volume 10 (1). Available from: http://jicru.oxfordjournals.org/.

Ezzell, G.A. et al. (2003). Guidance document on delivery, treatment planning, and clinical implementation of IMRT: Report of the IMRT subcommittee of the AAPM radiation therapy committee. *Medical Physics*, 30(8), pp.2089–2115.

Lanberg, T. et al. (2001). International Commission on Radiation Units and Measurements. ICRU Report 62. Prescribing, Recording, and Reporting

Photon Beam Therapy (Supplement to ICRU Report 50) Available from: http://jicru.oxfordjournals.org/.

Lee, N. et al. (2002). Skin toxicity due to intensity-modulated radiotherapy for head-and-neck carcinoma. *International Journal of Radiation Oncology Biology Physics*, 53(3), pp.630–637.

Sharp & Dohme Corp. (2021) MK-3475-867. Keynote 867 Radiation Manual for Investigator Sites, Version 6.0.

NIMRAD QA Team (2014). A randomised placebo-controleed trial of synchronous NIMorazole versus RADiotherapy alone in patients with locally advanced head and neck squamous cell carcinoma not suitable for synchronous chemotherapy or cetuximab. Radiotherapy planning, delivery and QA guidelines, version 1.1.

Owadally, W. et al. (2018). A Phase II / III trial of risk-stratified , reduced intensity adjuvant treatment in patients undergoing transoral surgery for Human Papillomavirus (HPV) - positive oropharyngeal cancer Radiotherapy Outlining , Planning , Delivery and Quality Assurance.

Thilmann, C. et al. (2002). Virtual Bolus for Inversely Planned Intensity Modulated Radiotherapy in Adjuvant Breast Cancer Treatment. *Strahlentherapie und Onkologie*, 178(3), pp.139–146.

Thomas, S.J. and Hoole, A.C.F. (2004). The effect of optimization on surface dose in intensity modulated radiotherapy (IMRT). *Physics in Medicine and Biology*, 49(21), pp.4919–4928.

Tyran, M. et al. (2018). Safety and benefit of using a virtual bolus during treatment planning for breast cancer treated with arc therapy. *Journal of Applied Clinical Medical Physics*, 19(5), pp.463–472.

University College London (2020). Stereotactic Ablative radiotherapy for Oligometastatic Non-small cell lung cancer. A randomised phase III trial. Protocol version 7.0.

Varian Medical Systems (2017) Eclipse Photon and Electron Instructions of Use. Version 15.5.

Wang, L., Cmelak, A.J. and Ding, G.X. (2018). A simple technique to improve calculated skin dose accuracy in a commercial treatment planning system. *Journal of Applied Clinical Medical Physics*, 19(2), pp.191–197.

Zhuang, A.H. and Olch, A.J. (2014). Validation of OSLD and a treatment planning system for surface dose determination in IMRT treatments. *Medical Physics*, 41(8).

5. Paper C

Superficial dose validation of four different planning methods used to compensation for excessive fluence in the build-up region for head and neck VMAT plans.

Authors: Julie Kirk[1], Carl Rowbottom[1]

[1] Department of Physics, The Clatterbridge Cancer Centre NHS FT, Liverpool, UK.

Target Journal – The Journal of Applied Clinical Medical Physics

Abstract

Purpose: Accurate calculation of the dose at the skin surface is important in head and neck radiotherapy especially when the CTV is to or close to the skin surface. Calculated skin dose between plans differ depending on the planning method used (Paper B). This study aims to confirm these differences and validate the results found in the planning study.

Method: Measurements were made with an advanced Markus parallel plate chamber and DOSEmappers^{TM} in a solid water phantom for a 6MV beam at three different angles of incidence: 0°, 30° and 60° and different field sizes: 4 x 4 cm^2, 10 x 10 cm^2 and 20 x 20 cm^2. Measurements were made at the surface and in the build-up region, and compared to Eclipse AXB. The effective depth of measurement of the DOSEmapper^{TM} was determined by comparing measurements to the dose measured by the advanced Markus chamber. DOSEmappers^{TM} were used to compare difference in surface dose from four planning methods used to compensate for excessive fluence. Plans were created and delivered to a locally manufactured Perspex (water filled) cylinder phantom and the head, neck and shoulders of a Rando anthropomorphic phantom.

Results: At depths of 1.0 mm and greater all measurements with the advanced Markus chamber were within 15% of the Eclipse calculated dose and within 0.3 mm when considering distance to agreement. Large uncertainties in measurement and extraction of the surface dose from Eclipse was found. Considering these uncertainties the advanced Markus chamber measurements show that dose is calculated accurately by Eclipse AXB at depths ≥ 1.0 mm for simple open fields. The effective depth of measurement of the DOSEmapper^{TM} was found to be 0.7 mm. Comparing dose between the DOSEmapper^{TM}, the advanced Markus chamber and dose calculated by Eclipse have shown that DOSEmappers^{TM} accurately measure dose at 0.7 mm and in the build-up region. DOSEmapper^{TM} results for different planning methods shows that Eclipse calculated dose and measured dose are correlated (Pearson correlation coefficient $r(10) = .918$, $p<.001$). These measurements confirm the skin dose results found in a previous planning study (Paper B).

Conclusion: DOSEmappers^{TM} are a suitable dosimeter for measuring near surface dose (effective depth of measurement 0.7 mm). Measurements using DOSEmappers^{TM} confirm the dose differences from different planning approaches found in a previous planning study (Paper B). This validates the results found in Paper B and gives confidence in determining the most superior planning method for head and neck VMAT planning.

5.1. Introduction

For head and neck cancer treatments; clinical target volumes (CTVs) are often close to or at the skin surface. In inverse planning; dose objectives are added to structures to achieve target coverage by adding a minimum dose objective. The treatment planning system optimises the plan with the aim to achieve this minimum dose by removing low doses within the structure, even when in the build-up region (Thomas and Hoole, 2004). This can result in excessive fluence being delivered to the build-up region and therefore the skin. A planning study was previously carried out to evaluate the planning methods that can be used to compensate for increased fluence at the skin surface, for inverse planned head and neck cancer treatment (Paper B). This study assumed an accurate Eclipse Acuros XB (AXB) calculation of dose at the surface and in the build-up region. Accurate surface dosimetry is important in head and neck radiotherapy, especially when CTVs are close to the skin. Acute skin toxicity can be a major dose limiting factor and insufficient target coverage at the surface can increase the risk of local recurrence. It is therefore important to determine the accuracy of the dose calculations in the region of the skin. The dermis layer of the skin is between 0.05 mm and 1.5 mm, depending on the anatomic location (Cao et al 2017). Determination of the dose at this depth is challenging due to steep dose gradients and the absence of charged particle equilibrium (Kim et al, 2012). The surface dose also depends on the electron contamination from the head of the linear accelerator, making dose measurements difficult and imprecise (Chow and Grigorov, 2008).

Surface and build-up dose accuracy of the Eclipse treatment planning system (TPS) has previously been investigated. Zhuang and Olch (2014) investigated the accuracy of Eclipse Anisotropic Analytical Algorithm (AAA). Eclipse calculated doses were

compared to optically stimulated luminescent dosimeters (OSLDs), an advanced Markus parallel plate chamber and Monte Carlo simulations. This study found that Eclipse calculates dose at the OSLDs effective depth of measurement (0.8 mm) with a distance to agreement of 0.3 mm. This was achieved when calculating on a 1.0 mm dose grid for direct, open fields. Akino et al (2012) investigated the accuracy of Eclipse AAA in the build-up region for various breast cancer treatment techniques including IMRT using Gafchromic EBT2 film. The measured dose at 3.0 mm was found to be 15% to 30% higher than Eclipse. A similar result was found by Akbas et al (2017) for head and neck plans using fixed field IMRT when calculated with Eclipse AAA with a dose grid size of 2.5 mm. In 2021, Kesen and Akbas showed improvements in superficial calculation when using Eclipse Acuros XB (AXB) algorithm compared to AAA. This confirmed the findings of Cao et al (2017). Cao et al used Gafchromic EBT2 film measurements and Monte Carlo simulations to investigate the accuracy of superficial doses calculated by four different algorithms. Comparisons were made for incident angles of 0°, 30° and 60°. AXB performed well, with a mean dose discrepancy of 2.41 ± 1.55%, 3.11 ± 2.40%, and 1.53 ± 1.05%, for incident angles 0°, 30° and 60° respectively at a depth of 0.007 g/cm^2.

This study aims to add to the findings of Cao et al; by determining the accuracy of the surface dose calculated by Eclipse AXB compared to measurements with an advanced Markus parallel plate chamber and TRUEinvivo® DOSEmappers^{TM}. The accuracy of skin dose calculations for clinical VMAT plans will also be determined in this study.

DOSEmappers^{TM} (TRUEinvivo®, Surrey, UK) are made from Micro Silica Bead thermoluminescent dosimeters (TLDs). DOSEmappers^{TM} are a 2D array of clear Micro Silica Bead TLDs and coloured Micro Silica Beads. The coloured Micro Silica Beads are used for coding and marking while the clear Micro Silica Beads are used for measuring radiation exposure. Clear Micro Silica Bead TLDs have a linear response to dose, have no angular dependence and response is independent of dose rate (Jafari, 2013). The glass beads show a relativity small energy dependence over the megavoltage range. When normalised to unity for 6MV X-rays, the responses decreases to 0.96 ±0.02 for 15 MV X-rays. (Jafari, 2014). These properties along with the small size (2 mm diameter and 1 mm thickness) make Micro Silica Bead TLDs a suitable detector for measuring doses in high dose gradients and for delivery techniques such as VMAT and non-coplanar beams. Feasibility studies (Jafari, 2015 and Jafari, 2017) have shown that the Micro Silica Bead TLDs are suitable for clinical plan verification and can be used for postal dosimetry

audits. When configured as 2D DOSEmappers^{TM} the Micro Silica Bead TLDs are placed on a carrier synthetic thread. TLDs are placed in pairs at each measuring point and are held in place within a thin layer of clear film. The measuring point separation and number of measuring points can be individually made to suit the measurement conditions of the end user. The DOSEmapper^{TM} can therefore be placed on an undulating surface without significantly perturbing the radiation beam and can be used to measure the dose across a large surface area if required. The properties of the clear Micro Silica Bead TLDs and the properties of the DOSEmapper^{TM} make it an ideal dosimeter for measuring surface dose. This study aims to determine the use of DOSEmappers^{TM} for validating the dose at the surface and in the build-up region.

In this study results are presented from head and neck VMAT plans that have been planned using four different planning methods. The goal of this study was to assess the agreement between the calculated surface dose from Eclipse and the measured dose from phantom measurements using DOSEmappers^{TM}. The aim is to better understand the accuracy of Eclipse AXB to confirm the skin dose differences from the planning study (Paper B); therefore validating the results of that work.

5.2. Method and Materials

5.2.1 Surface and Build-up Doses for open fields on a solid water phantom

To determine the accuracy of the surface dose and dose within the build-up region calculated by Eclipse AXB with dose-to-medium reporting; comparisons have been made with measurement. The Eclipse AXB beam model is based on TrueBeam representative beam data supplied by Varian and has been validated against measurement and shown to meet the standard Venselaar criteria (Venselaar et al, 2001).

Doses calculated by AXB in Eclipse have been compared to doses measured by an advanced Markus parallel plate chamber and by DOSEmappers^{TM}. Comparisons have been made for incident angles of 0°, 30° and 60° for field sizes 4 x 4 cm^2, 10 x 10 cm^2 and 20 x 20 cm^2. These angles were used by Cao et al (2017) when comparing the surface dose of different algorithms to Gafchromic EBRT2 film measurements and Monte Carlo Simulations. The extreme of 60° has also been selected in this study as it represents the extreme oblique angle that can be delivered with the setup described in section 5.2.1.1.

5.2.1.1 Advanced Markus Measurements

A plane-parallel plate advanced Markus chamber, PTW34045 (PTW, Freiburg, Germany) and a 30 x 30 x 30 cm^3 solid water phantom was used to measure the surface and build-up doses of a 6MV Varian Truebeam field (Varian, Palo Alto, CA). The quality assurance of the linac was up-to-date and performed according to IPEM Report 81 (2^{nd} Edition) (IPEM, 2018). The advanced Markus was embedded into a custom solid water phantom. This allows the waterproof protection cap of the advanced Markus to be removed during all measurements. Without the waterproof protection cap the effective point of measurement is at the inner surface of the 0.03 mm entrance foil (PTW, 2020). A dose of 100 MU, giving a dose of 100 cGy at D_{max} was delivered to the phantom for each measurement. Measurements were repeated four times at each measurement point for averaging purposes. Between each measurement the depth of solid water above the advanced Markus chamber was increased in 1.0 mm increments and the source to chamber distance increased by the same amount to maintain an SSD of 100 cm.

The chamber over-exposure at the surface and in the build-up region was corrected for, as done by Imae et al (2020). This correction uses a formulae described by Rawlinson et al (1992). For an incident angle of 0° the over-exposure of the advanced Markus at the surface was 3.4% and 1.3% at 4.0 mm. Corrections were applied to other depths measured using the method described in Rawlinson et al (1992). The dose was calculated by normalising the reading to a known dose, this being the average reading at a depth of 16.0 mm for a 10 x 10 cm^2 field with an incident angle of 0°.

5.2.1.2 DOSEmapper™ Measurements

Mini DOSEmappers™ (TRUEinvivo®, Surrey, UK) consisting of three Micro Silica bead TLDs were placed in a wax insert to ensure a flat surface. The same phantom and setup as the advanced Markus measurements was used. Each mini DOSEmapper™ was irradiated individually at the same depths as the advanced Markus measurements. Between each measurement the mini DOSEmapper™ was changed as the depth of solid water above the mini DOSEmapper™ was increased. The source to mini DOSEmapper™ distance was increased to maintain an SSD of 100 cm. Mini DOSEmappers™ were returned to TRUEinvivo® for readout using a reference that was irradiated to a known dose (same conditions as the advanced Markus reference) and a control that remains with

the DOSEmappers™ in storage and transportation. For each mini DOSEmapper™ an average and standard deviation of the three Micro Silica Bead TLDs was returned in a report from TRUEinvivo®.

The Micro Silica Bead TLDs used in the DOSEmappers™ have a thickness of 1.0 mm (Jafari, 2013). The effective depth of measurement will therefore be at a depth of between 0.0 mm and 1.0 mm. The effective depth of measurement has been determined by comparing the surface DOSEmapper™ result to the depth dose curve measured by the advanced Markus chamber for a 10 x 10 cm^2 field with an incidence angle of 0°. To facilitate the comparison the depth dose for the advanced Markus chamber and the DOSEmapper™ were fitted using third order polynomial functions.

5.2.1.3 Eclipse Calculated Doses

Eclipse depth doses were calculated on a 30 x 30 x 30 cm^3 phantom, using AXB algorithm with a 1.0 mm grid size. A dose grid of 1.0 mm is the minimum dose grid resolution that can be used for dose calculation in Eclipse. A material of water was assigned to the phantom. The same field arrangement as for the advanced Markus measurements was used. The dose for 100 MU was calculated and a profile plotted from the surface of the phantom to a depth of 1.2 cm, as shown in figure C1. When using these parameters; Eclipse plots the dose with depth in increments of approximately 0.1 mm. This step size cannot be changed by the user and therefore efforts were made to ensure it remained consistent between each dose profile. The step size is less than the dose grid resolution. It has been assumed that Eclipse interpolates the dose at each depth increment using the dose calculated at each calculation point. Court and Tishler (2008) found that steep dose gradients at the surface make a reliable dose calculation difficult. It was reported that pixel size, pixel location, calculation grid size and calculation grid location had an important effect on the calculated surface doses. This has been considered in this study by taking an average from six profiles. For each profile the calculation was repeated with a new external body contour, a new calculation grid and a new start position of the dose profile.

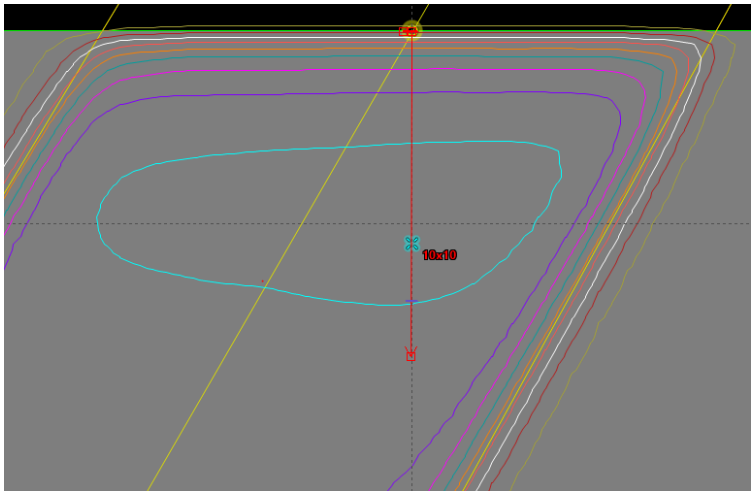

Figure C1. Red arrows shows profile drawn to determine PDD and dose at each measuring point

5.2.1.4 Analysis

At each measurement point the relative dose difference between the measured and calculated dose was calculated. This has been done for doses measured by the advanced Markus and the mini DOSEmapper^{TM}. In low dose gradient regions it is acceptable to compare dose directly. In high dose gradient regions, such as the build-up region, a small spatial error, either in the measurement or the calculation, results in a large dose difference. The concept of distance-to-agreement (DTA) can then be used to determine the acceptability of a TPS dose calculation (Low et al, 1998). The DTA is the distance between a measured data point and the nearest calculated point that gives the same dose. In this study both dose difference and DTA have been reported and will be used to complement each other in low and high dose gradient regions.

5.2.1.5 Measurement Uncertainty Analysis

For the Eclipse calculated depth dose profiles; the uncertainty was determined by creating six profiles for each setup. The average of the six profiles was used to compare to advanced Markus and DOSEmapper^{TM} measurements. The standard deviation of the six profiles at each depth was calculated to show how uncertainty in the dose reported from Eclipse changes with depth.

For each mini DOSEmapper™ the dose measured by three Micro Silica Bead TLDs was averaged to determine the dose at each measurement point. The standard deviation between the three TLDs shows uncertainty in the TLD response and readout process. Repeated measurements were not taken and therefore the uncertainty in setup of repeated measurements has not been included. For each field arrangement one measurement was made with the DOSEmappersTM. Steep dose gradients make measurements challenging in the buildup region. Doses measured with the DOSEmappersTM are therefore likely to be subject to further measurement uncertainty and possible measurement error.

Advanced Markus measurements were repeated at two separate measurement sessions. Between each session a different PTW advanced Markus chamber and electrometer was used. At each session four measurements were repeated.

5.2.2 Surface Dose on a Cylinder Phantom and Anthropomorphic Phantom

5.2.2.1 Phantom Setup

A locally manufactured Perspex (water filled) cylinder phantom, with a diameter of 17 cm and the head, neck and shoulders of a Rando anthropomorphic phantom were both used in this study. DOSEmappers™ were constructed by TRUEinvivo® that were 5 x 5 cm^2, with a 1 cm measuring point separation. At each measuring point there were two clear Micro Silica Bead TLDs. The DOSEmappers™ also contained a number of landmarks to help positioning and repeatability of exposures. The landmarks were marked on each phantom in order for DOSEmappers™ to be placed in the same position for each exposure. For the cylinder phantom a measurement set was made with the DOSEmappers™ at the surface of the phantom with and without 1.5 mm of dental wax placed over the DOSEmappers™. The 1.5 mm of dental wax aims to represent the maximum thickness of the dermis. The Rando anthropomorphic phantom had a custom made thermoplastic immobilisation mask. This served a number of purposes; it kept the DOSEmappers™ against the undulating phantom surface, replicated patient setup and improved setup accuracy of the phantom. As with the cylinder phantom; measurements were made with and without 1.5 mm of dental wax placed over the DOSEmappers™. The setup of the Rando anthropomorphic phantom is shown in figure C2.

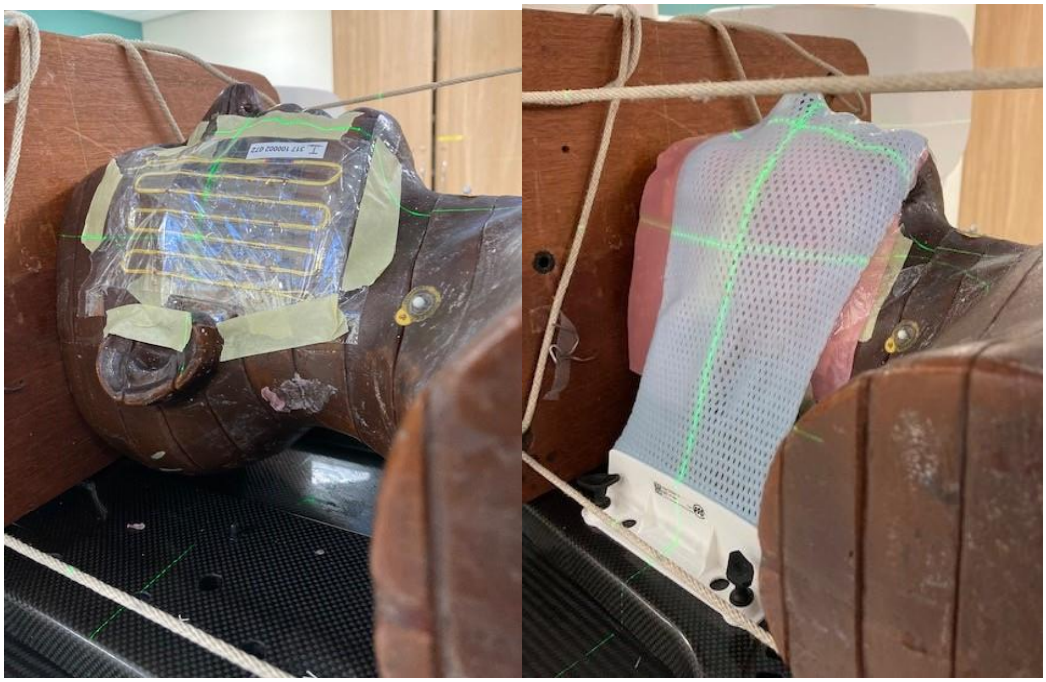

Figure C2 Left: Rando anthropomorphic phantom with DOSEmappers™ *in situ. Right: Rando anthropomorphic phantom with wax and thermoplastic cast in situ*

5.2.2.2. Scanning and Planning

Each of the phantoms with and without wax were CT scanned on a Siemens Go.Open Pro CT scanner (Siemens, Erlangen, Germany) using a head and neck protocol with a 1.0 mm slice thickness. On each scan a DOSEmapper™ was positioned on the phantom in order for the measurement points to be visualised. The position of the DOSEmapper™ landmarks were marked on each phantom to ensure accurate DOSEmapper™ positioning when new DOSEmappers™ were positioned for plan irradiation. A scan origin was defined by placing radio-opaque markers on the phantom surface.

The four datasets were imported into the Eclipse treatment planning system (Varian, Palo Alto, CA). For each dataset a clinician target volume (CTV) was contoured that extended to the phantom surface and included all the measurement points of the DOSEmapper™. A planning target volume (PTV) was created from the CTV with a margin of 5.0 mm in all directions. Treatment plans were created using the parameters in table C1.

Table C1. Planning parameters used when planning VMAT head and neck cancer treatments.

Treatment planning system	Eclipse 15.6 (Varian, Palo Alto, CA)
Field arrangement	Two complementary 6MV coplanar VMAT arcs (one counter clockwise, one clockwise)
Optimiser	Photon Optimiser Algorithm (PRO) v15.6

For each dataset four plans where produced. The plans differed by cropping the optimisation PTV 5.0 mm, 3.0 mm and 0.0 mm from the phantom surface as well as optimising with a virtual bolus. The full planning methods were described in a previous study (Paper B). The Eclipse calculated dose to each measurement point was recorded for each planning method on each dataset. This is achieved by placing a reference point at the centre of each Micro Silica Bead TLD.

5.2.2.3. Plan Delivery

Plans were delivered to the phantoms on a Varian Truebeam (Varian, Palo Alto, CA). For each plan a new DOSEmapper™ was placed on the phantom surface ensuring the DOSEmapper™ landmarks were positioned as for the CT scan. Phantoms were positioned in turn on the treatment couch using planned moves from the origin defined at the CT scan. DOSEmappers™ were returned to TRUEinvivo® for readout using references that was irradiated to known doses of 200 cGy and 100 cGy and a control that remains with the DOSEmappers™ in storage and transportation. For each DOSEmapper™ the dose was recorded to 36 measurement points. An average and standard deviation of the two Micro Silica Bead TLDs at all measurement points was returned in a report from TRUEinvivo®.

5.3. Results

5.3.1 Effective Measurement Depth of Measurement of DOSEmappers™

Figure C3 shows the PDD from Eclipse**,** advanced Markus measurements and DOSEmappers™ for a 10 x 10 cm^2 field with an incident angle of 0°. The advanced Markus chamber and DOSEmapper™ were positioned at the phantom surface for the first measurement. The advanced Markus measurements have been used to infer the effective measurement depth for the DOSEmapper™. With the DOSEmapper™ at the surface a dose of 39.2 cGy for 100 MU was measured. This corresponds to a depth of 0.7 mm on the depth dose plot measured with the advanced Markus chamber.

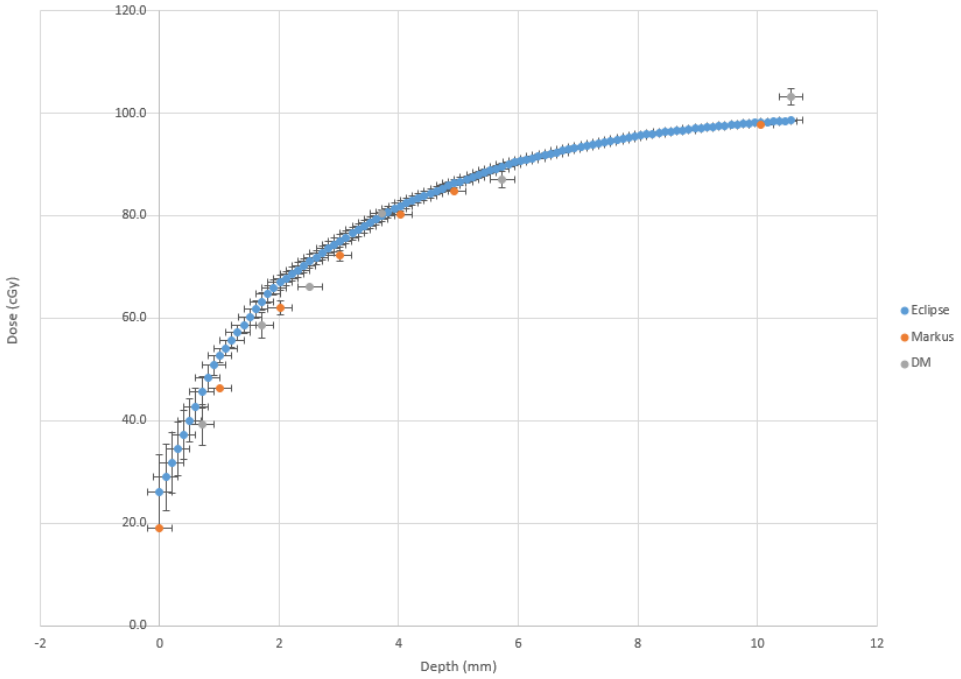

Figure C3. Eclipse calculated, advanced Markus and DOSEmapper™ measured depth doses in a 6 MV, 10 x 10 cm^2, 100 cm SSD, 0° setup. The depth dose measurements with the DOSEmapper™ have been used to infer the effective measurement depth from the advanced Markus chamber measurements.

5.3.2. Surface and Build-up Doses for open fields on a solid water phantom

Depth doses for Eclipse, the advanced Markus and DOSEmappers^{TM} have been plotted for each field size and angle of incidence, examples are shown in figures C3, C4 and C5. As expected; calculated and measured results show the dose close to the surface increases as field size increases and as the incident angle increases. Large uncertainties were seen in Eclipse calculated doses close to the surface as shown in figures C4 and C5.

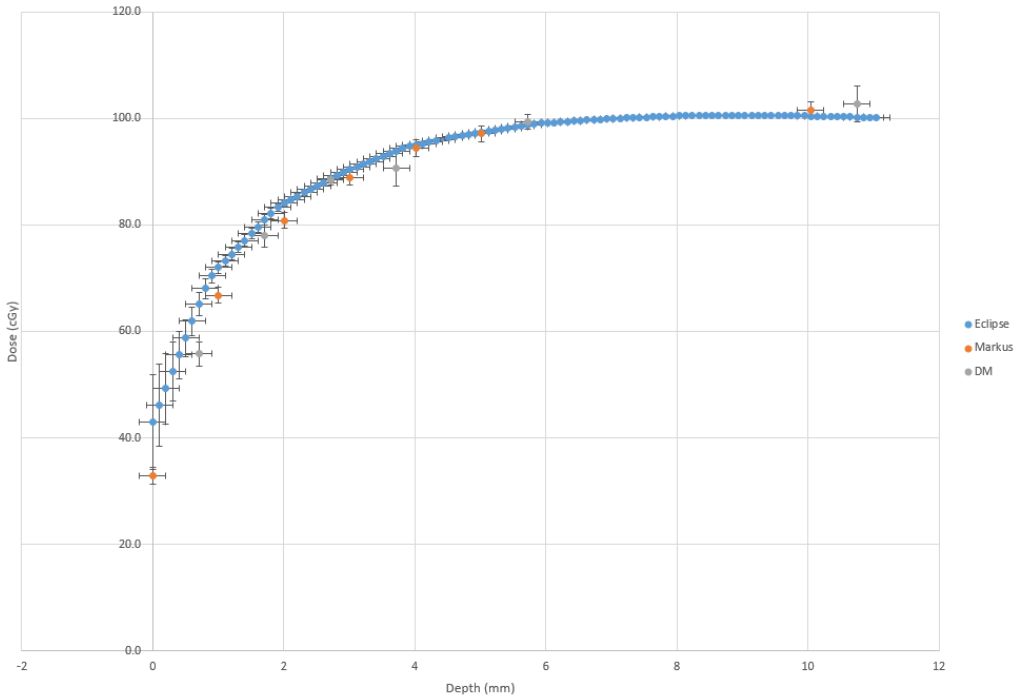

Figure C4. Eclipse calculated, advanced Markus and DOSEmapper^{TM} measured PDDs in a 6 MV, 10 x 10 cm^2, 100 cm SSD, 60° setup. Showing steep dose gradient in first 1.0 mm, step change at 1.0 mm and larger uncertainties at depths less than 1.0 mm.

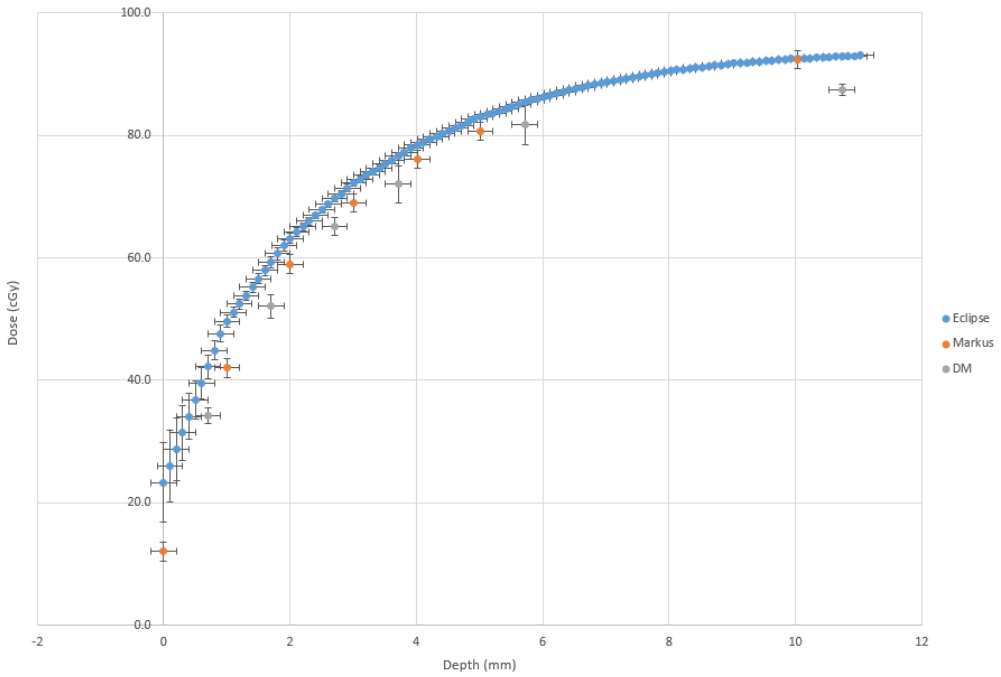

Figure C5. Eclipse calculated, advanced Markus and DOSEmapper™ measured PDDs in a 6 MV, 4 x 4 cm², 100 cm SSD, 30° setup.

Tables C2 and C3 show the relative dose differences between Eclipse and the advanced Markus measurement; and Eclipse and the DOSEmappers™ measurements respectively. A readout error occurred for the 20 x 20 cm² field at an angle of incidence of 30°, therefore there is no result for this field at a depth of 0.57 mm.

Table C2. Relative dose difference (%) between Eclipse calculated dose and advanced Markus measurements. Negative represents measured doses lower than calculated.

	0 degrees			30 degrees			60 degrees		
Depth (mm)	4 x 4	10 x 10	20 x 20	4 x 4	10 x 10	20 x 20	4 x 4	10 x 10	20 x 20
0	-41.6	-27.4	-4.1	-48.4	-27.4	-14.5	-32.0	-23.3	-10.8
1.0	-12.2	-11.9	-6.3	-14.9	-12.1	-11.6	-8.1	-7.2	-6.4
2.0	-7.9	-7.3	-2.3	-6.6	-5.0	-4.7	-3.4	-3.9	-2.1
3.0	-4.3	-3.8	-0.8	-4.4	-3.0	-4.2	-3.1	-1.6	-1.8
4.0	-2.5	-2.2	0.4	-3.0	-1.9	-2.6	-0.9	-0.7	-0.2
5.0	-2.3	-1.7	-0.6	-2.8	-2.0	-2.7	-1.0	-0.3	-0.1
10.0	0.3	-0.4	0.0	-0.2	0.1	0.9	0.8	1.2	1.1

Table C3. Relative dose difference (%) between Eclipse calculated dose and DOSEmapper measurements. Negative represents measured doses lower than calculated.

	0 degrees			30 degrees			60 degrees		
Depth (mm)	4 x 4	10 x 10	20 x 20	4 x 4	10 x 10	20 x 20	4 x 4	10 x 10	20 x 20
0.07	-7.1	-13.9	-10.3	-19.0	-18.8	-6.3	-11.4	-14.2	-4.6
0.17	-7.1	-7.3	-4.8	-12.1	-9.7	-5.1	-3.6	-3.7	1.1
0.27	-1.2	-7.1	-2.3	-6.5	-4.0	-0.3	-2.5	-0.2	-2.0
0.37	-2.0	0.6	-2.8	-6.0	-4.1	-0.9	2.5	-3.4	0.4
0.57	-2.7	-2.9	-2.0	-4.3	-3.8		1.4	0.6	0.3
1.07	0.4	4.7	0.5	-5.8	-0.9	2.5	0.8	2.5	1.9

The dose difference was greatest at the surface, where difference of up to 48% were measured. The uncertainty in Eclipse calculated doses is greatest at shallow depths and is dependent on the position of the external contour, the dose grid and the starting position of the dose profile. At depths less than 3.0 mm a distance to agreement comparison is more appropriate and are shown in tables C4 and C5. For the advanced Markus measurements at a depth of 0.0 mm the measured dose is lower than the calculated. It is therefore not been possible to determine a distance to agreement. At depths greater than 3.0 mm the change in dose with depth reduces and a small change in dose results in a larger change in depth. Distance to agreement for depths deeper than 3.0 mm have not been reported in this study.

Table C4. Distance to agreement (mm) between Eclipse calculated dose and advanced Markus measurements.

	0 Deg			30 deg			60 deg		
Depth(mm)	4 x 4	10 x 10	20 x 20	4 x 4	10 x 10	20 x 20	4 x 4	10 x 10	20 x 20
0									
1.0	-0.2	-0.2	-0.1	-0.2	-0.2	-0.2	-0.2	-0.2	-0.2
2.0	-0.3	-0.3	-0.1	-0.2	-0.2	-0.3	-0.2	-0.3	-0.2
3.0	-0.3	-0.2	-0.1	-0.2	-0.2	-0.3	-0.3	-0.2	-0.2

Table C5. Distance to agreement (mm) between Eclipse calculated dose and DOSEmapper™ measurements.

	0 Deg			30 deg			60 deg		
Depth(mm)	4 x 4	10 x 10	20 x 20	4 x 4	10 x 10	20 x 20	4 x 4	10 x 10	20 x 20
0.7	-0.1	-0.2	-0.2	-0.2	-0.3	-0.1	0.2	-0.2	-0.1
1.7	-0.2	-0.3	-0.2	-0.3	-0.4	-0.3	-0.2	-0.2	0.1
2.7	-0.1	-0.5	-0.2	-0.5	-0.3	0.0	-0.2	0.0	-0.2

5.3.3 DOSEmapper™ dose vs Eclipse dose for different VMAT planning methods

Each DOSEmapper™ has 36 measurement points. The dose reported at each measurement point is an average of the dose measured by two clear Micro Silica TLDs. Table C6 shows the percentage difference between the dose calculated by Eclipse and the dose measured by the DOSEmapper™ averaged over the 36 measurement points. The cylinder water phantom and the Rando anthropomorphic phantom show similar results; with DOSEmappers™ measuring a lower dose than calculated by Eclipse when measuring without wax over the DOSEmapper™. When the DOSEmapper™ is placed under 1.5 mm of wax the dose measured by the DOSEmapper™ is up-to 11% greater than that calculated by Eclipse for both phantom setups.

Table C6. Average percentage difference between Eclipse calculated dose and DOSEmapper™ measured dose

	Planning Method			
Phantom	**Virtual Bolus**	**Crop 0.0**	**Crop 3.0**	**Crop 5.0**
Cylinder	-6.36 (4.73)	-5.14 (4.45)	-6.58 (9.27)	-8.69 (10.63)
Cylinder with wax	5.10 (6.63)	9.87 (9.46)	0.7 (5.52)	3.54 (5.30)
Rando	-8.04 (4.42)	-6.77 (10.15)	-9.56 (5.76)	-2.66 (4.49)
Rando with wax	6.22 (4.71)	9.95 (5.28)	4.84 (4.94)	11.17 (5.71)

Figure C6 shows the average percentage difference in dose relative to the virtual bolus planning technique for both Eclipse and the DOSEmappers™. This has been averaged over the 36 measurements points. These results show that there is a positive correlation between the dose difference report by Eclipse and the DOSEmappers™, with Pearson correlation coefficient $r(10) = .918$, $p<.001$.

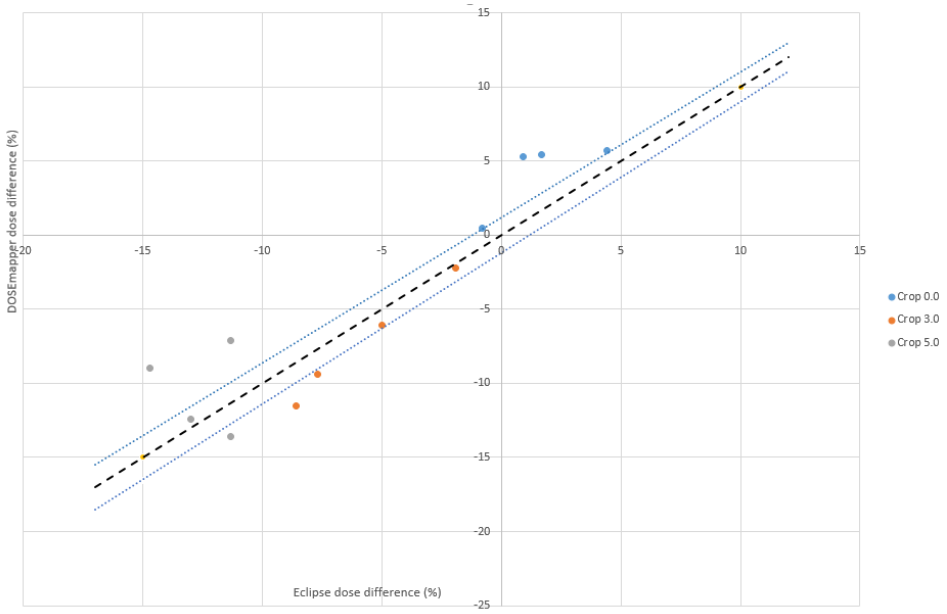

Figure C6. Average percentage difference in dose relative to the virtual bolus plan. Black dashed line represents DOSEmapper dose difference = Eclipse dose difference. Blue dashed line represents ±10%.

5.4. Discussion

5.4.1 Accuracy of Eclipse calculated surface and build-up dose

Cao et al (2017) showed that Eclipse AXB performed well for all angles and field sizes except for a small under-estimation of dose in the initial 2.0 mm of less than 3% for incident angles 0°, 30° and 60°. In this study Eclipse AXB calculated surfaces doses are higher than that measured by the advanced Markus for all setups, as shown in table C2. The differences in surface dose in this study are greater than determined by Cao et al. As in this study, Cao et al defined a water phantom in the TPS using volume contouring tools. Cao et al did not give details of the external body contour and uncertainty in the Eclipse dose at the phantom surface has not been defined. Table C2 shows there are large discrepancies between the dose measured at the surface and the dose calculated by Eclipse AXB. Dose difference of up-to 48% were measured at the surface. When comparing Eclipse AAA to GafChromic film measurements, Arbor et al (2019) reported a mean dose difference of 25% in the depth range of 0 to 5.0 mm, with a maximum discrepancy of 62%. Large dose differences at the surface should be expected due to the difficulties in measuring and computing a precise dose at the air-tissue interface (Arbor

et al, 2019). The depth dose curves in figures C3, C4 and C5 show large uncertainties in the Eclipse dose within the first 1.0 mm. For the depth dose curve shown in figure C4; at the surface the standard deviation of the Eclipse calculated dose is 28%, this reduces to less than 2% at depths between 1.0 mm and 2.0 mm. The surface dose extracted from Eclipse was dependant on the position of the external body contour, position of the dose grid and start position of the dose profile shown in figure C1. The uncertainty may be reduced by using a finer resolution voxel and dose grid size in the region of the air-tissue interface. Within the limits of the TPS it is difficult for Eclipse to match the real surface of the phantom (Arbor et al).

Table C4 shows that the distance to agreement is within 0.3 mm of Eclipse for all setups at depths ≥ 1.0 mm. At depths ≥ 1.0 mm, the accuracy of the dose calculated by Eclipse is less dependent on the variables described above.

The surface dose results show that reported skin dose should not be based on dose calculated at the surface due to the uncertainties shown here. These results therefore validate the approach of calculating dose to the skin using a shell structure of 2.0 mm or more (Court et al, 2008) (Chow and Grigorov, 2007) (Sharp and Dohme, 2021).

5.4.2 Suitability of DOSEmappers™ as a surface dosimeter

In this study the effective measurement depth of TRUEinvivo® Micro Silica Bead TLDs has been determined to be 0.7 mm. This compares well to the centre of the bead, Micro Silica Bead TLDs have a thickness of 1.0 mm. DOSEmappers™ therefore do not measure the dose at the surface; however a depth of 0.7 mm is more relevant when considering skin dose. The growing layer of the skin (dermis) is between 0.05 mm and 1.5 mm, depending on the anatomic location (Cao et al 2017).

This study and the findings of Cao et al (2017) confirm that Eclipse AXB can calculate dose accurately for single open beams at normal and oblique incidence for depths of ≥ 1.0 mm. The measured dose from the mini DOSEmappers™ can therefore be compared with Eclipse calculated dose to determine if doses measured by DOSEmappers™ are accurate under these conditions. Table C3 shows the absolute dose difference between the Eclipse calculated doses and doses measured by DOSEmappers™. The maximum absolute dose difference is 19%; when this is converted into distance to agreement this is equivalent to a depth difference of 0.2 mm. A depth of 0.2 mm is within the setup

accuracy of the DOSEmapper™ measurement and less than the accuracy of defining the Eclipse depth dose profile. It can therefore be concluded that for all setups compared in this study, DOSEmappers™ accurately measure the dose at a depth of 0.7 mm.

For greater depths in the build-up region table C3 and table C5 also show that DOSEmappers™ accurately measure dose. The setup that shows the greatest difference from Eclipse AXB is for a 4 x4 cm^2 beam at an obliquity of 30°. This can be seen in the depth dose curve for this setup, figure C5. For measurements at depths of 3.5 mm and 5.5 mm a larger standard deviation in dose has been measured across the three Micro Silica bead TLDs at these measurement points. Ideally these results would be confirmed by repeated measurements. This has not been possible in this study.

The DOSEmappers™ can accurately measure dose at a depth of 0.7 mm and in the build-up region. The properties of linear response to dose, no angular dependence, response independent of dose rate and small bead size (Jafari, 2013 and Jafari, 2014) make clear Micro Silica Bead TLDs a good dosimeter for near surface dose measurements. When the Micro Silica Bead TLDs are constructed into a DOSEmapper™ they are ideal for placing on the surface of the patient to measure dose across an area for a large number of measurement points.

5.4.3 Skin dose for different head and neck planning methods

In this study, the measured dose obtained from the DOSEmappers™ were compared to calculated doses by Eclipse AXB. Table C6 shows the percentage difference between measurement and calculated doses. The standard deviation of these results show there are large variations in the relative dose difference between Eclipse calculated doses and DOSEmapper™ measured doses. This demonstrates the uncertainty in individual measurement and extraction of dose from Eclipse. Therefore a single surface measurement point for clinical plans using Micro Silica Beads is not appropriate. An average from a 2D array of measurement points gives a more accurate representation of the plan.

Measurements were made under 1.5 mm of wax with the aim to be beyond the very steep dose gradient that was seen in the solid water measurements below 1.0 mm. This setup has not replicated the solid water measurements and has caused more uncertainty in measurement. A potential reason for this increased uncertainty is that the wax is not flush

with the phantom surface and creates an additional air gap in this steep dose gradient region. The difference between the measured and calculated doses for this setup will not be considered further in this analysis.

For both the cylinder phantom and Rando anthropomorphic phantom the DOSEmappers^{TM} measure less dose than calculated by Eclipse AXB for all planning methods when placed on the surface without wax. Due to the high dose gradient in depths of less than 2.0 mm the accuracy of the dose extraction from Eclipse is critical in comparing near surface doses. Reported Eclipse dose is dependent on the position of the dose point in Eclipse used to determine the calculated dose to the Micro Silica Bead TLD. Dose points have been positioned at the Micro Silica Bead TLD effective point of measurement in Eclipse. Variations in the external body contour, dose grid and position of the dose point in Eclipse have not been considered in this analysis. Repeating the positioning of dose points a number of times as done for the solid water analysis would reduce the uncertainty. The solid water results showed that a dose difference of 8.2% at near surface depths of less than 1.0 mm only results in a distance to agreement difference of 0.1 mm. The accuracy of positioning dose points in Eclipse is within ± 0.2 mm of the Micro Silica Bead TLD's effective point of measurement, therefore dose differences greater than 8.2% are expected.

Pearson Correlation Coefficient shows that the Eclipse and DOSEmapper^{TM} results are correlated and therefore the relative dose difference recorded in Eclipse have been confirmed by measurement. The exception to this is the planning method of cropping 0.0 mm from the surface. For the planning method of cropping 0.0 mm from the surface the measured dose from the DOSEmapper^{TM} differs from Eclipse. For the cylinder phantom the difference in dose from the plan of cropping 0.0 mm from the surface is 0.9% when calculated in Eclipse and 5.3% when measured with the DOSEmapper^{TM}. As shown in Paper B; this planning method gives excess fluence at the surface, making the plan less robust to changes in setup. A small change in setup will increase the dose at the surface, this can be seen for both the cylinder and Rando anthropomorphic phantom when the DOSEmapper^{TM} is placed under 1.5 mm of wax.

Figure C6 shows that as the amount the PTV is cropped back from the surface increases the surface dose reduces. These results validate the results found in the previous planning study (Paper B). The planning method of cropping 0.0 mm from the surface increases the

dose to the skin compared to the virtual bolus planning method, this is in agreement with the planning study.

5.5. Conclusion

Measurements with an advanced Markus parallel plate chamber at the surface and in the build-up region of a solid water cube phantom have shown that Eclipse AXB accurately calculates dose at depths ≥ 1.0 mm. Dose comparisons at these depths has been challenging due to steep dose gradients.

TRUEinvivo® DOSEmappers™ have an effective depth of measurement of 0.7 mm and can accurately measure near surface dose, making them an ideal dosimeter for skin dose measurements.

In this study DOSEmappers™ have been used to measure the near surface dose for four different planning methods. The relative dose difference between planning methods recorded by Eclipse have been confirmed by measurement. DOSEmapper™ results validate the results found in the previous planning study (Paper B). These results show that as the amount the PTV is cropped back from the surface increases the surface dose reduces; and the planning method of cropping 0.0 mm from the surface increases the dose to the skin compared to the virtual bolus planning method. This validates the results found previously (Paper B) and gives confidence in determining the most superior planning method for head and neck VMAT planning.

5.6. Acknowledgements

The authors wish to thank TRUEinvivo® for their flexibility in constructing bespoke DOSEmappers™ and their efforts in producing reliable DOSEmapper™ results.

5.7. Author Contributions

Julie Kirk contributed to study design, data collection, analysis and interpretation, and drafted the manuscript. Carl Rowbottom contributed to study design, study supervision, and critical revision of the manuscript.

5.8. References

Akbas, U. et al. (2017). Surface dose measurement with Gafchromic EBT3 film for intensity modulated radiotherapy technique. *EPJ Web of Conferences*, 154, pp.7–10.

Akino, Y. et al. (2013). Evaluation of superficial dosimetry between treatment planning system and measurement for several breast cancer treatment techniques. *Medical Physics*, 40(1).

Arbor, N. et al. (2019). A GATE/Geant4 Monte Carlo toolkit for surface dose calculation in VMAT breast cancer radiotherapy. *Physica Medica*, 61(April), pp.112–117. [online]. Available from: https://doi.org/10.1016/j.ejmp.2019.04.012.

Badkul, R., Nejaiman, S., Pokhrel, D., Jiang, H. and Kumar, P. (2015), SU-E-T-196: Comparative Analysis of Surface Dose Measurements Using MOSFET Detector and Dose Predicted by Eclipse - AAA with Varying Dose Calculation Grid Size. Med. Phys., 42: 3377-3377.

Cao, Y. et al. (2017). Superficial dose evaluation of four dose calculation algorithms. *Radiation Physics and Chemistry*, 137, pp.23–28. [online]. Available from: http://dx.doi.org/10.1016/j.radphyschem.2016.02.032.

Chow, J.C.L. and Grigorov, G.N. (2008). Surface dosimetry for oblique tangential photon beams: A Monte Carlo simulation study. *Medical Physics*, 35(1), pp.70–76.

Court, L.E. et al. (2008). Experimental evaluation of the accuracy of skin dose calculation for a commercial treatment planning system. *Journal of Applied Clinical Medical Physics*, 9(1), pp.29–35.

Imae, T. et al. (2020). Surface and build-up dose comparison between Elekta 6 MV flattening filter and flattening-filter-free beams using an advanced Markus ionization chamber and a solid water-equivalent phantom. *Journal of Applied Clinical Medical Physics*, 21(12), pp.334–339.

Jafari, S.M. et al. (2014). Low-cost commercial glass beads as dosimeters in radiotherapy. *Radiation Physics and Chemistry*, 97, pp.95–101. [online]. Available from: http://dx.doi.org/10.1016/j.radphyschem.2013.11.007.

Jafari, S.M. et al. (2014). Energy response of glass bead TLDs irradiated with radiation therapy beams. *Radiation Physics and Chemistry*, 104, pp.208–211. [online]. Available from: http://dx.doi.org/10.1016/j.radphyschem.2014.03.009.

Jafari, S.M. et al. (2015). Feasibility of using glass-bead thermoluminescent dosimeters for radiotherapy treatment plan verification. *British Journal of Radiology*, 88(1055), pp.1–6.

Jafari, S.M. et al. (2017). Feasibility study of silica bead thermoluminescence detectors (TLDs) in an external radiotherapy dosimetry audit programme. *Radiation Physics and Chemistry*, 141(July), pp.251–256. [online]. Available from: http://dx.doi.org/10.1016/j.radphyschem.2017.07.021.

Kesen, N. and Akbaş, C. (2021). The investigation of the anisotropic analytical algorithm (Aaa) and the acuros xb (axb) dose calculation algorithms accuracy in surface and buildup region for 6 mv photon beam using gafchromic ebt3 film. *Turk Onkoloji Dergisi*, 36(3), pp.365–372.

Kim, J.H., Hill, R. and Kuncic, Z. (2012). Practical considerations for reporting surface dose in external beam radiotherapy: A 6 MV X-ray beam study. *Australasian Physical and Engineering Sciences in Medicine*, 35(3), pp.271–282.

Low, D.A. et al. (1998). A technique for the quantitative evaluation of dose distributions. *Medical Physics*, 25(5), pp.656–661.

PTW. (2020) Detectors for Ionizing Radiation. Available from: https://www.ptwdosimetry.com/fileadmin/user_upload/Online_Catalog/DETECTORS_Cat_en_16522900_13/blaetterkatalog/index.html#page_1

Rawlinson A.J, Arlen D. and Newcombe D. (1992) Design of parallel plate ion chambers for buildup measurements in megavoltage photon beams. *Medical Physics*, 19(3).

Sharp & Dohme Corp. (2021) MK-3475-867. Keynote 867 Radiation Manual for Investigator Sites, Version 6.0.

Thomas, S.J. and Hoole, A.C.F. (2004). The effect of optimization on surface dose in intensity modulated radiotherapy (IMRT). *Physics in Medicine and Biology*, 49(21), pp.4919–4928.

Venselaar J, Welleweerd H, Mijnheer B. Tolerances for the accuracy of photon beam dose calculations of treatment planning systems. Radiother Oncol. 2001 Aug;60(2):191-201.

Wang, L., Cmelak, A.J. and Ding, G.X. (2018). A simple technique to improve calculated skin dose accuracy in a commercial treatment planning system. *Journal of Applied Clinical Medical Physics*, 19(2), pp.191–197.

Zhuang, A.H. and Olch, A.J. (2014). Validation of OSLD and a treatment planning system for surface dose determination in IMRT treatments. *Medical Physics*, 41(8

6. Critical Appraisal

6.1. Introduction

Clinical research can be used to inform and change clinical practices, thus affecting individual patient's care or the care of a large population. It is therefore important to critically appraise all clinical research. Critical appraisal is the process of carefully and systematically examining research evidence to judge its trustworthiness, its value and relevance in a particular context (Mhaskar et al, 2009). To ensure the process is systematic Young and Solomom (2009) described a method of how to critically appraise an article using a ten point checklist.

It is also important to critically appraise one's own research. In this chapter the aim is to critically appraise papers A, B and C.

6.2. Paper A: The Impact of Waiting for Radiotherapy Treatment to Start on Survival and Patient Experience for Head and Neck Cancer Patients at Clatterbridge Cancer Centre

6.2.1. Contribution to knowledge and current practice

In paper A the impact of waiting for radiotherapy treatment to start on overall survival and patient experience for head and neck cancer patients was studied. The study shows that when the time between decision to treat with radiotherapy and treatment commencement (TTS) exceeds 30 days the overall survival decreases. This was studied by Fortin et al (2002), with TTS greater than 30 days also found to impact overall survival for patients with early stage disease (T1 and T2). This study confirms the findings of Fortin et al in a modern UK setting.

The effect waiting for radiotherapy treatment to start has on head and neck cancer patient's quality of life has not been previously studied. In this study a patient experience questionnaire has been developed and used in practise to add knowledge to this field.

When combining both overall survival data and patient experience data it was concluded that there should be a greater focus on ensuring all head and neck cancer patients are treated within a TTS of 30 days. A TTS of 30 days does not reflect the seventeen day time frame recommended in the Radiotherapy service specifications (NHS England, 2019). This study shows that ensuring all patients are treated within 30 days should be prioritised before reducing the TTS below seventeen days for a smaller patient group as this will have a greater impact on overall survival.

6.2.2. Strengths and Weaknesses

Impact on Survival

In this study a patient cohort of 819 patients, treated between January 2017 and December 2019 were included in the analysis. In other studies the period over which patients were treated was greater. Fortin et al used data from 623 patients treated between 1988 and 1997, Polesel et al (2017) 1616 patients treated between 2003 and 2009 and Lio et al (2019) 956 patients treated between 2005 and 2017. The shorter time period used in this study has the advantage as other factors that could affect survival are less likely to have changed. For example, in this study treatment planning and delivery remained constant between 2017 and 2019, therefore reducing bias in the results.

Other studies that have found waiting for treatment to commence has a deleterious effect on survival considered the time between diagnosis and treatment initiation (TTI). As expected these studies determined a TTI that exceeds 30 days. Studying TTS over TTI has the advantage that the TTS can be controlled by the processes within a radiotherapy setting. If required, process redesign through a quality improvement project could be used to reduce the TTS for head and neck cancer patients.

The data collected in this study was limited by the data available in Aria. Aria is not an electronic patient record (EPR) system; therefore limited medical data is input into the system. Many of the studies mentioned in the literature review reported on the effect staging has on impact of waiting for treatment to commence. Polesel et al (2017) found that delays in early stage head and neck cancer had a stronger impact than late stages. Fortin et al found a difference in the TTS that affected outcome between T1 and T2 disease. Analysis by stage of disease was not carried out in this study but would have added to finding of Fortin et al.

In this study 88 patients (10.7%) had a TTS greater than 30 days. The reason for a delay was not investigated. Stordeur et al (2000) investigated the relationship between comorbidities and therapeutic delay, post treatment mortality, overall survival and relative survival. This study of head and neck cancer patients in Belgium found that comorbidity was not only significantly related to survival but also therapeutic delay. Adding comorbidities into this study would have strengthened the analysis. Ingarfield et al (2020) showed that socioeconomic status resulted in inequalities in survival for head and neck cancer patients. Socioeconomic statues may be a reason for delay and would also strengthen the study.

When statistically analysing the effect TTS has on survival; the data was categorised according to TTS. The categories were determined by using similar categories to other studies. The hazard ratio of death was only found to be significant for the patient category with a TTS greater than 30 days. The hazard ratios for other categories did show an increase in hazard ratio with increasing TTS; however, the 95% confidence interval did not show this as significant. Increasing the sample size and further adjustments in the TTS categories may result in a lower TTS that impacts patient survival.

Impact on patient experience

There is limited literature in studying patient experiences prior to radiotherapy treatment initiation. The development of a patient experience questionnaire has added to the field and strengthens the conclusions when determining an appropriate TTS.

More could have been gained from this section of the study with more experience in collecting this type of data. Some answers in the questionnaire did not reflect the questions being asked, as some responses focused on the care a patient had received from individual members of staff and explained how satisfied they were with the care. This needs to be considered in future questionnaires. It is important to give patients the space to do this; improved patient engagement could have improved the responses from some patients. When developing the questionnaire patient representatives that are part of this institution's Patient Experience and Inclusion Group provided assistance. This assistance ensured the questionnaire was appropriate for patient use while maintaining the aim of the project.

Of the 75 questionnaires distributed; only 22 responded. This could have been improved with more time given to the patient; explaining the reason for the survey verbally and in some cases talking through the questionnaire. Response rate may also have been improved if different forms of the questionnaire had been used. For example the use of online forms such a 'Survey Monkey' may have been more appealing to some patients. Improving patient engagement in the process would have taken more resources and face-to-face contact. At the time the questionnaire was distributed there was a large number of staff Covid cases. This caused staff shortage and increased infection risk. Face-to-face contact with patients was therefore minimised.

A grounded theory approach was used in the analysis of the questionnaire data. In this theory; analysis and development of a hypotheses happens after the data is collected. In qualitative research, results from two or more different methods of data collection can strengthen the hypothesis. Mays and Pope (2000) discussed ways to improve the validity of qualitative research. Triangulation compares the results from two or more different methods of data collection or two or more data sources. Patterns of convergence are then used to develop an overall interpretation. In this study one method and one data source has been used. Patient interviews would have added an additional data source; this data could then have been triangulated with the questionnaire data. This was not possible due to the Covid risk discussed above.

Combining overall survival and patient experience has not previously been studied. Adding patient experience to a study of waiting times has been shown to add complementary data and strengthen the conclusion. Overall survival and patient experience are important factors when considering any quality improvement studies with the aim to reduce the waiting time for radiotherapy treatment.

6.2.3. Future directions of research

This study shows that ensuring all patients are treated within 30 days should be prioritised over reducing the TTS below seventeen days for a smaller patient group. To achieve this a quality improvement project following the LEAN process would be required. A LEAN quality improvement methodology would be required to investigate the pre-treatment pathway via process mapping. LEAN tools and PDCA cycles could be used to redesign the process; in order to ensure the time between decision to treat with radiotherapy and

the start of treatment is less than 30 days for all head and neck cancer patients. Ongoing monitoring of performance data to ensure a TTS of less than 30 days is maintained would also be required.

The impact waiting for radiotherapy treatment to start has on patient experience could be expanded from this study. Improvements in the questionnaire and extending its use would add to this study. The addition of a longitudinal study of patient experience would provide additional data to strengthen the conclusions.

The patient data used in this study was from before the radiotherapy network service specifications were published with a guidance of a TTS less than seventeen days. Data from a small sample of patient's completing the questionnaire in 2022 suggests that TTS times have not reduced and there is still a large variation in times, with some patients exceeding 30 days. To determine the impact of the radiotherapy network service specifications the data collection and analysis could be repeated for patients treated after these specifications were published. The impact of Covid on patient survival for head and neck cancer patients could also be analysed in the future; using this study as a baseline.

6.3. Paper B: Evaluation of Planning Methods Used to Compensate for Increased Fluence at the Surface for Inverse Planned Head and Neck Cancer Treatment

6.3.1. Contribution to knowledge and current practice

This is believed to be the only study investigating the effect different VMAT planning methods used to compensate for increased surface fluence have on plan quality (CTV coverage and maximum skin dose) and plan robustness for head and neck cancer treatments.

The use of virtual bolus for the optimisation of inverse plans has been concluded to be the favoured planning method. This study shows that with more modern optimisation algorithms and delivery techniques the virtual bolus planning method provides the best CTV coverage and is robust to changes in setup and patient anatomy. The most commonly used planning method for head and neck cancer in the UK is the method of cropping the PTV back from the surface. There are no studies supporting this planning method; this study also shows that this planning method reduces CTV coverage near the patient's surface and reduces plan robustness to changes in setup and patient anatomy.

6.3.2. Strengths and Weaknesses

In this study the effect a planning method has on skin dose has been studied. Locally this has been a concern raised by oncologists. Lee et al (2002) investigated the cause of acute skin toxicity observed when treating head and neck cancer patients when IMRT was first introduced into clinical practise. Previous studies comparing planning methods have not reported the effect the planning method has on skin dose. Considering skin dose in the analysis of planning methods strengthens the conclusion in determining the most superior and robust planning method. This study has demonstrated that skin dose is similar between the planning methods when plan uncertainties are taken into account.

This study uses data from ten patients to compare planning methods. The target and OAR contours used in this study were used for the patient's treatment and have been considered accurate in the analysis. At the time the selected patients were treated; peer review had not been established locally and not all head and neck patients went through a peer review process. Therefore there is a potential of inter-observer variability in the CTV outlining. If the CTV contours were not accurate in this region and dose was not required at the

surface or close to the surface the results would become invalid. However, each dataset was outlined by one of four oncologists. This shows that outlining a CTV to the surface or close to the patient's surface is required and not dependent on the oncologist outlining, therefore strengthening the analysis of CTV coverage. Outside of the pandemic when more time from others could have been given to research; peer review of the CTV contours could have been gained before the planning study started.

Thomas and Hoole (2004) used phantom data and one clinical head and neck case to compare planning methods. This study has used ten clinical cases, this gives more confidence in the data analysis and conclusions of the study.

In this study four different planning methods were investigated. A further option for evaluation using an uncropped PTV extending into air is possible but was not included in this study. This option requires additional virtual bolus to include the PTV in air and extending 5.0 mm beyond the PTV. The inclusion of this planning method would have made the study more transferrable to other treatment sites such as breast planning.

Plan robustness was determined using the Eclipse plan uncertainty tool. An isocentre shift of 3.0 mm was applied to match the imaging tolerance used locally when daily imaging with CBCT. Validating this potential shift with real patient data could have been used to confirm the suitability of a 3.0 mm isocentre shift. A method similar to that used by Tyran et al (2018) where CTV coverage was evaluated on a CT scanned performed during treatment for each planning method may have added to this part of the study. This would have involved data from a large number of patients to ensure the range of potential setup and anatomical changes are captured. This may have involved an additional planning CT if the image quality of a CBCT was found to be inadequate and would have required ethical approval. Additional resources from a multi-disciplinary team including clinicians would have been required. As this part of the research was carried out during the COVID pandemic this would have been logistically difficult.

6.3.3. Future directions of research

There are a number of other sites treated with VMAT that also have a CTV that is to or close to the patient's surface. These sites include anus cancers, positive pelvic nodes and sarcoma cancers. The conclusions from this study can also be transferred to the planning of these sites; in order to improve CTV coverage and make treatments more robust to changes in setup and patient anatomy.

There has been an increase in the use of VMAT for treating skin cancers. It is likely that this will also require a virtual bolus planning method. To determine the most superior and robust planning method for skin radiotherapy treatments further planning studies will be required.

This study has found the most superior and robust planning method for head and neck plans when planned with Eclipse TPS. Other TPSs such as RayStation have a robust optimisation tool. This tool takes the effects of potential changes into account and makes the plan more robust to geometrical and dosimetric uncertainties (RaySearch Laboratories, 2022). Availability of these tools may have an effect on margins used and the planning method that compensates for excessive fluence in the build-up region. A multi-institution planning study, using different treatment planning systems would determine the most superior and robust planning method for all TPSs.

6.4. Paper C: Superficial dose validation of four different planning methods used to compensation for excessive fluence in the build-up region for head and neck VMAT plans.

6.4.1. Contribution to knowledge and current practice

In this study it has been determined that DOSEmappers are a suitable dosimeter for surface dosimetry. DOSEmappers are unique in that measurements can be made at a large number of points on the patient surface at once. Other dosimeters used for surface dosimetry, such as OSLDs and MOSFETs are larger in size and limited to the number of measurement points at one time.

This study has shown accuracy in dose calculations of Eclipse AXB for depths ≥ 1.0 mm direct and oblique incidence beams and for head and neck VMAT plans. This gives increased confidence when comparing the skin dose between plans calculated with Eclipse AXB algorithm.

6.4.2. Strengths and Weaknesses

This study has shown that extraction of the surface dose from Eclipse is challenging and has large uncertainties. This issue has not been discussed in previous studies when using Eclipse Acuros AX algorithm, but is important to consider when determining the accuracy of a TPS at the surface. Addressing and including this uncertainty is a strength of this study compared to others.

The Eclipse AXB beam model is based on TrueBeam representative beam data supplied by Varian, this was not optimised locally for surface dose or dose in the build-up region. The model was validated against measurement and shown to meet the standard Venselaar criteria (Venselaar et al, 2001). Zhuang and Olch (2014) found a high accuracy in surface dose calculations for IMRT plans required accurate commissioning in the build-up region. This was for AAA algorithm and has not been discussed in any studies using AXB. Results from this study show that for simple fields the Venselaar criteria is met, suggesting that adjustments in the beam model is not required. Monte Carlo comparisons could have confirmed this and would have added to the study.

For simple field measurements and VMAT plan measurements; only one measurement was made with the DOSEmappers. Dosimetry at the surface and in the build-up region is

challenging. Steep dose gradients make measurements difficult and small errors in setup can have a large effect on the measured dose. Repeated measurements with DOSEmappers would have provided an understanding of measurement uncertainty and measurement errors.

An advantage of using the DOSEmappers for surface dose measurements is that the dose to a large number of measurements points can be acquired in one irradiation. For the VMAT plan measurements each DOSEmapper had 36 measurement points and at each measurement point an average was taken from two Micro Silica bead TLDs. It therefore easy to identify individual TLD readouts that may be incorrect. Taking an average across all the measurement points gives a more accurate representation of the planned dose when measuring in a region of steep dose gradients.

6.4.3. Future directions of research

In this study no measurements were made on the surface of a patient, however DOSEmappers have the potential to be used for patient measurements. These dosimeters would be ideal to make surface measurements when new techniques, new dose algorithms or new versions of a TPS are introduced. DOSEmappers also have the potential to be used as an audit tool. All these uses would require further studies to ensure suitability of the DOSEmappers.

DOSEmappers could be used to measure the surface dose for other treatment sites. In the UK; internal mammary chain irradiation is becoming the standard of care for patients considered at intermediate risk of recurrence (Bird and Webster, 2021). This is increasing the use of VMAT in breast radiotherapy, the implementation of this technique has been varied across UK centres and is often dependant on the tools available in the TPS. In many dosimetric comparison studies between techniques; the skin dose has not been analysed (Sarkar et al, 2015). The use of DOSEmappers to measure surface dose would add to the dosimetric comparisons and could be used as an audit dosimeter for UK sites. Jafari et al (2017) showed in a feasibility study that Micro Silica Beads can be utilised as a postal dosimetry audit tool. This could be expanded to include a surface dosimetry audit for a particular treatment site where a high dose at the surface is expected, for example head and neck plans or breast plans. This would be similar to the work of Moncion et al

(2022) were accuracy of near-surface dose was evaluated between eight institutions using four different TPSs.

The treatment of skin lesions can be complex and there are number of treatment options available. Depending on location, treatment depth and other patient factors the following treatment options can be used; direct electron field, VMAT, kV X-rays and brachytherapy. Variations in treatment sites makes it difficult to have a modality that works for all patients. DOSEmappers have the potential to be used for all of these modalities and would ensure correct dose is delivered to the CTV. Jaferi et al (2014) showed that Micro Silica Beads have a relatively small energy dependence over the megavoltage range, for photon and electron beams. The energy response in the kV range significantly increases, making measurements at these energies more challenging. The use of DOSEmappers would require validation for each modality.

6.5. References

Bardies, M. et al. (2017). Virtual bolus for total body irradiation treated with helical tomotherapy. *Journal of Applied Clinical Medical Physics*, 16(6), pp.164–176.

Bird, A. and Webster, G. (2021). High quality planning technique for robust VMAT in Raystation for IMC breast radiotherapy, *ESTRO 2021, Radiotherapy and oncology* 2021-08, Vol.161, p.S1598-S1599.

Fortin, A. et al. (2002). Effect of treatment delay on outcome of patients with early-stage head-and-neck carcinoma receiving radical radiotherapy. *International Journal of Radiation Oncology Biology Physics*, 52(4), pp.929–936.

Ingarfield, K. et al. (2021). Inequality in survival of people with head and neck cancer: Head and Neck 5000 cohort study. *Head and Neck*, 43(4), pp.1252–1270.

Jafari, S.M. et al. (2014). Energy response of glass bead TLDs irradiated with radiation therapy beams. *Radiation Physics and Chemistry*, 104, pp.208–211. [online]. Available from: http://dx.doi.org/10.1016/j.radphyschem.2014.03.009.

Jafari, S.M. et al. (2017). Feasibility study of silica bead thermoluminescence detectors (TLDs) in an external radiotherapy dosimetry audit programme. *Radiation Physics and Chemistry*, 141(July), pp.251–256. [online]. Available from: http://dx.doi.org/10.1016/j.radphyschem.2017.07.021.

Lee, N. et al. (2002). Skin toxicity due to intensity-modulated radiotherapy for head-and-neck carcinoma. *International Journal of Radiation Oncology Biology Physics*, 53(3), pp.630–637. Mays, N. and Pope, C. (2000). Qualitative research

in health care: Assessing quality in qualitative research. *British Medical Journal*, 320(7226), pp.50–52.

Liao, D.Z. et al. (2019). Association of Delayed Time to Treatment Initiation with Overall Survival and Recurrence among Patients with Head and Neck Squamous Cell Carcinoma in an Underserved Urban Population. *JAMA Otolaryngology - Head and Neck Surgery*, 145(11), pp.1001–1009.

Mhaskar, R. et al. (2009). Critical appraisal skills are essential to informed decision-making. *Indian Journal of Sexually Transmitted Diseases*, 30(2), pp.112–119.

Moncion, A. et al. (2022). Evaluation of Dose Accuracy in the Near-Surface Region for Whole Breast Irradiation Techniques in a Multi-institutional Consortium. *Practical Radiation Oncology*, 12(4), pp.e317–e328. [online]. Available from: https://doi.org/10.1016/j.prro.2022.01.013.

NHS England (2019) Adult External Beam Radiotherapy Services Delivered as Part of a Radiotherapy Network. Available at: https://www.england.nhs.uk/wp-content/uploads/2019/01/External-Beam-Radiotherapy-Services-Delivered-as-Part-of-a-Radiotherapy-Network-Adults.pdf (Accessed: 20 February 2019)

Polesel, J. et al. (2017). The impact of time to treatment initiation on survival from head and neck cancer in north-eastern Italy. *Oral Oncology*, 67, pp.175–182. [online]. Available from: http://dx.doi.org/10.1016/j.oraloncology.2017.02.009.

RaySearch Laboratories (2022). RayStation Robustness in Treatment Planning. Available from: https://www.raysearchlabs.com/robustness-in-treatment-planning/#:~:text=RayStation%20utilizes%20a%20unique%20robust,the%20use%20of%20multiple%20images. (Accessed: 23 June 2022)

Sarkar, B. et al. (2015). Operated Left Breast and Chest Wall Radiotherapy: A Dosimetric Comparison Between 3DCRT, IMRT and VMAT. *Medical Physics*, 2015-06, Vol.42(Part21), p.3470. Available from: https://aapm-onlinelibrary-wiley-com.manchester.idm.oclc.org/doi/abs/10.1118/1.4924945

Stordeur, S. et al. (2020). Comorbidity in head and neck cancer: Is it associated with therapeutic delay, post-treatment mortality and survival in a population-based study? *Oral Oncology*, 102(November 2019), p.104561. [online]. Available from: https://doi.org/10.1016/j.oraloncology.2019.104561.

Thomas, S.J. and Hoole, A.C.F. (2004). The effect of optimization on surface dose in intensity modulated radiotherapy (IMRT). *Physics in Medicine and Biology*, 49(21), pp.4919–4928.

Tyran, M. et al. (2018). Safety and benefit of using a virtual bolus during treatment planning for breast cancer treated with arc therapy. *Journal of Applied Clinical Medical Physics*, 19(5), pp.463–472.

Young, J.M. and Solomon, M.J. (2009). How to critically appraise an article. *Nature Clinical Practice Gastroenterology and Hepatology*, 6(2), pp.82–91.

7. Concluding Remarks

This work contributes to the field of head and neck cancer radiotherapy. The time head and neck cancer patients should be treated within and a planning method that gives superior plan quality have been determined.

A study of the impact of waiting for radiotherapy to start has on overall survival and patient experience has shown that there should be a greater focus on ensuring all head and neck cancer patients are treated within 30 days from decision to treat with radiotherapy. The study showed that patient insight can add valuable information to research studies and can be used to direct effort to ensure patient benefit.

A study of planning methods used to compensate for excessive fluence at the surface of head and neck plans has shown that a virtual bolus planning method gives the most superior plan quality. These results have been validated by measurement using a novel surface dosimeter.

In the production of this thesis a broad range of research skills have been used. It is intended that these skills will be developed further and applied to future work at The Clatterbridge Cancer Centre.

Appendix A: List of AMBS A units and Medical Physics B units together with assignments

AMBS – A Units		
Unit title	**Credits**	**Assignment wordcount**
A1: Professionalism and professional development in the healthcare environment	30	Practice paper – 2000 words A1 – assignment 1 – 1500 words A1 – assignment 2 – 4000 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 – assignment 1 – 3000 words A5 – assignment 2 – 3000 words
Medical Physics – B Units		
B1: Medical Equipment Management	10	2000 word assignment
B2: Clinical and Scientific Computing	10	2000 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 Specialised External Beam Radiotherapy	10	1500 word report/piece of evidence for portfolio
B10f: Radiation Protection Advice	10	1500 word report/piece of evidence for portfolio
Generic B Units		
B5: Contemporary issues in healthcare science	20	1500 word assignment + creative project
B7: Teaching Learning Assessment	20	20 minute group presentation
Section C		
C1: Innovation Project	70	4000-5000 word Literature Review Lay Presentation

Appendix B: Innovation / Business Case

Executive Summary

Invivo dosimetry monitoring is recommended in 'Towards Safer radiotherapy' (BIR, 2008). This is a check of the radiotherapy pathway in delivering the intended dose. Invivo dosimetry measurements are currently made for the majority of radiotherapy patients. However, the invivo system is integrated into the planning and treatment system supplied by Varian.

An annual audit will provide an independent invivo dosimetry measurement, ensuring no system wide errors have occurred.

This audit will use a novel surface dosimeter. An upfront cost of £620.00 is expected and annual reoccurring cost of £2450.00. The audit will require additional physics resource in the analyses of the results.

Background and Context

For head and neck cancer treatments; clinical target volumes (CTVs) are often close to or at the skin surface. In these cases accurate calculation of the dose at the skin surface is important to ensure coverage of the CTV.

The planning method that achieves the most superior plan quality and is the most robust to changes in setup and patient anatomy is complex involves many manual steps. Accuracy of the surface dose calculation by the treatment planning system (TPS) is challenging due to steep dose gradients and the absence of charged particle equilibrium.

A suitable dosimeter for measuring surface dose on head and neck cancer patients has been tested and found to be suitable for this challenging measurement. DOSEmappers™ are a 2D array of Micro Silica Bead TLDs. The properties of this dosimeter make is ideal for measuring surface dose on an undulating surface, such as the neck. DOSEmappers are CE marked. They are placed in a layer of film that can be wiped clean with standard hospital disinfectants.

DOSEmappers are manufactured and supplied by a company called TRUEinvivo®. A TLD readout service is also offered. After irradiation the DOSEmappers are returned to TRUEinvivo®. TRUEinvivo® then determine the dose at each measurement point on the DOSEmapper.

This proposal is to purchase a regular supply of DOSEmapper in order to carry out an annual surface dose audit of head and neck plans.

Case for Investment

Current Process/ Risk

In vivo dosimetry monitoring is recommended in 'Towards Safer radiotherapy' (BIR, 2008). This is already carried out for the majority of patients treated with radiotherapy at The Clatterbridge Cancer Centre. The current process is quick, resource light and all equipment is already available. It is an acceptable process for measuring all patients. These in vivo measurements use a Varian system and is therefore not independent of the treatment planning system, record and verify system or the linac. The current process therefore carries a risk that an error could be transferred through the Varian systems and therefore affecting a large patient population.

Advantages of Proposal

An annual audit of the surface dose for head and neck cancer patients will ensure a high plan quality for this patient group.

The audit will also add to the quality assurance of the full radiotherapy process. This measurement is an end-to-end test from radiotherapy planning through to treatment delivery.

The proposed annual surface dose audit using DOSEmappers will be independent to the planning and delivery system. This is therefore an independent in vivo measurement that will detect errors or inaccuracies in the radiotherapy process.

DOSEmappers are a novel dosimeter and have not been used for surface dosimetry outside of a research setting. Using DOSEmappers for an annual audit will increase familiarity through their use. There is potential for DOSEmappers to be used as a national surface dosimetry postal audit tool. This supports the trusts 'Be innovative' objective.

Options Appraisal

1. TRUEinvivo® to supply and readout DOSEmappers. This annual audit will require the supply of 20 DOSEmappers and the readout of 10 DOSEmappers. Each DOSEmapper with be 5.0 x 5.0 cm^2 with a measurement point separation of 1.0 cm. No additional resource are needed for the measurement process. Additional physics resource will be required to analysis the results once returned.

   Costs

   Annual costs to TUREinivo based on 2021 prices.

Description	Unit Price £	Qty	Cost £
DOSEmapper2D 5cm x 5cm, with 10mm resolution (36 TLD measuring points	85.00	20	1,700.00
Control DOSEmapper1D	25.00	10	250.00
Reference DOSEmapper1D	25.00	10	250.00
DOSEmapper Reading Service* for DM2D-5x5-7	15.00	10	150.00
DOSEmapper Reading Service* for Control/References	10.00	10	100.00
Total			2,450.00

2. TRUEinvivo® to supply DOSEmappers. Same as option 1 but readout to be carried out at CCC. Additional dosimetry technician resource required for readout process. Additional physics resource will be required for the analysis of results. This would also require a TLD reader to be purchased. Based on the table in option 1, this option would reduce the annual cost by £250. This audit will only be carried out annually, a large upfront costs in purchasing a TLD reader will not be cost effective. This option will therefore not be considered further in this options appraisal.
3. Continue to use current in vivo process only, accepting the risk discussed above.

Implementation

An MPE will be responsible for the implementation and management of the audit. The implementation will be a physics project and will follow the physics department's project process.

The use of DOSEmappers to measure skin dose has already been carried out. This has been for phantom measurements only. For patient skin measurement the dose contribution from CBCT will need to be considered. This will require further phantom measurements before patient measurements. It is expected that this can be done with the purchase of five DOSEmappers and readouts, control and reference will also be required. This will therefore be a one off setup costs of £620.

Recommendations

To carry out an annual audit of skin dose of ten head and neck plans, using DOSEmappers to measure the dose at the patient's surface.

Appendix C: Patient Questionnaire

NHS
The Clatterbridge Cancer Centre
NHS Foundation Trust

Radiotherapy Department Head and Neck Patient Survey

Thank you for taking the time to complete this survey. Your feedback is important to us and will help use improve the Radiotherapy services we provide at The Clatterbridge Cancer Centre. Completion of this survey can be anonymous, only provide your name if you are comfortable to do so. The completion of this survey is confidential and entirely voluntary. If you prefer not to participate in the survey, the care that you receive will NOT be affected. If you require any help completing this survey please discuss this with your treatment radiographers.

We want to understand how the time between knowing your treatment would be radiotherapy and the start of your radiotherapy treatment affected you.

Name (optional) : _____ Date: _____

Any timings given should be an estimate of what you remember

1. How long did you wait between knowing your treatment will be radiotherapy to starting radiotherapy?

2. Were you satisfied with the timescale from consultation with your radiotherapy doctor to the start of your radiotherapy treatment?

☐ Very satisfied ☐ Satisfied ☐ Neither satisfied or dissatisfied ☐ Dissatisfied ☐ Very dissatisfied

3. If we could plan your treatment quicker, would you have been ready to start your radiotherapy treatment sooner than you did?

☐ Yes ☐ No ☐ Not sure

4. Were there any personal circumstances that affected how quickly you could start your radiotherapy treatment?

e.g. work, transport, holiday, preparing yourself psychologically, care arrangements

5. If you could have started radiotherapy sooner in another hospital would you have been prepared to travel?

☐ Yes ☐ No ☐ Not sure

6. If yes, how much further would you have been prepared to add to your travel time?

☐ Half an hour ☐ 1 hour ☐ 2 hours

7. Was the time needed between visits explained to you?

☐ Yes ☐ No ☐ Can't remember

8. Were you told a date for starting your radiotherapy treatment within 2 days of your mould room/CT planning appointment?

☐ Yes ☐ No ☐ Can't remember

9. Did your start date change at any point?

☐ Yes ☐ No ☐ Can't remember

10. If so, were you told why your start date changed?

☐ Yes ☐ No ☐ Not Applicable

11. During this time on an average day how often did you think about starting treatment?

Score between 0 and 10, 0 being none of the time and 10 being all the time. ☐

12. During this time can you give details of any concerns you had?

e.g. financial, emotional, relationship, work, treatment outcome

13. Please explain how these concerns affected your daily life

e.g. perform tasks, work, relationships

14. Please let us know of any improvements we could make to improve the experience for future head and neck patients.

15. How would you rate your overall experience while undergoing radiotherapy planning and treatment?

Score between 0 and 10, 0 being poor and 10 being excellent. ☐