RADIOBIOLOGICAL OPTIMISATION OF LUNG STEREOTACTIC ABLATIVE RADIOTHERAPY (SABR) FOR PERSONALISED TREATMENT FRACTIONATION

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List of Abbreviations

BED – Biological Effective Dose

CTV – Clinical Target Volume

DVH – Dose Volume Histogram

EQD2 – Equivalent Dose in 2 Gy Fractions

GTV – Gross Tumour Volume

LKB – Lyman-Kutcher Burman

LQ – Linear Quadratic

NSCLC – Non Small Cell Lung Cancer

NTCP – Normal Tissue Complication Probability

OAR – Organ at Risk

PET – Positron Emission Tomography

PTV – Planning Target Volume

SABR – Stereotactic Ablative Radiotherapy

TCP – Tumour Control Probability

VMAT – Volumetric Modulated Arc Therapy

Abstract

Stereotactic ablative radiotherapy (SABR) is an effective non-surgical alternative treatment for early stage, inoperable, non-small cell lung cancer (NSCLC). These patients are often elderly with co-morbidities. UK recommendations have been that treatments can be delivered in 3, 5 or 8 sessions ('fractions') for peripheral targets; often decided on the proximity of the normal tissues to the tumour, with treatments close to the chest wall frequently delivered in 5-8 fractions. For these patients, extra hospital trips and additional radiotherapy resources are required despite the risk of a rib fracture and lung toxicity being low. The purpose of this research was to determine if the calculation of the radiobiological parameters for the chest wall and ribs could be used to personalise the number of treatment fractions whilst maintaining reasonable tumour control. In addition, patient opinion was sought on personalised fractionation via a service evaluation questionnaire.

Dose volume histogram (DVH) data obtained from 200 previously treated lung SABR patients was used to determine baselines for publication of tumour control probability (TCP) and normal tissue complication probability (NTCP) for rib fracture and radiation pneumonitis using the software, Biosuite (Version 12.01). The survival data, TCP and NTCP was disaggregated to confirm there was no sex bias.

A service evaluation was conducted to obtain the patient perspective on personalised fractionation during the corona virus (COVID-19) pandemic of 2020 -2022. Most patients surveyed thought that they could cope with their previous treatment schedules but would be willing to accept as many as recommended, with few saying it would affect their decision to undergo radiotherapy. Three quarters of those surveyed were willing to consider alternative fractionation schemes. Moving towards alternative fractionation schemes for the purposes of reducing hospital footfall or to capitalise on radiobiological optimised dose schemes may therefore be well tolerated with high patient compliance.

This thesis shows that a consideration of TCP and NTCP may prove useful for individual patients to trade off acceptable toxicity and number of visits, instead of resorting to the binary choice currently employed of whether the tumour is in close proximity, or not, to the chest wall. The results suggest that there is potential for improved tumour control whilst maintaining current levels of toxicity, by reducing 8 fraction treatments to 5 fractions for some patients. The overall population risk of both radiation pneumonitis and rib fracture in this cohort is low as compared to some historically reported values for lung SABR and for standard radiotherapy.

Declaration

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

The period of study included the COVID-19 corona pandemic episode which impacted on working conditions and author availability. Whilst this impact was felt to be minimal, it undoubtedly will have affected the sample of patients who were sent the survey and is therefore likely to influence the outcome of the research.

Copyright statement

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I would like to thank my department for allowing me to put myself forward for the HSST programme, particularly my supportive line manager Peter Colley, but also all my colleagues both in Medical Physics and in Radiotherapy including the lung SABR Clinical Oncologists. The opportunity to study whilst working has had an immeasurable impact on me personally and professionally. I have enjoyed every aspect of learning during the last five years, partly due to excellent peers within my cohort. I received fabulous support from my D.Clin.Sci. supervisors Craig Moore and Michael Merchant. Thank you for putting up with my questions and enthusiasm lapses.

I would also like to thank all those that love me; my family and friends. I would be lost without their support and encouragement. Freya and Hestia, I might nearly be a doctor now…

The Author

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I have worked for the last twenty years as a Clinical Scientist in Radiotherapy Physics at Hull University Teaching Hospitals NHS Trust, following my basic training at Nottingham between 1998 and 2000. I have been involved with significant improvements in radiotherapy over the years, such as linac replacements, the introduction of IMRT locally in 2002, the introduction of HDR brachytherapy in 2009, the move towards a paper-less radiotherapy workflow and the recent installation of our Varian Halcyon treatment machines.

During my time as a Specialist Healthcare Scientist, Higher Principal Physicist in Clinical Development, I have presented my work at regional and national meetings such as the national SABR conference in 2019. I have been heavily involved in leading the local implementation of lung and oligometastatic SABR services and act as a Medical Physics Expert (Certificate Number 355) performing treatment planning, checking and patient specific quality assurance on lung SABR. I am involved in national and regional groups related to radiotherapy quality improvements and standards such as the SABR QA subgroup.

My role covers brachytherapy, general radiotherapy responsibilities such as planning and quality assurance, and local, regional and national training and education. I act as the Training Coordinator for the basic Scientific Training Programme in my centre and shortlist, interview and examine clinical scientist trainees.

In May 2021, I successfully completed the professional examination ('IAPS') for the work-based competency component of the Higher Specialist Scientific Training (HSST) scheme for becoming a Consultant Clinical Scientist.

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Journal Format

This thesis is submitted in journal format, which was deemed suitable for the body of work collected over the last three years of the Higher Specialist Scientific Training (HSST) scheme to include both taught and research elements. The emphasis of this National School for Healthcare Science (NSHCS) scheme is the application of science at a high level in the clinical workplace. Hence journal publications were an important part of the work in order to disseminate information to others practising in the field.

Section 1 provides an overview of the research question and aims, including a literature review.

Section 2 presents the novel work prepared in the format of papers for publication.

Section 2.1 describes the work carried out to benchmark Lung SABR TCP clinical data, which was published in the Journal of Radiotherapy in Practice in October 2020. Cambridge University Press allows the paper to be included in this thesis provided that the typeset and formatting remains as published, hence the style and references are self contained.

Section 2.2 describes the investigation into patient preference for fractionation changes using a service evaluation questionnaire, and is a qualitative study drawing from the cohort of previously treated patients. This paper was submitted for publication in the journal, 'Lung Cancer' but declined. I am looking into other possible publication avenues in 2022/23.

Section 2.3 describes the benchmarking of the NTCP data for the same cohort of patients for radiation pneumonitis and rib fracture and the subsequent analysis of the data showing that 8 fraction treatments could be delivered in 5 with no significant detriment when considering TCP and NTCP.[1] This is expanded in an Innovation Proposal including financial data for a business case in Appendix 3.

Section 2.4 includes an accepted poster abstract and a peer reviewed proffered talk, which was given at the 2019 UK SABR Consortium meeting relating to sex disaggregated data and equity of service.

Section 3 provides a critical review and analysis of the research with discussion, conclusions and suggestions for follow up work.

1 Marsden, J. (2022). Normal tissue complication probabilities of lung SABR patients from a UK centre and its implication on personalised radiotherapy. Journal of Radiotherapy in Practice, 1-5. doi:10.1017/S1460396922000024

Section 4 contains the appendices, including attained D.Clin.Sci taught module credits, the patient information letter and survey together with the survey data, and the HSST Innovation Proposal.

1. Introduction

Lung cancer has been a leading cause of cancer related mortality in the world for decades[1,2] and therefore a prime focus for improving treatment efficacy. Although surgical resection is the first line of treatment where patient condition and other factors allow, Stereotactic Ablative Radiotherapy (SABR) is now an alternative treatment option for early lung cancer for those who are inoperable or refuse surgery. Radiotherapy is the use of high energy X-rays to treat cancer, with SABR deviating from traditional courses of therapy by delivering large radiation doses over a small number of treatments (fractions). In typical radiotherapy the dose per fraction is of the order of 2 – 3 Gray (Gy), whereas in hypofractionated SABR it can be between 18 – 20 Gy. When delivering such high doses in a single session, the accuracy and precision of the plan and delivery must be highly targeted and quality assured to a significant level.

SABR (also referred to as SBRT, stereotactic body radiation therapy) is an effective non-surgical alternative for early stage, inoperable, non-small cell lung cancer (NSCLC).[3,4] NSCLC comprises approximately 80% of lung cancers diagnoses[5] with the average age at diagnosis being 70 years.[6,7] SABR is particularly beneficial for co-morbid patients who are 'medically inoperable' and for elderly patients. Although lung SABR treatments began in the UK in 2009, the NHS widened commissioning in 2013[8] subject to compliance with national guidance.[9,10] In spite of the emergence of a UK wide NHS SABR service 30% of over 35, 000 patients in a 2015 national audit had *no therapy at all* for early stage NSCLC, regardless of the various options available.[11] A review of data from 2013[12] indicated that distance to travel (and hence, it could be argued number of visits) was a key factor in declining treatment, and there was a higher refusal in patients aged 70 years and over when offered radiotherapy.

The aim of this research is to investigate the personalisation of SABR radiotherapy for the target population by means of radiobiological modelling and the use of a direct, service evaluation, patient survey. The possibility of reducing the number of visits whilst maintaining the therapeutic benefit of the treatment and keeping side effects minimal is explored. Patient acceptability for changing the standard of care is also considered.

The introductory section of the thesis will review the literature surrounding lung cancer, lung SABR as a treatment option, prospective personalisation of fractionation using radiobiological modelling and aspects of patient involvement in cancer care. The research project aims will also be presented.

1.1.The Position of SABR in the Lung Cancer Landscape

Lung cancer prognoses are generally poor, as compared with other types of cancer. However, improvements across various disciplines have contributed to survival improvements over time, with 5-year *net* survival rates currently at around 20%.[13] Key to these improvements are advances in early diagnosis, accurate staging, treatment strategies including surgery, ablation and radiotherapy and systemic therapies. As surgery and radiotherapy are the two main treatment modalities, they will briefly be discussed here prior to the topic specific literature review.

1.1.1. Surgery

Thoracic surgery is the primary treatment for early stage NSCLC for those deemed fit and the technique corresponds to 5-year survival rates of 66 – 80%[14] depending on the type of surgery. Open lobectomy has been overtaken by less invasive methods such as video-assisted thoracoscopic surgery (VATS) lobectomy. There is an in-hospital mortality associated with surgery of around 2% but VATS techniques are associated with lower complication risks and short hospital stays. However, this is inconsequential if the patient is not suitable for any element of general anaesthetic or the risks of surgery are considered too high.

The 2013 review by Solda et al., showed there was little difference in the survival outcome between surgery and SABR for stage 1 NSCLC patients.[4] In the absence of successful prospective randomised trials, where selection bias for either surgery or SABR can be better addressed, this retrospective analysis showed that outcomes were broadly equivalent regardless of patient selection for either treatment. However, surgery still remains the primary first line of treatment for peripheral early stage NSCLC.

The VALOR trial (Veterans Affairs Lung Cancer Surgery Or Stereotactic Radiotherapy - ClinicalTrials.gov NCT02984761) is attempting to address the inherent preferences which patients (and their referring clinicians) form when choosing between SABR and surgery, and should report remarkable insights into patient choice factors. It is interesting to note the barriers to SABR trial accruals[15] and the publication bias related to the authors' background (surgery or radiotherapy)[15]. The belief of the treating radiotherapy clinician, the institution and the referring clinicians of whether SABR is harmful or beneficial altered the likelihood of a patient being recruited to a randomised trial. This essentially means that clinicians may present treatment options without a true level of equipoise, which will clearly have an effect on patient choices. It should also be noted that surgical techniques, whilst not part of the

literature review, will have similarly modernised and so patient choices based on outcomes and techniques cannot always be fully informed by looking at past scientific literature.

1.1.2. Radiotherapy and SABR

Technical advances in the engineering and computer controls of radiotherapy systems have enabled incredibly complex, bespoke dose distributions to be created, particularly for lung cancers.[16] Over the last two decades mega-voltage energy photon beams, often with fast flattening filter free (FFF) modes,[17] can be delivered using linear accelerators ('linacs') and combined with multifaceted image guidance at planning and delivery. These techniques have evolved so that volumetric arc therapy, involving rapid rotational deliveries finely tuned to the tumour shape with the use of multileaf collimators (MLCs), has become standard around the world.[18] UK recommendations for linear accelerators give a nominal ten-year life span, which ensures that technological developments are updated on the hardware reasonably regularly, and a minimal specification for this type of equipment exists if hospitals wish to use typical financial mechanisms for purchase.[b] NHS service specifications for radiotherapy departments also require certain standards to ensure consistent compliance with national guidelines for lung radiotherapy provision and modernisation , for example, a mandated high proportion of radical patients receiving complex radiotherapy such as inverse planned intensity modulated radiotherapy (IMRT).[19] Respiratory guided and/or gated radiotherapy, advanced planning algorithms and image guidance using cone beam computed tomography (CBCT) are also mandated. These technical and technique developments taken together support accurate and safe delivery of lung SABR; precise treatment targeting and delivery are enabled, 3D and 4D imaging innovations can localise small tumours readily and radiotherapy treatment can be corrected to account for patient breathing.

1.1.3. SABR Dose Fractionation

In addition to technical advances, clinical changes to the delivery of radiotherapy in terms of dose and fractionation were explored. In order to obtain large dose escalations at standard 2 Gy fractionations, longer overall treatment times were required which were associated with high levels of toxicity. To overcome this, groups in America and Japan began to use hypofractionated regimes of 3 x 20 Gy[20] and 4 x 12.5 Gy[21] to obtain Biological Effective Doses (BEDs) of over 100 Gy for lung tumour treatment giving rise to stereotactic ablative radiotherapy, or 'SABR'. The successes seen with these types of regimens were unfortunately

[b] https://www.england.nhs.uk/wp-content/uploads/2013/06/b01-radiotherapy.pdf

tempered by high toxicity, including some deaths, when treating centrally located lesions with similar dose fractionations. These experiences highlighted the criticality of considering peripheral lesions for treatment where the normal pulmonary tissue is the key organ giving rise to toxicity. As small volumes of normal lung can receive very high radiation doses but still retain function (parallel organ), SABR can be delivered safely if other, more serial, organs are far from the treatment area. Subsequent work was carried out to define the central areas and the organs at potential risk that should be avoided.[22] These include the trachea, oesophagus, spinal cord, brachial plexus, heart and main bronchi, all of which could lose function if a small area is irradiated to a very high dose. There is still further work to be done in gathering safety profile data from prospective trials on SABR for central lung tumours. This has led to caution being employed when treating central, and particularly ultra-central, lung lesions. Ultra-central lesion SABR is not recommended in the UK except within clinical trials. This thesis is purely concerned with peripheral lung tumours.

In the UK, interest in peripheral lung SABR was high and the first patient was treated in 2009 in Leeds, which subsequently became the national referral centre for patients of various disease sites, including lung. In order to maintain high quality treatment in the UK, and to avoid the potential toxicities seen in other countries, a UK SABR Consortium was set up to provide advice over clinical implementation, dose fractions and quality assurance necessary for a safe service roll out in the UK. The dose fractionations are also recommended for delivery every other day to decrease the likelihood of toxicity and allow for normal tissue recovery. The recommended evidence based schedules are a standard 54 Gy (3 x 18 Gy), a conservative regime of 60 Gy (5 x 12 Gy) or 55 Gy (5 x 11 Gy) or a very conservative schedule of 50 Gy (8 x 6.25 Gy).[10] With updated revisions of the guidance over time, the very conservative schedule was removed from the guidance in version 6.1 but some centres, including the author's, continue to use this regimen to reduce the risk of toxicity.

1.1.4. Treatment Planning Algorithms

For lung planning the choice of algorithm and the dose reporting methodology is of particular concern as the photon transmission and dose deposition through areas of different density when traversing ribs, lungs and soft tissue interfaces is crucially important. These elements of quality control were highlighted in the first published consortium guidance. Treatment planning systems model an approximation of the dose distribution in the patient using an algorithm chosen for accuracy and speed. The simplest and fastest 'Type A' algorithms model the primary radiation beam ('pencil beam') but do not model the electron transport and have

been widely replaced by 'Type B' models accounting for 3D lateral scatter and electron transport ('collapsed cone' or 'anisotropic analytical algorithm'). Monte Carlo algorithms offer the 'gold standard' of computation as they track millions of particle histories through the patient, but they are not commonly implemented in commercial planning systems due to their computing requirements and slow speed. 'Type C' algorithms, such as employed in this research (Acuros-XB, Varian Medical Systems, Palo Alto, USA) bridge the gap between speed and accuracy. This algorithm directly solves the Linear Boltzmann Transport equation that accounts for particle behaviour in a medium to give the dose deposited and include patient heterogeneity. The speed of calculation is very fast (order of minutes) and the outcome similar to Monte Carlo, considering the assumptions and limitations made. Doses observed in the planning system are validated by measurement using traceable dosimetry equipment in phantoms, and not (usually) in the patient, and require high quality data for initial commissioning.[23]

Under the current guidance, type B are 'mandatory for lung patients and preferred for all other indications' of SABR as a minimum. The algorithms used to calculate dose are geometrically and dosimetrically superior to those available a decade ago, enabling users to calculate dose on sub-millimetre grid sizes and to display dose in terms of Dose to Water (D_W) or Dose to Medium (D_M), with D_M being recommended for reporting dose in clinical trials.[24]

It is vital to understand that the visualised dose distributions and even the dose prescription point or volume may change over time and not be identical between radiation dose algorithms, even if the quoted 'doses' remain the same. Changes in the coverage of the target volume, and organ at risk constraint differences, are expected as algorithms improve, and consequently there needs to be understanding as to what these models address.[25] As these dose distributions are connected to patient outcomes, dose-effect relationships will change with time and may result in systematic differences. This may limit the comparison of dose related parameters such as radiobiological probabilities between historical and modern cohorts.

Quality assurance and verification of produced radiotherapy plans has also become more advanced, with systems available that mimic what the measured treatment delivery would translate to dosimetrically if it were applied to the patient[26] and these are used routinely in the clinic. Anthropomorphic phantoms, which can include breathing motion, have also been developed for use.[27] All these innovations enabled SABR to become an even higher quality treatment option.

1.1.5. SABR Outcomes

Improved outcomes require time and significant follow up to be observed after the implementation of technical developments, and occur within the context of other clinical advances. However, as an example, median survival in clinical trials for stage III NSCLC improved from around 16 months in 2000 to 28 months in 2019.[28] Local failure rates for lung cancer ranged from 6 – 70% for 'patients of any age with stage I/II NSCLC receiving radiotherapy at a dose of >40 Gy in 20 fractions over 4 weeks or its radiobiological equivalent', as described in the 2001 Cochrane-based review.[29] Some of this variation may be attributed to a broad selection of patients and to variations in treatment methods and other factors over the time span of the trials and other studies reviewed. In circumstances where new techniques are restricted in locality, in patient cohort, in access and in availability of qualified workforce, the effect on patient outcomes is often not as distinct as expected due to some elements of the patient pathway not achieving the same level of high quality at all stages or geographical locations. If changed outcomes do result, it can take significant follow up time of the patient cohort post-treatment to fully assess any quality improvement (or detriment). Existing pitfalls in the pathway can still give rise to poor outcomes if not addressed. For example, variation in the accurate outlining of the gross tumour volume is not reduced by implementing new radiotherapy treatment delivery hardware.

Despite this, a positive evidence base for SABR outcomes is growing rapidly. The SABR Consortium guidance document quotes the Murray et al.,[5] systematic review showing that for early stage peripheral NSCLC, 'Overall local control rates were excellent at 1 year (92.7 % (64.7 - 100)), 2 years (89.9 % (77.4 - 98.5)), 3 years (86.7 % (40 - 97.6)), and 4 - 5 years (89.6 % (83 - 95)) with corresponding overall survival rates of 87 % (78 - 100), 82.9 % (48 - 96), 59.6 % (32 - 95) and 39.6 % (17 - 83) with a mean follow-up of 29.4 months.' The review also discusses the toxicity seen, including pneumonitis, dyspnoea, chest pain and pneumonia at grades 3 and 4 for between 2.7 % and 27 % of patients reviewed. Lower grade toxicities, including fatigue, are often not reported due to the self-limiting nature of the conditions despite being very common.

Early tumour diagnosis of very small solitary pulmonary nodules (SPN) in asymptomatic individuals is now possible and so significantly improved outcomes can be realised. More accurate staging with positron emission tomography (PET)[30,31] and functional imaging has improved the detection of these early stage lung cancers. Asymptomatic lung cancers are occasionally incidentally diagnosed.[32] Early stage lesions are often peripheral, very small, and

generally located away from critical normal tissues and organs at risk often irradiated in larger, more advanced lung cancers. These lesions are ideally suited to SABR. Assuming a positive outcome of the UK Lung Screening Trial,[33] more symptomless, SABR suitable, patients are likely to present. The trial used low dose CT to screen targeted individuals aged between 55 and 75, who smoke or used to smoke who are pre-assessed as having a 5 year increased lung cancer risk ≥ 5%. The low dose CT scan identifies any lung nodules, which may be cancerous, at an early stage and provides a volumetric assessment that aligns well with the inclusion criteria for lung SABR (≤ 5 cm). It is suggested that detecting cancers this early should ensure that curative treatment could potentially be delivered in over 80% of cases. The roll out of 'Lung Health Check' in some areas of England, including in Yorkshire,[34] is a type of 'commissioning through evaluation' of the screening pilot[35] and NHS England are collecting data on the outcomes at the time of writing.[36]

SABR is cost effective for inoperable cases over other forms of treatment such as radiofrequency ablation and conformal radiotherapy.[37] It is also an attractive proposition for patients declining surgery for other reasons (such as caring for relatives, cost and difficulty of travel and leaving home for long periods) which is hinted at in the literature despite there being no reported studies looking at patient preference. Trifiletti et al.,[38] analysed the patterns of care for over 40,000 elderly (≥ 80 years) NSCLC patients in the USA and showed that overall survival was similar between SABR and surgical lobectomy. There are additional inherent risks to surgery, such as undergoing anaesthetic, which are not present in SABR.

Factors associated with nonparticipation in the UK lung screening trial included older age, currently being a smoker, lower socioeconomic group and female gender,[39] some of which may translate to the reasons why patients decline lung cancer treatment itself. The exact number of SABR treatments each patient requires is variable, although clinicians usually give prescriptions according to historical generic protocols formed by early data on the toxicities exhibited by patients treated by the original pioneers in the field such as Timmerman et al.,[22] Typically in the UK 3, 5 or 8 treatments are used which, whilst small compared with conventional radiotherapy, could still be a burden for the relatively elderly patient population where the number of visits might be an important consideration.

The rationale for the dose-fractionation regimes employed by the UK has evolved over time as evidence has been collected. Up to 2019, 3, 5 and 8 fractionation schemes were recommended as the standard, conservative and very conservative dose fractionations for peripheral lung. The eight fraction schedule was intended to be used if the dose constraints could not be met

for the treatment plan. As mentioned earlier, this regime was excluded from the most recent guidance (version 6.1, 2019) for non-central tumours and presented as the schedule for centrally located tumours. However, the current local and regional (Yorkshire and Humber) clinical protocols still include this fractionation, with Leeds explicitly including both 50 Gy *and* a 60 Gy in 8 fractions schedule within their non-central protocol for tumours close to the chest wall and where other organs at risk are likely to exceed a given tolerance dose. The removal of this scheme from the guidance may imply that it is not radiobiologically useful, as indeed this thesis suggests, or it may have been removed for other reasons. Certainly, it continues to be employed for patients where there are concerns over the toxicity, or the ability of the patient to handle potential toxicity arising from treatment. From local audit data, the proportion of 3, 5 and 8 fraction patients treated at Hull University Teaching Hospitals NHS Trust was 15%, 50% and 35 % respectively for the financial year 2020-21. The relatively high proportion of 8 fraction treatments may be a reflection of the poor performance status of patients presenting due to delays in diagnosis from the COVID-19 pandemic or due to other clinical or non-clinical reasons.

Most of the study types initially found in the literature review were retrospective planning or cohort analyses rather than prospective trials. Toxicity, local control and overall survival were common endpoints rather than patient choice factors.[4,40] This was also demonstrated for younger, medically operable early stage NSCLC cases.[41] For an elderly USA cohort,[38] the proportion of patients receiving no therapy (of any kind) increased with age, with over 40% of patients ≥ 90 years having no local therapy. If it is indeed true that surgery and SABR are comparable, and that there is potential for a personalised, small number of outpatient radiotherapy treatments to be offered, then this research may have a significant impact on therapy utilisation.

1.2. Literature Review Methodology

A review of the literature specifically related to radiobiological model optimisation and personalisation for NSCLC patients, concentrating on SABR doses and fractionations was carried out using the PRISMA methodology on an annual basis during the three years of the research project. Figure 1 shows the final search on which this literature review is based. The articles identified are presented in Appendix 1. Additional references were also selected from other sources including the National Institute for Health and Care Excellence (NICE) evidence search, personal communications with those in the field and various radiobiology book chapters and bibliographies. Many other references were sourced from the bibliographies of the retrieved papers and complemented with wider reading. Further literature was sought related to quality improvement and patient voice in radiotherapy which would otherwise be difficult to capture in a search of this kind.

The last search was carried out in April 2021 and abstracts reviewed for relevancy from PubMed and Web of Science. Initially papers were restricted to SABR alone (no chemotherapy or immunotherapy) from January 1999 up to April/May 2021. The search terms were as follows: “SBRT”, “SABR”, “patient choice”, (OR) “radiobiology”, “SABR” “lung” (OR) biological optimization” (note the Americanised spelling included all hits with the English spelling and more) “SABR” within PubMed.[c] These terms were also used in the Web of Science search.

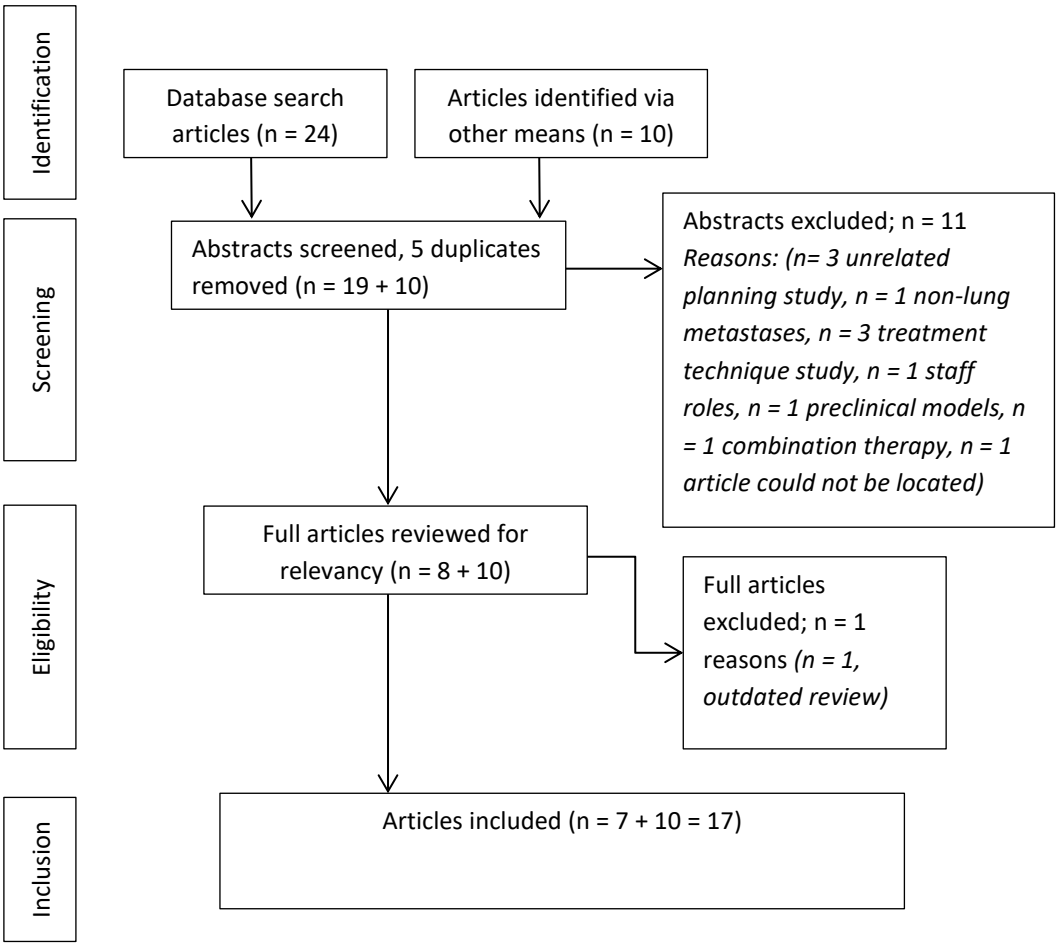
There has been little published related specifically to patient choice in prospective, personalised fractionation schemes for lung SABR using radiobiological modelling. However, there are various studies demonstrating the application of radiobiological optimisation tools for alternative fractionation. Many of these studies were reviewed by D’Andrea et al.,[42] and most use the LQ model or other phenomenological models. Personalised fractionation schemes have been suggested in many of the works of Nahum et al.[43-47]

However, other groups worldwide have recognised this as a topic of importance, and a recent study by Lu et al.,[48] brings relevant and complementary data to this analysis. This study calculated the ‘individualized fraction regime’ based on minimising the uncomplicated tumour control probability function. However, a smaller group of patients (n=33) was used, unevenly

[c] PubMed final search data string: ((((((((SBRT[All Fields] AND SABR[All Fields]) AND (("patients"[MeSH Terms] OR "patients"[All Fields] OR "patient"[All Fields]) AND ("choice behavior"[MeSH Terms] OR ("choice"[All Fields] AND "behavior"[All Fields]) OR "choice behavior"[All Fields] OR "choice"[All Fields])) AND ("1999/01/01"[PDAT] : "2021/01/01"[PDAT])) OR ("radiobiology"[MeSH Terms] OR "radiobiology"[All Fields])) AND SABR[All Fields]) AND ("lung"[MeSH Terms] OR "lung"[All Fields])) AND ("1999/01/01"[PDAT] : "2021/01/01"[PDAT])) OR (("biology"[MeSH Terms] OR "biology"[All Fields] OR "biological"[All Fields]) AND ("SIAM J Optim"[Journal] OR "Optimization"[Journal] OR "optimization"[All Fields]))) AND SABR[All Fields] AND ("1999/01/01"[PDAT] : "2021/01/01"[PDAT])

distributed between men and women, with a different fractionation and dose typical for China but not the UK. A different tumour control probability model as compared to this thesis was also used in subsequent analysis. Sood et al.,[49] also studied clinical outcome correlations albeit using Monte-Carlo based TCP and NTCP calculations for 84 patients. These similar studies are critiqued further in Chapter 3, Critical Appraisal.

Figure 1. Article selection strategy following the PRISMA methodology (search terms given in footnote 'a' on the previous page). Additional references selected from other sources including the National Institute for Health and Care Excellence (NICE) evidence search, personal communications with those in the field, radiobiology book chapters and bibliographies. The included list of articles is given in Appendix 1.



1.3.Lung Radiobiological Modelling in Radiotherapy

Mathematical modelling of irradiated tissues has been attempted almost since the time ionising radiation was first used medically.[50] Many modern radiotherapy dose schedules are based on radiobiological modelling to determine the number of treatments or "fractions" (#) and their individual doses, expressed in terms of physical absorbed dose to water, via the Gray (Gy). This is because there is a fundamental difference in cell recovery and metabolism if a radiation dose is given all at once, or split into smaller doses, even if the total physical dose remains static. For example, 54 Gy in 3 # does not have the same effect as 54 Gy in 20 #, introducing the concept of a biologically effective dose (BED). Protocolised fractionation schemes for patient cohorts with similar diagnoses and staging categories are commonplace

but individualised, patient-specific regimens are not applied routinely. Whilst prospective personalisation is seldom considered because of the uncertainties in radiobiological models and in the variability of individual patients. However, retrospective adjustments due to gaps in treatment[51] or summating contributions from external beam radiotherapies and high dose rate brachytherapy[52] is customary. This is frequently performed in the case of a patient being retreated with radiotherapy. Often the 'ubiquitous' linear quadratic, or LQ, model is used to perform such summations, and describe the probability of the surviving cell fraction. The application of this model remains highly controversial, especially for hypofractionated treatments,[45,53] as detailed in the critical review by McMahon.[54] However, despite theoretical weaknesses and empirical data supporting both sides of the argument, the LQ model can still be used clinically in a comparative way by accepting the current treatment dose fractionation as adequate and tuning those parameters which are less contentious.[53] This is explained further in Section 2.3.2.

SABR is significantly hypofractionated (3 - 8 fractions of 6 - 18 Gy) and there is considerable debate regarding the applicability of radiobiological modelling in moving away from conventional 2 Gy per fraction schemes. As the LQ model is effectively an empirical (or 'phenomonological') model fitted to cell survival data, the underlying radiobiology is frequently disputed despite its original basis of mechanistic processes leading to cell death. There is particular controversy regarding the alpha (α) and beta (β) terms used to describe irradiated tissues.[55] Typically tumours have a high alpha/beta ratio (10 Gy), whilst normal tissues have a lower value (3 Gy). Brown et al.[53] conclude that the standard radiobiology concepts (that of Repair, Repopulation, Redistribution, Reoxygenation and Radiosensitivity, often termed 'the 5 R's') more than adequately describe the excellent results demonstrated by SABR. However, a review by D'Andrea et al.[42] concluded that it was not yet possible to achieve the 'optimal radiation treatment plan' using radiobiological models. Their call was for futher research into tumour and normal tissue response where SABR regimens are employed, implying that the development of new radiobiological models was needed. Whilst this may be true, and modern mechanistic models making use of Monte Carlo computation (for example Geant4-DNA[56]) are in use across many fields of radiotherapy research, it is entirely possible to demonstrate an *improvement* to individual radiotherapy plans by applying existing models in a comparative or relative way. Tools which can include both the cellular level or micro-environment together with the macroscopic behaviour of irradiated tissue and organs are likely to be developed, but these are highly computationally complex and currently remain restricted to research environments. In the clinic, it is possible to optimise current

radiotherapy for patients using radiobiological (and other) metrics. An important step in this process is to understand restrospective distributions of delivered radiobiological doses within past clinical cohorts, correlate these with observed outcomes if possible, and then make measureable quality improvements.

Hypofractionated regimens involving a small number of large dose fractions are currently enjoying a renaissance as demonstrated in the prostate CHHiP and breast START clinical trials.[57,58] The purpose of altering the number and size of each dose fraction via this type of radiobiological modelling is to maximise the therapeutic ratio by gaining more tumour cell kill whilst reducing the likelihood of, mainly late but sometimes acute, damage to normal tissues. There are, however, more subtle reasons for altering fraction delivery such as ease of service provision, financial considerations and patient acceptability.

Radiobiological probability modelling was identified as a potentially useful optimization tool in the 1970's and 1980's.[59] Kutcher and Burman used the effective volume irradiated (relying on the assumption that each sub-volume element independently acts with the same dose-volume relationship as the whole organ) as an adjunct to Lyman's representation of the dose (D) and volume (V) dependence on the Normal Tissue Complication Probability (NTCP) (Equation 1).[60] Further discussion can be found in Section 2.3.2. This 'LKB' NTCP model allowed the application of TD_{50} (the dose that would result in a 50% complication probability of the 'normal' organ after 5 years) to any clinical dose distribution, once the dose volume histogram (DVH) was obtained provided the fitting parameters (m and n) could be determined.

$$NTCP = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{t} e^{-t^2/2}\, dt, \qquad \text{[Equation 1]}^{59}$$

where $t = (D-TD_{50}(V))/m.TD_{50}(V)$ and $TD_{50} = TD_{50}(V).V^{-n}$,

Ideally, NTCP values are low, or at least acceptable for the potential gains expected from the radiotherapy and the control of disease.

The probability for Tumour Control (TCP) can also be calculated, via Poisson statistics using the DVH data and ideally should be high (Equation 2).[61] N_m is the mean number of cancer cells surviving and can be re-expressed further with the tumour volume, υ, with clonogenic cell density, ρ, and a dose response curve of fixed value, α. The total dose can be compartmentalised into d_i, and summed over all the elements. The equation can also be modified to correct the dose for radiobiological effect by using the LQ model to take account of the total dose and fractionation combination. This is known as the LQ Marsden model and is

implemented in the Biosuite software[47] utilised for this research. The formulae used within Biosuite are given in Section 2.1.2.

$$TCP = exp^{-N_m} = exp(-(\rho\upsilon)\sum_i \exp(-\alpha d_i)) \qquad \text{[Equation 2]}^{61}$$

For body sites where normal tissues and the tumour impinge on each other there may be difficulty in finding the best compromise between therapy and toxicity, but for peripheral lung tumours this is less of a concern as the tumour and critical normal tissues are often physically separate. In practice, radiotherapy plans are ordinarily created within the treatment planning system (TPS) and compared without initial resort to biological modelling. Instead, the use of dose tolerances or constraints is common, although these are modified depending on the dose and fractionation using a common currency of biological effective dose (BED) or the 2 Gy per fraction dose equivalent (EQD2). The dose tolerances for organs at risk are largely derived from experience or clinical trials and can be found in works such as Emami et.al.[62] and the Quantitative Analysis of Normal Tissue Effects in the Clinic work streams, QUANTEC.[63] These published works often 'normalise' to EQD2. However, for high doses per fraction other guidance such as can be found within the UK SABR Consortium Guidelines, gives evidence based summaries of the organ at risk tolerances and tumour prescription doses. These tolerance doses can be input into a treatment planning system to form 'Clinical Goals' so that the plan can be automatically tested against these constraints during the planning process (see Figure 2). Locally, the author's centre has composed scripts within the Eclipse TPS, which check these and other plan conformality and quality checks in addition to the DVH OAR and PTV constraints (see Figure 3). At the conclusion of the treatment planning process a treatment plan should be achieved which is optimised to best meet the clinical goals, and as such, the radiotherapy process is already personalised for the patient to this extent despite being constrained to the general population-based prescription doses and fractionations, and tolerances.

As more cancer research discoveries are made, particularly in understanding genetic and immune factors, the nascent discussion has moved on to how to create further bespoke patient-centred cancer treatments.[64] Although a truly personalised approach may be out of reach for some years yet (and perhaps never, given the multitude of micro- and macro-environmental factors), it is entirely possible to move towards a *less* generalised treatment strategy. Indeed, it is now feasible to stratify patients into risk categories by identifying an individual's radiosensitivity with genome-wide association studies distinguishing those with a high chance of organ at risk (OAR) or normal tissue complications.[65-67] Personalising

radiotherapy using radiobiological rather than physical dose concepts could be integrated. Patients could be given further choice over their personalised treatment options which should go towards improving their experience of cancer treatment, and possibly outcomes.

Figure 2. Example of a SABR plan for a peripheral right lung tumour. Planning Target Volume (PTV) = 27.7 cc. The legend on the transverse slice (A) depicts the isodose levels shown in the plan with bold lines also visualised in the coronal plane (B); the other coloured outlines represent organs at risk and structures used within the planning process. The pink rind typifies a clinical chest wall structure encompassing the ribs. The light blue and yellow contours show the right and left lungs respectively. On the next page in Figure 3, (C) shows the 'clinical goals' within the treatment planning system, Eclipse, and the in-house script output (D) providing the other SABR Consortium metrics required for this plan.

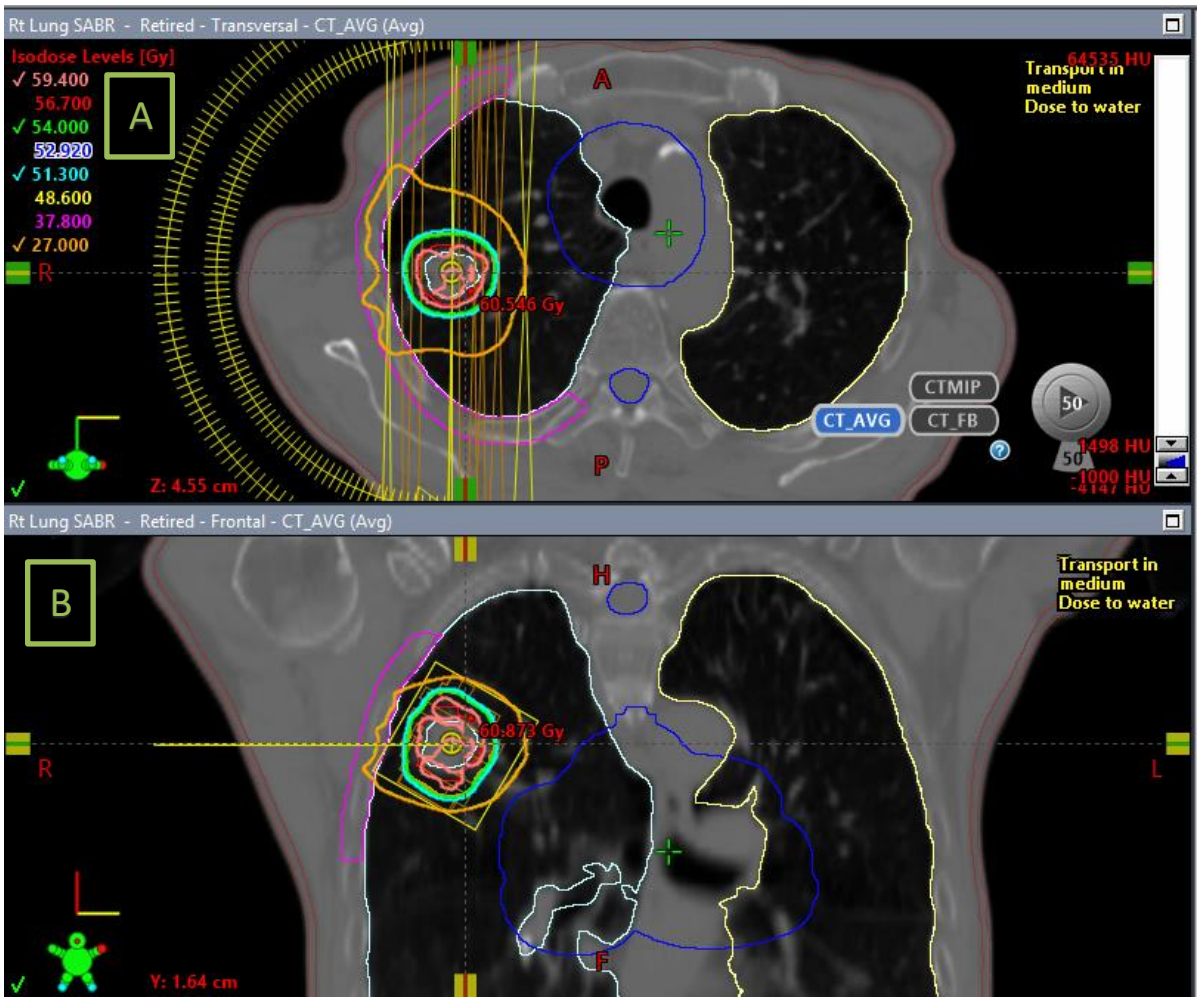
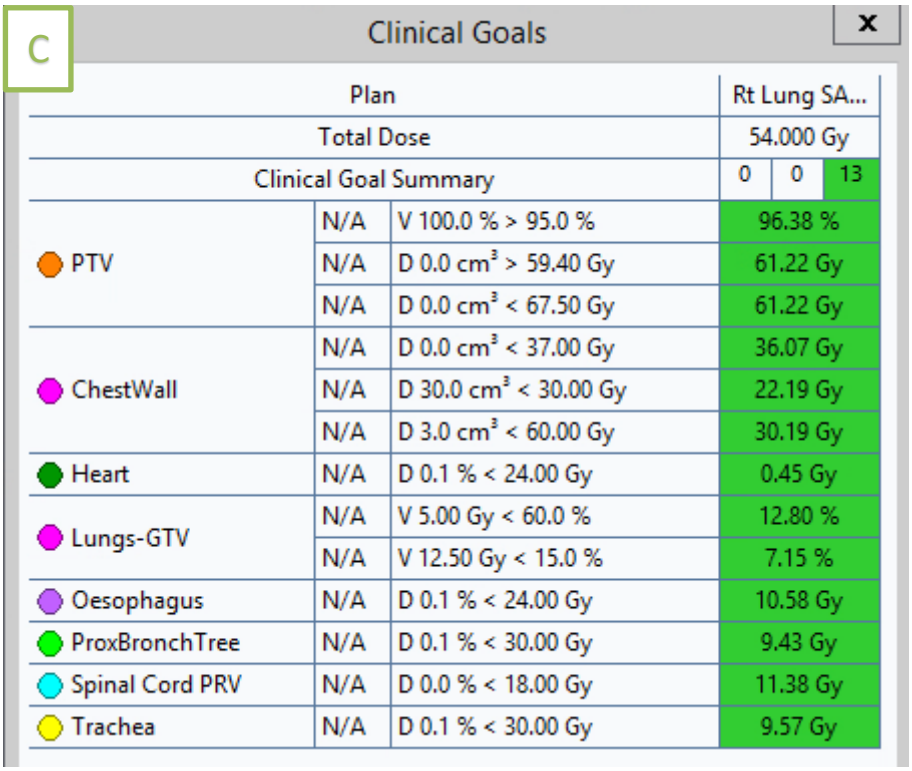
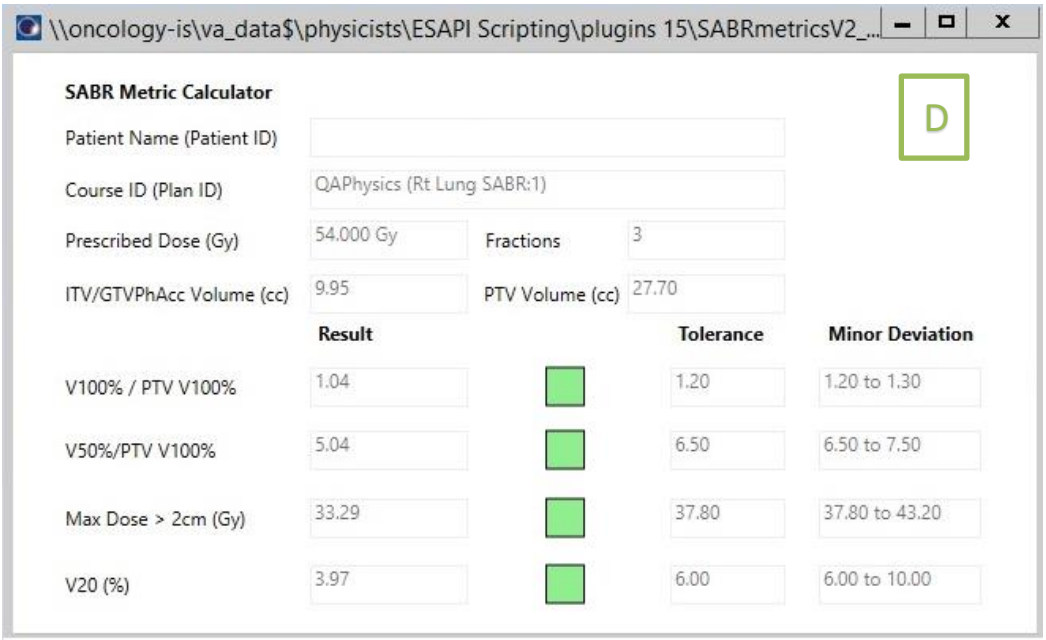


Figure 3. 'Clinical goals' within the treatment planning system (C), Eclipse, and the in-house script output (D) providing the other SABR Consortium metrics required for the plan above. In this case, all the metrics have been achieved within tolerance. The in-house script, D, provides assurance that the treatment plan is adequately conformal using a conformality index known as the 'prescription dose spillage' (V100%/PTVV100%), and with a sufficiently high dose drop off from the PTV using a 'modified gradient index' (V50%/PTVV100%), and that the maximum dose 2 cm away from the PTV is within a tolerance. These metrics are volume specific to the PTV. The V20% refers to the lungs-GTV combined structure.





1.4.Patient Involvement

Patient involvement and choice in healthcare is a cutting edge topic, and explicit in Section 3a of the NHS Constitution.[68] Patients also want to be involved in their cancer care.[69] This should include their involvement in considering the acceptability of new treatments in terms of number of hospital visits, side effects, complexity of the treatment, patient compliance and recovery time etc., and the 'little things' as discussed by Cornwell.[70]

The 2019 NHS Long Term Plan (https://www.longtermplan.nhs.uk/online-version/overview-and-summary) sets out a vision for a 21st century service model in which 'patients get more options' and where 'health inequalities' will be addressed and actioned. Health care workers across many landscapes, both local, regional (cancer ODNs, or operational development networks) and national are mobilising to address 'unexplained local variations' and are scrutinising radiotherapy services and clinical protocols. Patient involvement groups and individual patient voices will be called upon to enhance this work to ensure that 'taxpayers' investment will be used to maximum effect. Given that lung patients have given clear, unaddressed, reasons as to why they have declined SABR[12] and that some appear to have (or be presented with) no treatment choices at all,[11] it is clear that patient voice is a missing element. How should we assess the patient appetite for making changes to treatment strategies, other than directly involving them? There are many elements of care which need to be integrated (social, mental and physical, primary and specialist) as recognised in the Long Term Plan, and so the research presented in this thesis aligns with the wider themes of patients' perception of the care they receive. Thus, service evaluation and studies in service quality improvement are vital, and should be considered alongside scientific, evidence-based approaches for cancer management.

1.5. Hypothesis/Aims

The three original aims of this research were:

1. To determine the radiobiological dosimetric Normal Tissue Complication Probability (NTCP) and Tumour Control Probability (TCP) for a sample of previously treated SABR patients. All patients received SABR in the Radiotherapy Department of the Hull University Teaching Hospitals NHS Trust.
2. To correlate these radiobiological doses with already published toxicity and outcomes.
3. To assess and suggest alternative, isotoxic, fractionation regimes (either aligning with the 3, 5 and 8 fraction regimens or otherwise) which would achieve the same Tumour Control Probability (TCP) with the minimum number of personal patient attendances.

Additional aims which arose during the study were:

1. To confirm the absence of any sex bias in the survival data, TCP or NTCP.
2. To conduct a qualitative service evaluation involving patient responses to a survey to determine if there is any appetite for personalised treatment fractionations.
3. To expand the work into an 'innovation project' on how the altering of given fractionations may affect departmental workload and income generation (Appendix 4.4)

2. Publications and Empirical Papers

2.1. Tumour control probability of a UK Cohort of lung SABR patients

This paper was submitted to the Journal of Radiotherapy in Practice as a short Technical Note. My contribution to this paper was as follows: I was responsible for the initial concept. I planned and authored the paper, acquired the data, performed the analysis, and then dealt with the correction and proof reading as required by the journal. I sought assistance from my supervisors in proof reading the drafts as explicitly mentioned in the acknowledgements section. This paper was published in October 2020.

The total DVH data for each lung SABR patient treated in Hull between 201 and 2019 was exported from the Eclipse treatment planning system in our Radiotherapy Department and required some manipulation prior to import into the Biosuite software. This required each structure to be isolated into a separate file (using the 'EclParser' application supplied with Biosuite) but the formatting of the subsequent files had to then be corrected (saving the *.txt files in 'ANSI' coding, and removing superfluous lines which were added in the most recent versions of Eclipse) to enable the read-in and simple import. Although a technical coding solution was considered, all 198 usable patient DVH files were manually adjusted by the author. The DVH data was exported in absolute dose (Gy) and absolute volume (cc).

It should be noted that although the abstract and the main text shows the correct TCP ranges, there was a typographical error in Table 2 introduced at the type setting stage, which was not identified at the final proof read. Incorrect ranges have therefore been struck out when including this article in the thesis; the correct data should read:

Table 1. JRP Article Average Tumour Control Probabilities and ranges (Table 2. in publication [Thesis Table 1])

	Tumour Control Probability (%)		
LQ Marsden TCP model α/β (Gy)	**3 Fractions**	**5 Fractions**	**8 Fractions**
10	**100**	**100**	**97 (92-99)**
20	**100**	**99 (97 – 100)**	**64 (48-79)**

How patients might respond to a shortening of a radiotherapy regimen, from 8 to 5 fractions to improve TCP, is elicited in Chapter 2.2. The reference to further work examining the NTCP

for the same cohort within the 'Discussion' section of this paper is presented in this thesis within Chapter 2.3.

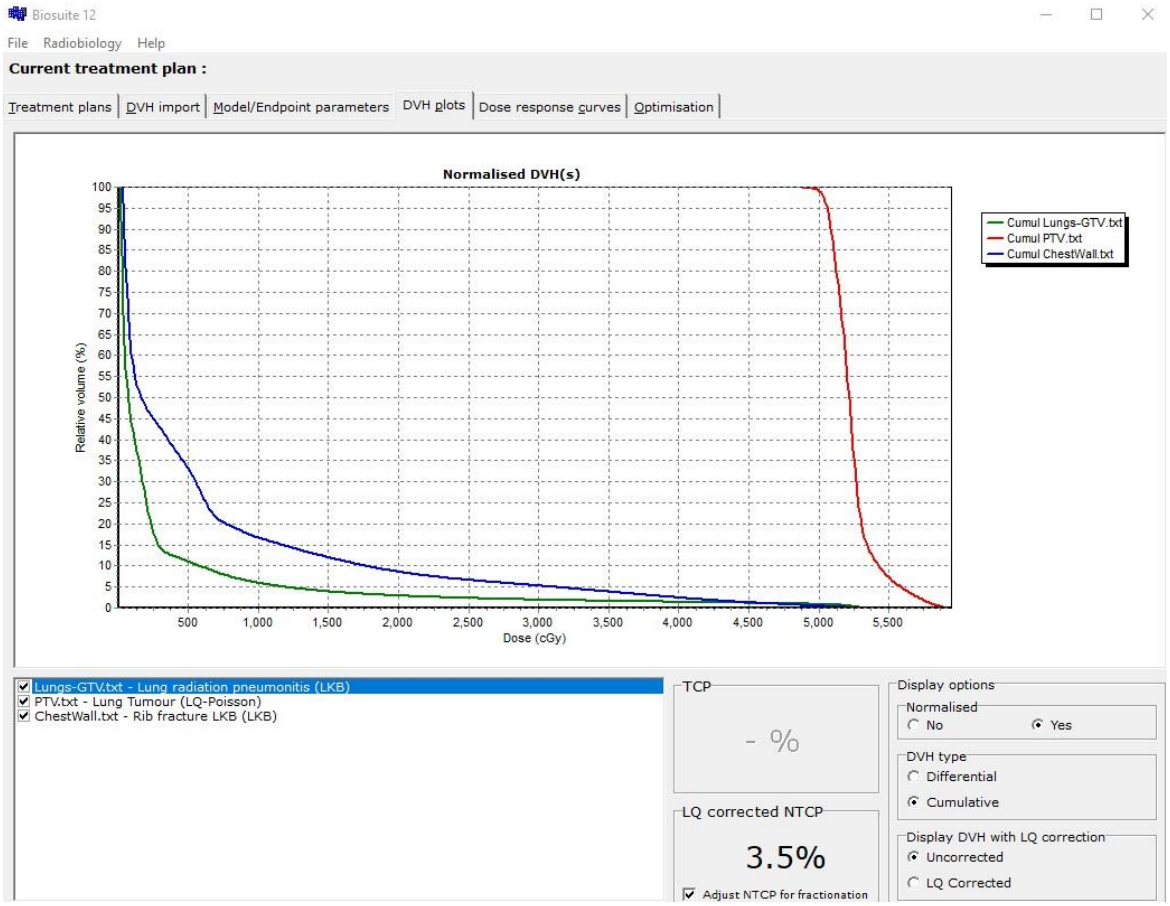
2.1.1. Biosuite

The Biosuite software was developed at Clatterbridge Cancer Centre, UK, as an in-house software tool for estimating NTCP and TCP in 2012.[47] It was developed for illustrative purposes only, and is often used within radiobiological modelling teaching in the UK graduate and post-graduate medical physics courses, and wider. It should not be used clinically as a medical device as it has not been CE/UKCA marked, which is explicitly stated in the disclaimer when the tool is initiated.

The software was developed in C++ and runs as an executable file whereby patient DVH files can be uploaded into the tool and various models and their parameters can be modified to visualise cause and effect. It can be used for computing probabilities and also optimising fractionation or dose based on probability trade-offs (isotoxic planning). Figure 4 shows the Biosuite graphical user interface. The advantages of using Biosuite include the degree of visualisation of the concepts of radiobiological modelling in addition to the numerical outputs.

Biosuite was chosen for this work because is it freely and immediately available, which was important for the time frame of the research, and due to its ease of use. Similar commercial products are available, including treatment planning system 'plug-ins' but none were available to the author due to cost and accessibility.

Figure 4. Graphical User Interface from Biosuite (Version 12.01) showing replotted DVH data for the PTV, Lungs-GTV and Chestwall structures, with the NTCP value for the Lungs-GTV showing as 3.5%, for a representative patient (54 Gy in 3 #). The various tabs at the top of the tool are used to input the parameters for the treatment plan (total dose, fractionation and overall treatment time), to import the DVHs and to adjust the Model and Endpoint parameters for target volumes and organs at risk.



2.1.2. Biosuite TCP Model and Limitations

The tumour control probability model in Biosuite (Version 12.01) used in this research is the LQ Poisson Marsden TCP model, which is described by Dale[71] and further explored, as presented here by Webb and Nahum.[61] It is based on clonogenic cell density radiobiological effects.

Taking Equation 2 from Section 1.3 further,[72] the TCP to calculate the probability that zero clonogenic cells survive is:

$$TCP = \exp\left\{-N_o \exp\left[-\alpha D\left(1+\frac{\beta}{\alpha}d\right)\right]\right\} \qquad \text{[Equation 3]}$$

Where N_0 is the initial number of clonogenic cells, α is the parameter describing the slope of the cell survival curve with β describing the degree of curvature and D is the total dose delivered in equal fractional doses of d. The α/β ratio is a required parameter within Biosuite.

Because α varies between patients, a normally distributed range of values is assumed with a standard deviation term (or parameter 'Alpha spread' in Biosuite) which gives rise to Equation 4.

$$\overline{TCP}(D,d,\alpha,\beta,N_o) = \sum_i g_i TCP(D,d,\alpha_i,\beta_i,N_o) \qquad \text{[Equation 4]}$$

g_i is the fraction of individuals in the population ($\Sigma g_i = 1$) for whom $\alpha = \alpha_i$ so:

$$g_i \propto \exp\left[-(\alpha_i-\bar{\alpha})^2/2\sigma_\alpha{}^2\right] \qquad \text{[Equation 5]}$$

A further term can be added to the TCP expression to take into account repopulation, and although Biosuite requires these parameters (repopulation constant and delay before repopulation), the term is not used for the SABR fractionations studied here because all treatments are completed before the assumed start of repopulation or proliferation.

It can be seen that the TCP expression utilises a single dose, D, however in reality the dose received by the tumour is non-uniform and different for each sub-volume of the PTV. The differential DVHs exported from the treatment planning system provide the subvolumes, dV, receiving doses, dD, and by considering the clonogenic cell number density per cc, the number of clonogenic cells, $N_{0,i}$, that receive a dose, D_i, can be computed. In addition, the 'dose' may be impacted by the treatment planning system algorithm in use, as described in Section 1.1.4.

Equation 6 shows the resultant average number of cells surviving as a result, summed over all n DVH bins.

$$N_s = \sum_i^n N_{o,i} \exp\left[-\alpha D_i\left(1+\frac{\beta}{\alpha}d_i\right)\right]$$

[Equation 6]

The TCP can now be expressed:

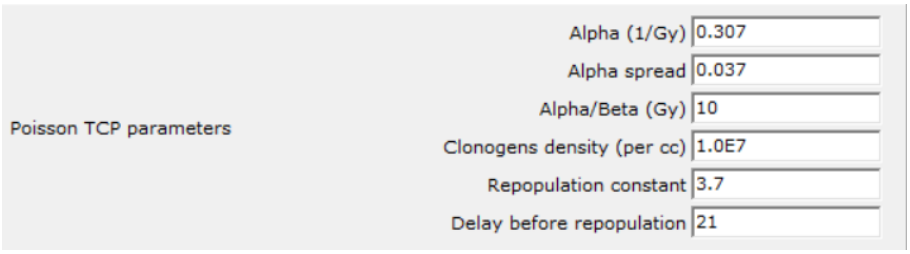
$$TCP = \frac{1}{\sigma_\alpha\sqrt{2\pi}}\int_o^\infty \left(\prod_i \exp\left[-\rho_{clon}V_i \exp\left\{-\alpha D_i\left(1+\frac{\beta}{\alpha}d_i\right)\right\}\right]\right)\exp\left[-(\alpha-\bar{\alpha})^2/2\sigma_\alpha^2\right]d\alpha$$

[Equation 7]

where V_i is the volume in the i^{th} dose bin (obtainable from the structure DVH) and ρ_{clon} is the clonogenic cell density (assumed to be non-varying with position here).

Figure 5 shows the Biosuite variables which can be used to adjust the TCP estimate.

Figure 5. Biosuite Poisson TCP parameter interface showing parameters which can be varied to estimate the TCP. All parameters must be entered, however the repopulation term is not used as no SABR fractionation exceeds 21 days total treatment time.



Biosuite also includes an 'enhanced Marsden TCP model' which can include sublethal damage by utilising two additional parameters, the sublethal damage repair constant and the time for fraction delivery, however this was not utilised in this research because all SABR fractionations were given on alternate days, and so full repair has been assumed. The time for fraction delivery can be estimated at approximately 2 minutes for a FFF (flattening-filter-free) delivery and between 3 and 6 minutes for a flattened beam.[17] All SABR fractionation schemes were completed within 21 days and so repopulation is not considered, even though a delay parameter is entered.

There are limitations to using software such as this for probability calculations, despite it being a useful tool for study and research. These include the implementation of the mathematics, the binning of the DVH data, the parameters adjusted and selected by the user and the

fundamental planning data itself which could be created with varying algorithm types over the period of study, although in this work the same algorithm was used throughout. Earlier algorithms are likely to overestimate the dose compared to later Type B or C, or Monte Carlo methods of dose calculation and this reduces the usefulness of comparing probabilities over time using DVH analysis.

The PTV was chosen to calculate TCP, however this is an expansion of the tumour and so includes volumes where there are zero clonogenic cells. The PTV is the GTV plus a 0.5cm isotropic margin. Despite this, the total volume is treated as if it has the same density of clonogens throughout when clearly this is not the case. It is also difficult to accurately identify the true clonogen density and this may vary both within and between patient populations. Although there is a standard distribution term allowed for the α component of the cell survival curve, there is no spread accounted for in the β term, when in fact there will be individual differences within this parameter also, which could be taken into account if the software was updated. Further limitations are discussed in chapter 3.

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Tumour control probability of a UK cohort of lung SABR patients

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Technical Note

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Abstract

Aims: The aim of this work is to report on the tumour control probability (TCP) of a UK cohort of lung stereotactic ablative radiotherapy patients ($n = 198$) for a range of dose and fractionations common in the UK.

Materials and methods: TCP values for 3 (54 Gy), 5 (55 and 60 Gy) and 8 (50 Gy) fraction (#) schemes were calculated with the linear-quadratic Marsden TCP model using the Biosuite software.

Results: TCP values of 100% were computed for the 3 # and for 5 # ($\alpha/\beta = 10$ Gy) cohorts; reduced to 99% (range 97–100) for the 5 # cohort only when an α/β of 20 Gy was used. The average TCP value for the 50 Gy in 8 # regime was 97% (range 92–99, $\alpha/\beta = 10$ Gy) and 64% (range 48–79, $\alpha/\beta = 20$ Gy). Statistical significant differences were observed between the α/β of 10 Gy versus 20 Gy groups and between all data grouped by fraction.

Conclusion: TCPs achievable with current planning techniques in the UK have been presented. The ultra-conservative 50 Gy in 8 # scheme returns a significantly lower TCP than the other regimes.

Introduction

Lung cancer is the leading cause of cancer-related mortality in the world for which stereotactic ablative radiotherapy (SABR) is proven as an effective non-surgical treatment.[1] In the UK, the technical roll out of SABR was mainly carried out with adherence to the UK Consortium Guidelines[2] which suggested set dose fractionation based on risk. The outcomes for SABR are generally exceptionally good, in large part because of the requirement to only treat small, peripheral tumours (< 5 cm) which are located far from any potential organs at risk (OAR).

Radiobiological modelling based on tumour control probability (TCP) and normal tissue complication probability (NTCP) can be used to optimise radiotherapy treatments to find the most appropriate trade-off and improve the therapeutic ratio.[3] Various types of TCP modelling have been carried out for lung SABR treatments[4] and the resultant probabilities align with the good outcomes seen clinically.[5] Large variation in both theoretical probabilities and observed outcomes or toxicities can be seen in data spanning time periods covering significant changes in techniques, or if the planning techniques did not follow consistent and rigid guidelines (ibid). The use of the linear-quadratic (LQ)-based TCP model for high doses per fraction also remains controversial.[6] However, it continues to be used, in one form or another, in optimisation studies.[7]

There are limited reported data on the TCP prediction values in the UK; hence, the objective of this study was to report the values obtained from a centre adhering to the UK Consortium Guidelines. The lack of specific publications on the values of TCP for lung SABR in the UK means that it is sometimes difficult to compare current practice with suggested technique improvements and service developments. The data here provide a benchmark and can also be compared with existing or future publications, drawing in national and international studies.[7]

Materials and Methods

This retrospective review of 198 previously treated patients was an extension of a hospital audit conducted annually as part of the regional network service delivery conditions. Radiotherapy treatment plans consisted of two half arcs within the Eclipse treatment planning system (Varian Medical System, Inc., Palo Alto, CA) at 6 MV or 10 MV FFF (RapidArc on Varian machines). The Acuros algorithm was used with a 2 mm grid, and the final plans reported absolute dose to water. All plans were created in accordance with the contemporary UK SABR Consortium Guidelines at the time they were produced. Data spanned the period

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2014–19. All plans met the majority of Consortium[2] requirements (with some minor deviations), and all were approved by a radiation oncologist.

Dose–volume histogram (DVH) data were imported into the freely available Biosuite software[3], and the LQ Marsden TCP model was used with the parameter settings for non-small cell lung cancer as per Nahum et al.[4] That is, an $\alpha/\beta = 10$ Gy, $\alpha = 0{\cdot}307$ Gy^{-1}, a clonogen density of 10^7 and a clonogen doubling time of 37 days. The planning target volume DVH data, rather than the gross target volume, were used to conservatively calculate the TCPs. The 100% prescription dose was used as the TCP prediction dose. TCP was also calculated with an $\alpha/\beta = 20$ Gy, which some literature cites as an appropriate modification to the LQ model for SABR fractionation.[5]

Results

Patient characteristics and centre data are shown in Table 1. The TCP values obtained are given in Table 2. The TCPs were all 100% for 54 Gy in three fractions (#), regardless of the α/β value used.

For the 5 # group at both dose levels (55 and 60 Gy), the TCP was 100% when using $\alpha/\beta = 10$ Gy but reduced to an average of 99% (range 97–100) when using $\alpha/\beta = 20$ Gy. The average TCP value for 50 Gy in 8 # was lower and showed a broader variation with mean values at 97% ($\alpha/\beta = 10$ Gy) and 64% ($\alpha/\beta = 20$ Gy).

A paired samples T-test was performed to compare all the TCP values when using an α/β ratio of 10 Gy versus 20 Gy. There was a significant average difference between groups ($p = 0{\cdot}001$). On average, the TCP values using an α/β of 10 Gy were 1·76 percentage points [0·76–2·46] higher than the TCP values using an α/β of 20 Gy. Because greater variation was shown in the $\alpha/\beta = 20$ Gy group, these TCP values were used when comparing groups by fractionation as a worst-case scenario.

Significant statistical differences were found between the 3 # and the 5 # groups (T-test, $t_{79} = 10{\cdot}315$, $p < 0{\cdot}001$), the 3 # and the 8 # groups (T-test, $t_8 = 9{\cdot}434$, $p < 0{\cdot}001$) and the 5 # and the 8 # groups (T-test, $t_8 = 9{\cdot}434$, $p < 0{\cdot}001$).

There are no statistical difference seen between tumour status (grouped generically by T1, T2 and T3).

There was no difference between male and female groups.

Table 1. Patient characteristics and centre

Patient cohort	198 (50% Female)
Mean Age	75·2 years (54–93)
Tumour status	T1: 60%, T2: 36%, T3: 3%, Missing: 1%
Mean PTV volume (cc)	34·7 (5·0–133·4)
Planning technique	4D CT (10 bins), Eclipse TPS with þ5 mm ITV to PTV expansion, 2 partial arcs, using Acuros (2 mm grid), transport in medium, dose to water
Dose regimen treated	3 × 18 = 54 Gy (55%)
	5 × 11 = 55 Gy (35%)
	5 × 12 = 60 Gy (6%)
	8 × 7·5 = 50 Gy (4%)
	Risk adapted on PTV location as per the UK SABR Consortium Guidelines Versions 4.1 to 6

Table 2. Average tumour control probabilities and ranges

	Tumour control probability (%)		
LQ Marsden TCP model α/β (Gy)	3 Fractions	5 Fractions	8 Fractions
10	100	100	97 (~~52–59~~)
20	100	99 (~~57~~)	64 (~~14–39, 60–65~~)

Discussion

This study sought to present TCP prediction values from a typical UK centre adhering to the UK Consortium Guidelines, which is largely absent in the literature.

The TCP was 100% in all cases for the 3 # schedule regardless of the α/β ratio used. The majority (55%) of clinically treated schedules in our institution are 54 Gy in 3 #. For the 5 # schedules, some variation in the TCP was seen, but all probabilities were greater than 97%. For the 8 # schedule, a broader range of TCP values was seen regardless of α/β ratio used.

There is considerable debate regarding the accuracy and appropriateness of the various parameters used for radiobiological modelling, as described in the excellent review by McMahon.[6] New and complex modifications to the basic TCP model and its parameters are published frequently.[7] One of the limitations of this study is that the LQ Marsden TCP model was used without any of these types of modification, for example, regrowth. This was intentional as relatively simplistic modelling using LQ parameters is used clinically in many hospitals to compare and contrast patients' fractionations and does not depend on the availability of advanced mathematical computational skills. Recently, the impact of the COVID-19 pandemic has influenced treatment fractionation and increased the use of radiobiological calculation in radiotherapy clinics with the intention of reducing radiotherapy outpatient footfall and correcting for breaks in the treatment.

Although there were significant differences between each groups, the TCP values can be considered high compared with conventional radiotherapy,[7,8] and therefore demonstrate why excellent clinical results can be observed for patients undergoing lung SABR despite them so often being elderly, non-operable and presenting with other comorbidities. The values here are consistent with those published by Lu et al.[9] and the more recent multiple cohort data by Alaswad et al.[7] However, it should be noted that in this study, the 8 # schedule, often used when constraints cannot be met for 5 # plans, gave worse TCPs which were similar to those values published for 3D conformal radiotherapy (ibid). This regime is reserved for poorer performance status patients. It has the effect of losing the advantages of SABR in terms of tumour control.

Given that the TCP may be much reduced for patients receiving eight fractions, the advantages of even shorter fractionation (e.g., reduced overall treatment time, reduced patient visits and improved therapeutic gain) could be considered to improve tumour control in parallel to any potential increased risk of normal tissue toxicity. This work has not considered the corresponding NTCP for the toxicities associated with OAR for lung SABR, namely, chest wall pain, rib fracture and radiation pneumonitis. The literature suggests that some rates of OAR toxicity have been historically high[10–12], but our initial observed clinical outcomes[13] suggest that by following the UK SABR Consortium Planning Guidelines these rates reduce considerably. Published toxicity rates

need to be appraised carefully, especially when reported over long periods of time. This is because of the huge technological advances that have emerged over those same time periods such as 4D verification imaging and more sophisticated, semi-automated planning techniques. OAR toxicity should therefore be reviewed within each centre on a regular basis and compared with current literature. Preliminary results using this same dataset suggest that our NTCPs across a range of toxicity end points can easily be kept below 3–5%. Benchmarking values of NTCP will be further work for our institution.

Following the Consortium Planning Guidance constraints and considering only those OAR that fail to meet tolerance doses would make patient-specific appraisals relatively simple to perform in the clinic. Only failing OAR DVH need be exported and assessed. An individual assessment of the acceptable TCP and NTCP values for a given patient initially considered for the eight fraction scheme could be carried out prospectively to improve tumour control and individualise fractionation. This could be implemented simply by first considering the existing 3 and 5 # regimes as possible alternatives, before contemplating non-standard schemes.

Conclusion

The data presented provide a benchmark for TCPs achievable with current planning techniques in the UK and give an insight into why the majority of these patients do so well, despite being elderly and often non-operable. The ultra-conservative 50 Gy in 8 # scheme gives a significantly lower TCP, comparable to 3D conformal radiotherapy techniques.

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2.2. Patient Experience of Lung SABR: Is there a desire for a personalised service?

My contribution to this short communication was as follows: I planned and authored the paper including design and creation of the questionnaire, acquired the data, performed the analysis, and then dealt with the correction and proof reading.

I sought assistance from two previous radiotherapy and cancer patients to design the patient information sheet and the survey. I took additional advice on the qualitative aspect of the data collection from my lecturer, Dr Adrian Nelson, Lecturer in Healthcare Management, Alliance Manchester Business School. After reviewing the literature, I found a few papers of this nature published in the journal, 'Lung Cancer' so I submitted it in October 2020, however it was declined with the reason, 'Although the observation is of interest, the news value for the Journal is just not high enough to consider it for publication.' I will attempt to submit it to an alternative publication shortly.

The report and the data were also lodged and published as a clinical audit within my NHS Trust (Project NLA.2020.001), and discussed within our Quality Meetings in regard to patient feedback, which is a key component of our certification from BSI and our UKAS BS70,000/MPACE accreditation.

The full data from this service evaluation can be found in Appendix 4.4.

The references for this paper have been added to Chapter 5, References.

Patient Experience of Lung SABR: Is there a desire for a personalised service?

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Key words: Lung SABR, Survey, Patient Experience, COVID, alternative fractionation,

No grants funded this work.

Abstract

Aims: The aim of this short communication is to report on a service evaluation undertaken to determine if there was a patient preference for personalised lung stereotactic ablative radiotherapy (SABR) (i.e., fewer or more fractions than offered), and to gather feedback on patient experience in a UK centre. Understanding patients' willingness to accept alternative radiotherapy fractionation schemes compared to the standard of care might be important when radiobiological calculations indicate individual benefit, or for service considerations such as reducing footfall during the COVID pandemic and departmental scheduling.

Materials and Methods: One hundred previously treated peripheral SABR lung patients were provided with an anonymous postal survey, which could also be completed online, covering treatments both prior to and during 2020. Questions covered patients' ability to cope with the number of treatments experienced, if this affected their decision to undergo radiotherapy, if they would have preferred fewer or accepted more fractions, or consented to a personalised number of treatments. Free text space was allocated for further comment.

Results: From the 50% return rate, 96% of patients felt that the number of SABR treatments (between 3 and 8) was reasonably easy to cope with. The same proportion stated they would have accepted as many treatments as recommended by their healthcare professional. Only 6% of respondents felt this number affected their decision to undergo radiotherapy. 76% of those surveyed would have taken advantage of a tailored, personalised service.

Conclusions: Most patients surveyed thought that they could cope with 3 - 8 fractions of SABR but would be willing to accept as many as recommended, with very few saying it would affect their decision to undergo radiotherapy. Three quarters of those surveyed were willing to consider alternative fractionation schemes. Moving towards alternative fractionation schemes for the purposes of reducing hospital footfall or to capitalise on radiobiological optimised dose schemes may therefore be well tolerated with high patient compliance.

Introduction

Patient satisfaction surveys are a useful tool for evaluating services and improving care,[73] including in radiotherapy,[74,75] There is limited data on patients' experience of lung stereotactic ablative radiotherapy (SABR) and this article seeks to contribute to the literature by publishing the results of such a service evaluation. A survey was conducted to determine if there was a patient preference to have personalised radiotherapy treatment (i.e., fewer or more treatments than offered) and to determine if the existing treatment schedules affected patient decision making. Although SABR is inherently a short fractionation regimen, patient access and compliance for this cohort was considered important as this treatment is still mostly limited to inoperable, often elderly, patients with additional comorbidities who may present specific challenges in terms of treatment attendance. The findings of the survey were intended to complement publications regarding shortening radiotherapy courses with a view to reducing COVID-19 risk by lowering hospital footfall,[76] and disparities in the tumour control probability for eight fraction SABR regimes as compared with those receiving fewer treatments.[77]

Materials and Methods

One hundred previously treated peripheral lung SABR patients were selected for the survey, half of whom were included in a sample from a previous publication[77] and half from the most recent SABR patients treated in 2020 during the COVID pandemic. It was hoped that this would capture patient experiences related to accessing and experiencing radiotherapy during UK government 'lockdown' restrictions. Equal representation of men and women were included, as identified by hospital records. Patient records were checked to ensure no surveys were erroneously sent to deceased patients. The median age of participants at the time of the survey was 77 years (range 56 – 96 years). 35% of surveys were sent to those who had received 3 fractions of treatment, 39% 5 fractions and 26% 8 fractions. The surveys were anonymous and no patient identifier or pseudo-anonymisation was used. Surveys were sent out in November 2020 and the close date of receipt for analysis was March 2020.

The patient information sheet (PIS) and survey was original, written by the researcher and is not validated. Permissions were sought from the Health Research Agency (HRA) who classed the study as a 'service evaluation' which did not need further ethical approval (HRA REF 525/88/86/81). An audit notification was also lodged with Hull University Teaching Hospitals NHS Trust to ensure traceability and governance (No. LA.2020.001). The PIS was modified with advice sought from Dr Adrian Nelson, Lecturer in Healthcare Management, Alliance

Manchester Business School. Care was taken to ensure the PIS complied with the Trust Information Governance and GDPR policy, duty of care and consent requirements. Suggested alterations to the survey were to include free text areas to allow patients' freedom to give further information. This allowed more in-depth capture of issues regarding patient compliance and ability to attend the whole course of radiotherapy.

Additional patient input was sought over the draft version with two previous radiotherapy patients offering invaluable advice over language, content and layout. The main changes were to extend the survey to two pieces of paper to allow participants to retain the information sheet independently when posting off the response, altering the language to make it more comprehensible and consistent, and allowing more than one answer to be selected for some of the questions. An online version of the survey was also appraised by the reviewers.

The survey asked questions relating to the personally reported number of treatments experienced and perception of ability to cope with these treatments, if fewer or more appointments would have been tolerated and if this affected their decision to undergo radiotherapy. The final question related to the preference of patients to utilise a tailored, personalised service over the 'standard' number of appointments, interpreted as however many that particular patient had experienced. A free text comments section was included.

Results

Most surveys were returned by post (48/100) with a further two being completed online and by telephone. The total return rate was 50%. Of the respondents, 28% claimed to have received 3 fractions, 38% 5 fractions, 26% 8 fractions, and 6% couldn't recall the number of treatments they had. One respondent (2%) had 6 treatments (due to a treatment gap) out of a planned 8 and indicated this on the return form despite it not being an option. The proportion of replies for each fractionation scheme closely mirrors those in the originally targeted group.

96% of respondents felt that the treatment they had was easy to cope with. Of those that didn't, reasons given were related to their generalised radiotherapy experience such as weight, appetite and energy loss, and minor claustrophobia rather than number of attendances.

96% of patients sampled would have attended as many treatment appointments as the healthcare professional recommended.

Only two respondents felt that the number of treatments affected their decision to undergo radiotherapy but this was not always in a negative way, with one patient following up with text stating, 'It was not every day but spread over a week and a half'. Although a highly individualised response, this patient clearly considered alternative days easier to manage than daily appointments.

In regard to personalised treatment schedules (which was interpreted in the survey to mean number of radiotherapy treatment appointments rather than radiation dose or beam on or couch time, which would be harder for patients to compare), 76% would have taken advantages of a tailored personalised service, even if it meant having fewer or more appointments.

Twenty-five free text comments were collected. Many referred to the good service received, and covered several experiences of patients being treated during the COVID restrictions in place in the local area. These comments were identified and a thematic framework applied to code them. A summary of the main themes is presented in Table 1.

Discussion

The results of this survey confirm that most patients are content with the number of fractions they received, and would comply with whatever recommendations were given by their health care professional, stating that this would not affect their decision to undergo radiotherapy. Approximately three-quarters of those surveyed were willing to accept alternative fractionation schedules, deviating from standard of care, even if it means having fewer of more treatment appointments. This implies patient compliance should be high.

It may be considered obvious that patients would accept fewer treatments. The addition of the possibility of more or a bespoke number of fractions was included in the question to encompass the possibility that radiobiological optimisation (the trade-off between tumour control probability and normal tissue complication probability) may not always result in a reduction of total treatment time. Current practice in radiotherapy means that standard dose fractionations are delivered even though radiobiological optimisation per patient could result in a more optimal plan. Some evidence exists within trial screening logs that shows patients who perceive they are getting 'less' may prefer more treatments to fewer. For example, in the POSNOC breast trial, patient acceptability of the trial was reduced if randomised to the treatment arm of breast radiotherapy *without* the additional fractions of axilla treatment,[78] reducing trial recruitment and retention. During the 2020 COVID-19 outbreak, many

radiotherapy departments reduced fractionations for clinical indications across a range of disease sites with and without high quality evidence for doing so.[79] The author is aware of one, professionally knowledgeable, local breast patient refusing the imposed reduction of 15 to 5 fractions of radiotherapy. This also raises the question of how patients are able to make informed decisions with their health professionals if the risks and benefits of alternative fractionations (if offered) are not clearly expressed.

Because of the anonymity of the survey it was not possible to link the returns back to individual patients and correlate against age, fractionation received (other than self-reported), staging or outcome. This is a limitation of the study. Further limitations to the study were cost, time and accessibility to patients during the pandemic, removing the possibility for face-to-face, structured patient interviews that would offer more contextualised qualitative feedback data. A possible bias was that only patients who underwent radiotherapy were surveyed. Patients may have declined radiotherapy as a treatment option and these reasons were not assessed by the survey because those individuals were not captured in the treated cohort. The reasons for refusal *before* radiotherapy would need to be elicited in a separate study. The return rate of the survey was reasonable considering they were posted during the pandemic. It was notable that although an online form was provided the majority of returns were by post. This may reflect the age profile and digital skills of the participants, which should be carefully noted as the survey occurred when many social and hospital services had gone online due to the COVID-19 pandemic restrictions. Digital access and computing ability may still be a barrier to patient participation in surveys and evaluations, and may even skew larger data mining tools in the future.[80]

One other limitation of this study is that the sampling used to identify the two cohorts for the survey could have been better designed as there were more 5 and 8 fraction patients in the 2020 cohort as compared with the data from 2014-2019. It is unclear why this might be. It could be because the survey was posted to living patients, skewing the cohort as those with higher fractionations may have originally been screened as having more potential complications, or having a poor prognosis and so a lower toxicity risk regime was proposed. Or, it is possible that during COVID, clinicians who had safe access to radiotherapy were more conservative and used the 5 or 8 fraction regimes more often to avoid other areas of the hospitals having to deal with side effects. On reflection, a future survey should aim to have more equivalent cohorts in terms of the proportion of fractions whilst also maintaining the male/female balance.

It is also recognised that SABR is already a short fractionation regime so extending this survey to other lung patients covering longer radiotherapy treatment regimens would create more generalisable data. However, the demographics of SABR patients (elderly, co-morbid, potentially susceptible to various hospital acquired infections including COVID-19) make the responses of this cohort significant with regard to reducing hospital visits. Indeed the community are pushing towards single fraction SABR treatment, an extreme hypofractionation which may have a place in palliative scheduling.[79]

This work only considered radiotherapy treatments and not pre-treatment CT appointments or follow up. Additional work on streamlining workflow processes (such as radiotherapy 'one-stop-shops') and offering flexible follow up should be prioritised if the intent of service provision continues to be a reduction in footfall for vulnerable patients, such as those with lung cancer. Payment tariffs for radiotherapy may not be consistent with streamlining services, and this needs to be addressed by commissioners and providers.

Conclusion

Although a small sample size, this data provides a unique insight into SABR lung patient experiences, including capturing some values during the COVID-19 pandemic in 2020. Overall patients are content with the number of fractions they received, and would comply with their health care professional recommendations, stating that this would not affect their decision to undergo radiotherapy. It also complements the scientific and pragmatic evidence of the current time in that patients seem willing to comply with changes to the standard of care, with 76% of those surveyed willing to consider alternative fractionation schemes as part of a tailored, personalised service. There is no evidence here that argues against health care professionals recommending different fractionation schemes based on patients' individual clinical and logistical preferences.

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Table 1. Summary of free text comments from the service evaluation. Twenty-five comments were received but many contained multiple themes. Percentages rounded up hence total = 101%. Example comments are given for context. (Table 1 in publication [Thesis Table 2]. All comments available to view in Appendix 4)

Theme				
Mentions taking expert's advice as to number of treatments	Mentions 'good' staff or hospital experience, or 'happy' or 'thankful'	Mentions 'negative' experience	Mention of service during lockdown/ COVID	Mention of difficulties or treatment side effects
17%	57%	7%	7%	13%
'I can only accept what the experts advise so would think that tailored treatments are the sensible way to go' 'Would definitely follow advice given.'	'I was very happy with the treatment, staff and service.' 'They couldn't have been nicer, plus the cheerfulness of the staff made me feel so much better. Thank you all.'	'time waiting for it was very frustrating. Out of 8 sessions spent 2 days waiting.' 'the number of treatments severely complicated my bowel operation'	'feel we have been lucky to have had the treatment in such troubled times' 'Treatment was under 'lockdown' but could not have been better.'	'The only after effects I had were a few days tiredness.' 'tired and sleepy'

2.3. Normal tissue complication probabilities of a UK cohort of lung SABR patients

This paper has been prepared for the Journal of Radiotherapy in Practice as a companion paper to Section 2.1, was submitted in August 2021 and accepted in January 2022[4]. It summarises the thesis research outcomes.

My contribution to this paper was as follows: I planned and authored the paper including design and creation of the research, acquired the data, performed the analysis. I sought assistance from my HSST supervisors for reading drafts.

The outcome from this paper is that for the sample of patients analysed, the mean TCP and NTCP were not different between 8 and 5 fractions, meaning the majority of 8 fraction patients could have had three fewer visits without significant detriment.

Additional analysis of the data for the 8 fraction patients and two further figures (8 and 9) were added in Section 2.3.1 of this thesis but not included in the journal publication due the timing of it being accepted (and the limit of figures) and the thesis correction window. These figures show the variation in the NTCP per patient with dose and fractionation for those patients treated with 8 fractions. A simple sensitivity analysis example is given to show the variation of the resultant probabilities with varying parameters.

4 Marsden, J. (2022). Normal tissue complication probabilities of lung SABR patients from a UK centre and its implication on personalised radiotherapy. Journal of Radiotherapy in Practice, 1-5. doi:10.1017/S1460396922000024

Normal tissue complication probabilities of lung SABR patients from a UK centre and its implication on personalised radiotherapy

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Abstract

Aims: This work reports on the normal tissue complication probabilities (NTCP) of a UK cohort of previously treated lung SABR patients (n = 198) supplementing our previous publication on tumour control probabilities (TCP).[77] Each patient was recalculated for alternative schedules.

Materials and methods: NTCP for 3 (54 Gy), 5 (55 and 60 Gy) and 8 (50 Gy) fraction (#) schemes were calculated with the Lyman Kutcher Burman (LKB) model in the software platform 'Biosuite' (Version 12.01) for lung and chest wall. Patients treated with 5 # or 8 # were then recomputed for alternative fractionations and doses (3 # and 5 #, for both 55 Gy and 60 Gy).

Results: The mean lung NTCP ($NTCP_{LUNG}$, for the outcome of radiation pneumonitis) was 2.8% (range 0.6 – 10.6). The mean chest wall NTCP ($NTCP_{CW}$, for the outcome of rib fracture) was 1.4% (range 0.0 – 55.9). There were no statistically significant differences observed between male and female, tumour status or fractionation groups except for the $NTCP_{LUNG}$ between 5 # and 3 #.

When recalculating NTCP and TCP individually, for 8 # patients no differences were observed between mean TCP, $NTCP_{LUNG}$ or $NTCP_{CW}$ compared with 3 # or 5 # indicating that fractionation reduction is possible. Parity was observed between the 60 Gy group when recalculated for 55 Gy. For the 60 Gy in 5 # group, the $NTCP_{CW}$ increased significantly when recalculated for 3 #.

Conclusion: NTCPs achievable with current UK planning techniques have been presented indicating SABR Consortium compliant centres are likely to have low complication population risks (< 3%). 5 # schedules could be justified for 8 # patients thereby reducing the number of treatment visits. Where there is a large overlap of PTV and chest wall, this indicates an NTCP/TCP calculation is required to investigate if fractionation reduction is individually appropriate.

Introduction

Stereotactic ablative radiotherapy (SABR) is proven as an effective non-surgical treatment for inoperable peripheral lung cancer.[5] Adherence to the UK SABR Consortium Guidelines[10] risk-based dose fractionations and organ tolerances ensures that side effects from SABR are generally low whilst tumour control is high. Prior to 2020, when NHS England launched the SABR expansion programme, most UK centres were treating only peripheral lung tumours located away from most potential organs at risk especially those found within the 'central' zone, resulting in highly optimal therapeutic ratios.[47] Treatments are usually given every other day for 3, 5 or 8 fractions dependent on the location of the tumour in relation to the chest wall, as per the guidelines.

Using radiobiological modelling via trading off tumour control probability (TCP) and normal tissue complication probability (NTCP) is one way of assessing theoretical gains from planning technique and delivery improvements. Radiotherapy plans which are more conformal to the planning target volume (PTV) and deliver less dose to normal tissue organs at risk (OAR) will improve this therapeutic ratio. In an ideal radiotherapy plan, one would want the highest possible TCP (approaching 100%) with the lowest possible NTCP. Deviations in lung TCP and NTCP calculated over time (and observed in outcomes) can be large, especially when the period of study includes significant technological improvements in standard of care or where planning techniques are not consistent.[81] Radiobiological modelling continues to be used in optimisation studies despite controversy.[82]

To design quality improvements, baseline values for TCP and NTCP need to be established alongside careful observation of patient outcomes in terms of survival and treatment side effects captured at patient follow up. In the UK peripheral lung SABR was, and continues to be, implemented by centres adhering strictly to the SABR Consortium Guidelines due to commissioning requirements, which means centres are well placed to share data and outcomes and expect to see reasonable transferability. Therefore, this study seeks to add to the literature by reporting theoretical benchmark values of NTCP for those organs at risk commonly associated with lung SABR side effects. This study also supplements our previous publication benchmarking TCP values for the same dataset.[77] The data acts as starting point for what can be achieved if plans meet the tolerances expressed within the (widely utilised) UK guidance, and can also be compared with existing or future data.[82]

Recently the impact of the COVID 19 pandemic has influenced treatment fractionation and increased the use of radiobiological calculation in radiotherapy clinics for individual patients. The reasons for

carrying out bespoke radiobiological calculations include reducing radiotherapy outpatient footfall (i.e., with fewer or single fractions), scheduling (i.e., to complete treatment before the start of a self/family isolation period or public transport travel ban) and correcting for breaks in treatment (i.e., following self/family isolation). This research is therefore timely.

Materials and Methods

Radiotherapy treatment plans from 198 previously treated patients were analysed from the period 2014 - 2019, with a median follow up time of 16 months. Planning technique was as per Marsden, 2020,[77] that is two half arcs at 6 MV or 10 MV FFF (Varian Medical System, Inc., Palo Alto, CA) utilising the Acuros algorithm and reporting absolute dose to water. Patient characteristics are shown in Table 1. All plans met the majority of UK SABR Consortium tolerances required at the time (with some minor deviations) and were approved by a radiation oncologist and subsequently treated.

Dose volume histogram (DVH) data for the chest wall (CW) and the lungs excluding the gross tumour volume (Lungs - GTV) was imported into Biosuite[47] to calculate the $NTCP_{CW}$ and $NTCP_{LUNG}$, chosen to represent the most common toxicities. The volumes for Lungs - GTV were created according to the UK SABR Consortium Guidelines (all versions were consistent) and used without modification so as to be useful to other centres for comparison. The volumes created for the chest wall were consistent between patients but not in accordance with the latest guidance as these patients were planned prior to its publication in 2019. The chest wall volumes were created by contouring a rind of the ipsilateral hemi-thorax outside the lungs covering all the ribs approximately 1.5 cm above and below the PTV, which was standard practice during the period. However, it did not extend out by 3cm nor was it contoured the full 5 cm above and below the PTV as stated in the latest guidelines (page 18, SABR Consortium Guidelines, Version 6.1).[6] Therefore, these volumes were smaller than will be observed for centres following the latest guidelines, but as such conservatively over-estimate the $NTCP_{CW}$. The clinical prescription dose fractionations were used for each patient as treated, covering 54 Gy in 3 fractions (#), 55 and 60 Gy in 5 # and 50 Gy in 8 #. All NTCP were LQ-corrected, taking account of the total treatment time in days and fractionation.

For the Lungs-GTV, the end point was radiation pneumonitis (Grade >2) using the Lyman Kutcher Burman (LKB) model with the parameters as per Nahum et al.,[43] That is, an $\alpha/\beta = 3$ Gy, TD50 = 24.5 Gy, n = 1, m = 0.45.

For the Chest Wall, the end point was chosen as rib fracture also using the LKB model with the parameters as in Chairmadurai et al.,[83] and Stam et al.,[84] with the parameters α/β = 3 Gy, TD50 = 65.0 Gy, n = 1 (parallel organ), m = 0.3.

For the purposes of this study, the TCP quoted used α/β = 10 Gy rather than α/β = 20 Gy, both of which were investigated in our previous publication.[77]

The data obtained, per patient, for the various recommended lung SABR fractionations were derived and the mean control and toxicity probabilities were compared with the treated schedule. The schedule with the lowest number of fractions was 54 Gy in 3 #. For patients who were treated with this schedule, recalculations were not performed for more fractions (5 # or 8 #).

Results

The mean calculated $NTCP_{LUNG}$ (radiation pneumonitis) was 2.8% (range of maximum to minimum 0.6 – 10.6); the median was 1.9%.

The mean calculated $NTCP_{CW}$ (rib fracture) was 1.4% (range of maximum to minimum 0.0 – 55.90); the median was 0.6%. The large outliers in $NTCP_{CW}$ were due to PTVs overlapping with the chest wall. Removing the largest data point, the average $NTCP_{CW}$ was 1.2% (0.0 – 27.6).

The mean NTCP values are given in Table 2. Overall, the mean NTCP was less than 3.0% for both $NTCP_{LUNG}$ and $NTCP_{CW}$. There was no correlation between the chest wall and lung probabilities as shown in Figure 1 (Pearson, r = 0.14).

Independent t-tests were performed to compare groups. There was no statistical difference seen in $NTCP_{LUNG}$ or $NTCP_{CW}$ between tumour stage status (grouped generically by T1, T2 and T3 rather than using sub group categorisation such as T1aN0M0, for example), between male and female groups or by fractionation (3, 5, 8) with the exception of the 3 # and 5 # (t-test, $t_{187} = 2.808$, p = 0.006) where the mean $NTCP_{LUNG}$ for 3 # was 3.2% compared with the 2.3% for 5 # patients.

For the per-patient comparisons (see Table 3), paired t-tests showed there was no statistically significant difference between the mean TCP, $NTCP_{LUNG}$ or $NTCP_{CW}$, for the 8 # compared with 3 # or 5# indicating that this schedule could be reduced, although the numbers in this group were small (n = 9). Baseline values for these nine patients treated with 8 # are shown in Figure 2.

Supplementary tables are given for each 8 # patient in the thesis (Section 2.3.1, Figure 8 and Figure 9) for the NTCP variation per patient with dose and fractionation.

For the group of patients treated with 55 Gy in 5 #, there was no statistically significant difference for the mean TCP or the $NTCP_{CW}$ between any of the other groups using an ANOVA test ($p < 0.001$). For the $NTCP_{LUNG}$ a statistically significant difference was seen when moving from 55 Gy in 5 # to 60 Gy in 5 # (paired t-test, $t_{68} = -2.3826$, $p = 0.01$) and to 54 Gy in 3# (paired t-test, $t_{68} = -5.284$, $p < 0.001$), however this change was small with the $NTCP_{LUNG}$ increasing from 2.0% to 2.3% and 3.0% respectively, which may not have clinical significance.

For the group of patients treated with 60 Gy in 5 #, the 55 Gy in 5 # schedules were statistically equivalent over all metrics (TCP, $NTCP_{LUNG}$ and $NTCP_{CW}$). In moving from 60 Gy in 5 # to 54 Gy in 3 #, parity remained for the TCP and $NTCP_{LUNG}$, however the $NTCP_{CW}$ was significantly different increasing from a mean of 3.1% to 11.0% (t-test, $t_{10} = 3.103$, $p = 0.006$). This may be significant clinically and supports some use of risk adapted fractionation schemes for SABR.

Discussion

NTCP prediction values from a typical UK centre adhering to the UK Consortium Guidelines have been presented. The mean values for both $NTCP_{LUNG}$ and $NTCP_{CW}$ were less than 3% so the theoretical risk of radiation pneumonitis and rib fracture can be considered low compared with conformal radiotherapy in general where examples of $NTCP_{LUNG}$ may range from 10 to 30%.[85] For both types of complication probabilities, despite some specific patient variations, 99% of the cohort had a theoretical risk of complication much less than 10%. Within the uncertainties of the calculated values these are comparable with the observed toxicity rates reported in the systematic review by Murray et al.,[5] The data reviewed by Murray et al., spans the period 2005 to 2016 when SABR was being developed using different platforms and techniques (static beams versus VMAT, treatment planning with and without constraints, gradual implementation of risk based fractionation). It is important for centres to acquire their own data (theoretical and observed, on toxicity and survival) so that the effects of change in technique can be monitored to see if an improvement in quality has been achieved at a suitable period following change.

Unlike the PTVs in the TCP data from our previous paper using the same cohort which are all restricted in size to meet the treatment criteria of 'small' (less than 5 cm), the natural variation in normal organ size can be seen in this data. A wider variation of NTCP might have been expected compared with the same patient TCP and the group TCP. The volume of normal lung irradiated as a proportion of the total lung can vary depending on technique, however in this study all patients were treated with two ipsilateral half arcs reducing the radiation, and therefore risk, to the total lung

volume. Treatment techniques using a single 360° arc irradiating both lungs would yield worse $NTCP_{LUNG}$.

Although the Lungs – GTV structure is closely related to the true lung volume of each patient, the chest wall contour structure is less anatomically defined. The current guidelines (v 6.1, 2019) suggest contouring this structure as a '3cm rind of the ipsilateral hemi-thorax outside the lungs' and to cover 'at least 5 cm above and below the PTV'. However, the cohort of patients considered in this work were treated during a period (2014 – 2019) prior to this and so the chest wall structure used is not strictly defined. It consisted of a rind covering all the ipsilateral ribs beyond the superior and inferior levels of the PTV. However, the consequence of this is that the NTCP values are more conservative than if the volume was larger using the suggested 3 cm rind. For some patients it is impossible to create a 3 cm rind as this would extend the structure outside of the external body contour.

The data for the two different prescription dose 5 # regimes show equivalence. This evidence also shows that the theoretical increased risk of developing radiation pneumonitis is still small if the majority of these patients were to be treated with 3 #. The mean $NTCP_{LUNG}$ for 3 # was 3.2% compared with the 2.3% for 5 # patients. Individual patients may have higher risks dependent on tumour size.

One patient (50 Gy in 5 #) had a $NTCP_{CW}$ of 55.9%, i.e., the risk of rib fracture from the treatment was over 50%. This patient did not develop a subsequent rib fracture (38 months follow up). On inspection, a large part of the chest wall structure was included in the PTV when the GTV was expanded and so the structures overlapped. 15% of the volume of the PTV was within the chest wall; all received 100% of the prescription dose. The chest wall structure was contoured as per local practice above, however when redrawn according to the current guidelines with a 3 cm rind (although cropped to within the patient surface), the NTCP value reduced significantly to less than 1%. The next largest $NTCP_{CW}$ of 27.6% also occurred where there was large overlap between the PTV and chest wall and re-contouring the chest wall structure had the same effect, reducing the $NTCP_{CW}$ to less than 1%. The reasons behind this are linked to the use of the volumetric Equivalent Uniform Dose (EUD) within the LKB model in Biosuite, and demonstrate the sensitivity of NTCP calculations to the accuracy and/or reproducibility between patients of the OAR contouring. In Stam et al., 41 patient CT scans were used to manually and automatically create rib structures for the purposes of calculating NTCP.[86] Although the automated segmentation technique gave rise to slight volume differences the parameters obtained from these volumes that were used in the NTCP (EUD and the dose to a specific volume or 1 cc) were not significantly different. This allowed the authors to use the automated method in subsequent work where the ribs had not been delineated manually.[84] The

group found that the maximum rib dose best predicted rib fractures, although they also used the TD_{50} in their NTCP model. Automated segmentation of organs at risk, using atlas or Artificial Intelligence (A.I.) methods to improve planning efficiency may improve the reproducibility of NTCP and other volume based metrics in the future.[87]

The values given for the $NTCP_{CW}$ are low, as well as conservative, in respect to the smaller chest wall volumes used in this study. With the exception of the $NTCP_{CW}$ discussed above, the remaining $NTCP_{CW}$ were less than 10% and so these outliers comprised 1% of the sample. For the $NTCP_{LUNG}$ only 1% of the cohort were over 10%. The values here are consistent with those published by Lu et al., in 2019[48] and the more recent multiple cohort data by Alaswad et al., 2019[82] Care should be taken when comparing these values as absolute, due to their inherent uncertainties.

Together with the high TCP values,[77] the low NTCP values (as compared with conventional radiotherapy[82,88]) demonstrate why excellent clinical results can be observed for patients undergoing lung SABR despite them so often being elderly, non-operable and presenting with other comorbidities (see Graph 1.). In our previous 2018 study[89] 74% of patients did not report any grade of toxicity, with only one patient suffering from a rib fracture which was likely due to osteoporosis rather than being radiation induced, according to the patient's medical review notes. The NTCP values for that particular patient for chest wall and lung were 3.0% and 6.3% respectively giving more weight to the theory that the fracture was not radiation induced. The NTCP models used here for rib fracture do not include metrics to account for co-morbidities such as osteoporosis. The limitations of our previous study were the short follow up period. Stam et al.,[84] suggested that the median time to rib fracture was 22 (range 5 -51) months and so longer follow up periods need to be reported. However, for very elderly patients the onset of side effects may be a moot point. Unlike in the UK, all patients in the Stam et al., study were initially planned with no constraints applied to the ribs at treatment planning, and treated with no risk adapted fractionation; almost all patients being treated in 3 fractions. Their conclusions led to them changing strategy to a risk adapted scheme based on minimising rib fracture. In the UK it would be possible to uphold the Consortium suggestions and risk adapt, whilst also taking into account the patient burden, for instance by completing the treatment within a week and having minimal detriment.

Whilst the majority (55%) of clinically treated schedules in our institution are 54 Gy in 3 #, the chest wall is contoured and constraints applied at the planning stage for all patients regardless of intended fractionation. The approach taken when the local service was first clinically implemented was to initially plan for a 3 fraction regimen with corresponding organs at risk (OAR) tolerances, and then alter the fractionation where required to 5 # or 8 #. However, it has also given a database from

which to interrogate data such as presented here. It was shown in our previous study that the 8 # scheme has the effect of slightly reducing the TCP. There may therefore be real practical and clinical advantages for the patient in opting for a 5 # treatment over the 8 # schedule.

Given the advantages of even shorter fractionation (for example, reduced overall treatment time, reduced patient visits and burden on the elderly patient, and possible improved therapeutic gain) alternate schemes could be considered when necessary by utilising an individual assessment of the acceptable TCP and NTCP values for a given patient, in addition to the standard assessment of plan constraints and tolerances. This may also improve patient compliance in some cases.

Conclusion

Benchmark values for NTCPs for lung and chest wall achievable with current planning techniques in the UK have been presented with the mean probabilities being less than 3%. The data supports the observations that many patients tolerate treatment well and few have notable side effects.

Contouring definitions provided in guidance documentation are important for NTCP value consistency and comparability between centres, and studies need to clearly state how contoured structures were created to allow meaningful comparison.

In this study there was no significant difference in terms of NTCP and TCP means for the 8# regimes as compared with the 5 # regimes, where 60 Gy and 55 Gy were shown to be equivalent. This suggests that patients currently offered 8 # could be treated in 5 # without detriment. Individual personalisation of the number of treatments needs to be discussed with the clinical team and the patient to ensure appropriate consideration of the relevant factors for the individual.

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References (included in Chapter 5)

Table 1 Patient characteristics and centre data.

(Table 1 in publication [Thesis Table 3])

Patient cohort **Mean age at treatment** **Tumour stage**	198 (50% Female) 75.2 years (54 - 93) T1: 60%, T2: 36%, T3: 3%, Missing:1%
Planning technique	4D CT (10 bins), Eclipse TPS with + 5mm ITV to PTV expansion, 2 partial arcs, using Acuros (2mm grid), Transport in medium, Dose to water
Dose regimen	3 x 18 = 54 Gy (55%) 5 x 11 = 55 Gy (35%) 5 x 12 = 60 Gy (6%) 8 x 7.5 = 50 Gy (5%) Risk adapted on PTV location as per the UK SABR Consortium Guidelines Versions 4.1 to 6

Table 2. Mean Normal Tissue Complication Probabilities with minimum to maximum ranges in round brackets. Median values also given in square brackets

(Table 2 in publication [Thesis Table 4]).

			Normal Tissue Complication Probability (%)			
Structure	**Model and parameters**	**End point**	**3 Fractions**	**5 Fractions**	**8 Fractions**	**All**
Lungs-GTV	Lyman Kutcher Burman (LKB) model α/β = 3 Gy, TD50 = 29.2Gy, n = 1, m = 0.45	Radiation pneumonitis	3.2 (0.8 – 10.6) [2.2]	2.3 (0.6 – 10.1) [1.6]	1.8 (0.6 – 6.5) [1.0]	**2.8** **(0.6 – 10.6)** **[1.9]**
Chest Wall	Lyman Kutcher Burman (LKB) model α/β = 3 Gy, TD50 = 65.0Gy, n = 1, m = 0.3	Rib fracture	1.0 (0.0 – 9.0) [0.5]	2.3 (0.1 – 55.9) [0.7]	0.8 (0.1 – 3.0) [0.4]	**1.4** **(0.0 – 55.9)** **[0.6]**

Table 3. Same-patient alternative fractionation data. For each patient within each group originally treated with a dose and fractionation schedule in the first, left hand, column, the mean NTCP (and TCP) were recalculated as if the treatment were given in the alternative fractionations along the rows. The shaded entries show the mean NTCP and TCP values obtained as treated clinically. 54 Gy in 3 # was not recalculated for longer fractionations. Median values also given in square brackets. (Table 3 in publication [Thesis Table 5]) It should be noted that only 11 patients comprised the originally treated 60 Gy in 5 # group and so when comparing the mean and median NTCP values between this and the 55 Gy in 5# group, the statistical comparison of groups should be considered showing that the values are similar (see Results), rather than the absolute direction of change.

Originally treated schedule	Lung Normal Tissue Complication Probability, $NTCP_{LUNG}$ (%)			
	54 Gy in 3 #	**55 Gy in 5 #**	**60 Gy in 5 #**	**50 Gy in 8 #**
55 Gy in 5 #	3.1 [1.9]	2.0 [1.5]	2.3 [1.6]	1.5 [1.2]
60 Gy in 5 #	10.6 [9.4]	4.9 [4.4]	4.2 [4.3]	2.1 [2.0]
50 Gy in 8 #	6.4 [1.9]	3.1 [1.3]	4.3 [1.5]	1.8 [1.0]
	Chest Wall Normal Tissue Complication Probability, $NTCP_{CW}$ (%)			
	54 Gy in 3 #	**55 Gy in 5 #**	**60 Gy in 5 #**	**50 Gy in 8 #**
55 Gy in 5 #	4.5 [1.1]	2.1 [0.6]	2.7 [0.7]	1.1 [0.4]
60 Gy in 5 #	11.4 [9.1]	3.5 [2.9]	3.1 [2.0]	0.9 [0.8]
50 Gy in 8 #	6.1 [1.4]	1.9 [0.6]	3.2 [0.9]	0.8 [0.4]
	Tumour Control Probability, TCP (%), α/β = 10 Gy			
	54 Gy in 3 #	**55 Gy in 5 #**	**60 Gy in 5 #**	**50 Gy in 8 #**
55 Gy in 5 #	100.0 [100.0]	100.0 [100.0]	100.0 [100.0]	99.9 [100.0]
60 Gy in 5 #	100.0 [100.0]	100.0 [100.0]	100.0 [100.0]	99.7 [100.0]
50 Gy in 8 #	100.0 [100.0]	100.0 [100.0]	100.0 [100.0]	97.6 [98.5]

Figure 1. Distribution of NTCP values for treated patients, excluding the two $NTCP_{CW}$ outliers of 27.5% and 55.9% which are due to large overlap between the PTV and the chest wall. These are explained further in the discussion. There was no correlation between the parameters. (Figure 1 in publication [Thesis Figure 6])

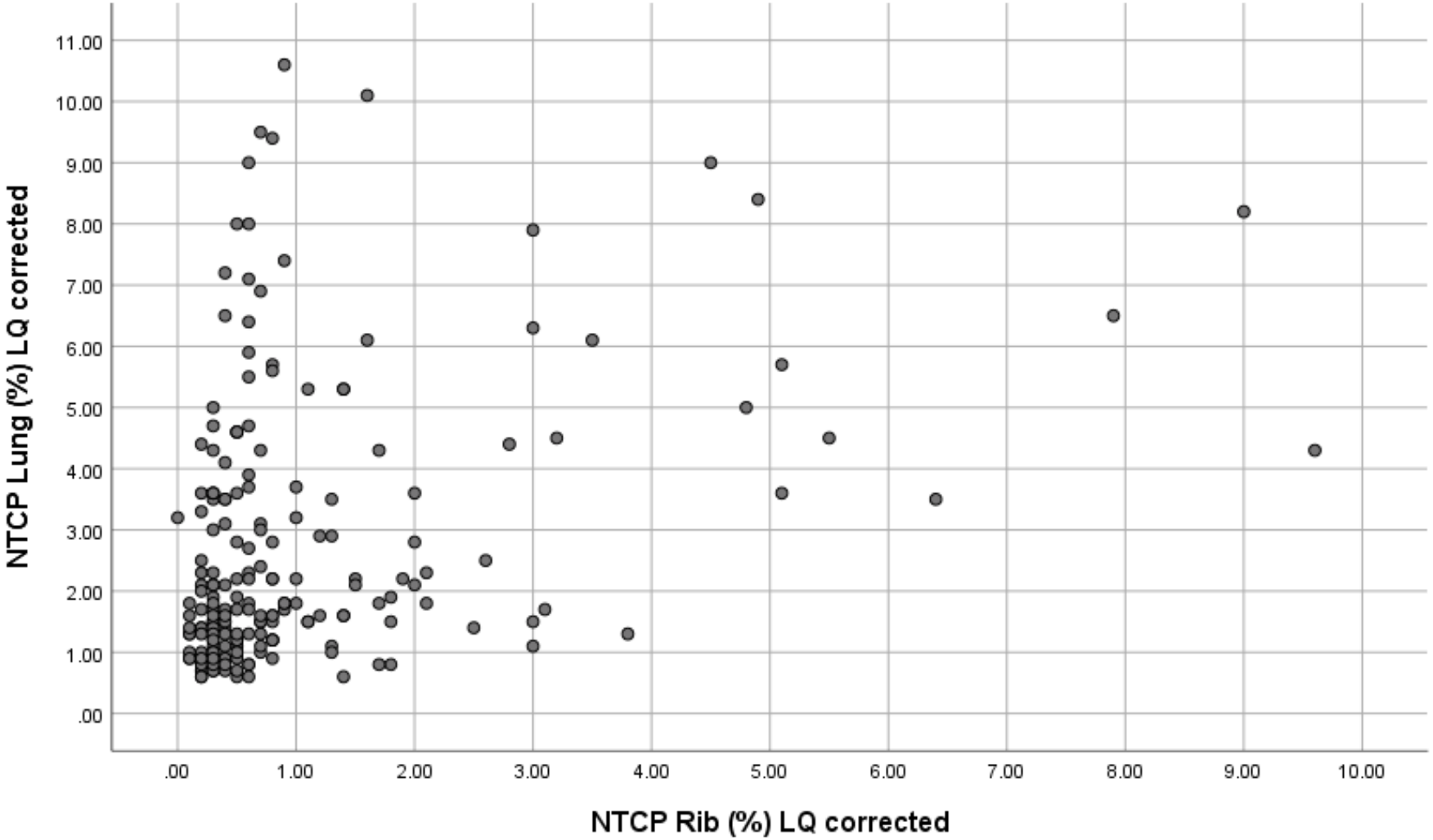
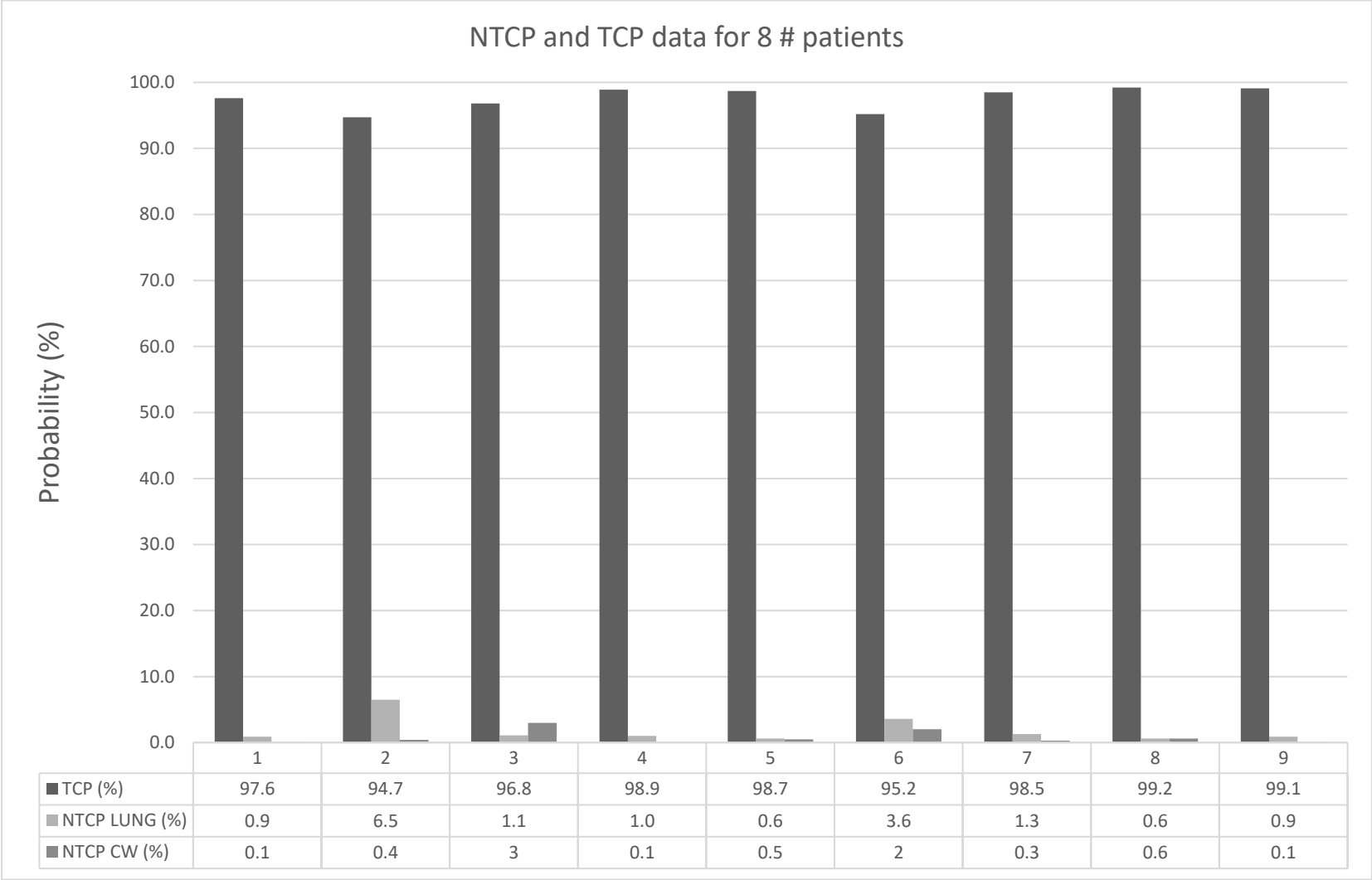


Figure 2. Representative NTCP values for nine 8 # regimen patients, plotted with each patient's corresponding TCP. The probabilities for each patient are also given in the table below the figure. (Figure 2 in publication [Thesis Figure 7])



	1	2	3	4	5	6	7	8	9
TCP (%)	97.6	94.7	96.8	98.9	98.7	95.2	98.5	99.2	99.1
NTCP LUNG (%)	0.9	6.5	1.1	1.0	0.6	3.6	1.3	0.6	0.9
NTCP CW (%)	0.1	0.4	3	0.1	0.5	2	0.3	0.6	0.1

2.3.1. Additional Discussion and Sensitivity Analysis of patient NTCP data

This section of the thesis includes the patient specific NTCP data for the small cohort of 8 fraction patients in the study sample. The data is graphed but also shown numerically below the bars for each patient (1 to 9) in figures 8 and 9. On average, the data analysis showed that these patients could be treated with fewer fractions but on an individual level the probabilities should be independently assessed, as recommended above, and a level of acceptable toxicity chosen by the clinical oncologist team. The data shows that decreasing fractionation increases the potential risks of toxicity for both lung and chest wall, however this is most marked for two or three patients. For patients 2, 3 and 6 maintaining a 50 Gy in 8 fraction dose regimen would allow these normal tissue control probabilities to remain close to or below 5%.

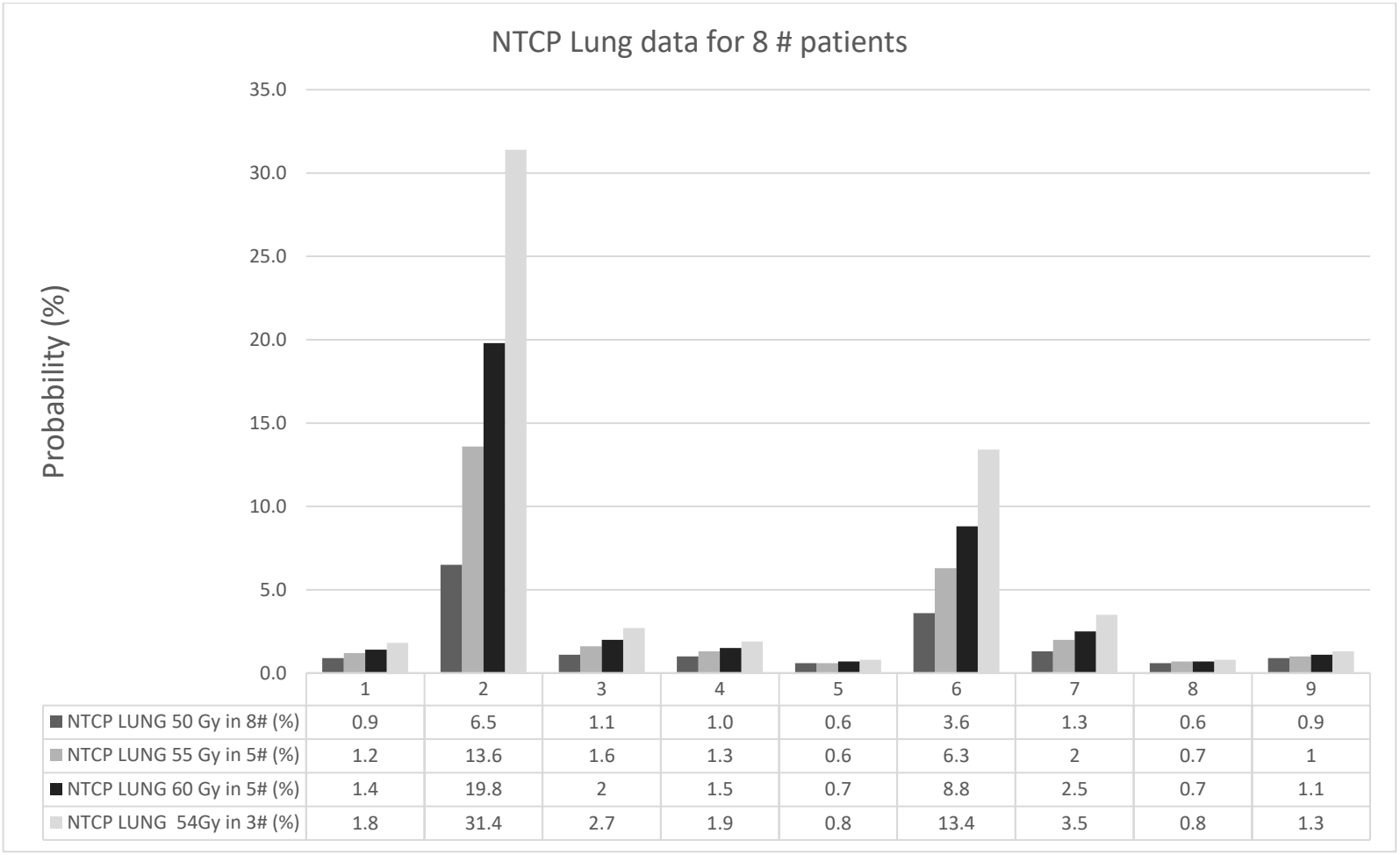
With reducing fractionation, patients 2 and 6 show the most extreme changes in $NTCP_{LUNG}$ and patients 3 and 6 show the greatest change in $NTCP_{CW}$. All these patients had larger than average tumours with PTV volumes of 111.1 cc (Patient 2), 82.1 cc (Patient 3) and 133.4cc (Patient 6) compared to average PTV volume of 34.7 cc. This is likely to be significant because the distance from the high dose areas surrounding the treatment volume to the organs at risk is smaller for these patients, and consequently side effects related to proximal normal tissue are more possible due to the higher incident doses. The distances between PTV and OARs are highly variable depending on the location of the tumour. Slide 11 of Section 2.4 demonstrates the variable location of the tumour masses for this study cohort. However, tumours can abut the chest wall (meaning zero distance to this organ) or can typically be between 4 or 5 cm away from this and other OARs if centrally located within average sized lungs.

For patient 2 the reduction in fractionation increases the $NTCP_{LUNG}$ the most, with almost five times the probability of toxicity occurring for a 3 # treatment than at 8 # (Figure 8). On inspection, not only did this patient have a larger PTV, but their overall lung volume was smaller than average, meaning that a larger proportion of the lung was taken up by tumour which has affected the DVH for the Lungs-GTV structure. The tumour was not large enough (or vastly peripheral) to impinge on the chest wall which is why the $NTCP_{CW}$ is not affected in the same way. All probabilities for this patient for chest wall toxicity are below 1.5% regardless of varying fractionation and dose. This patient was male and 79 years at treatment. During treatment, they self-reported Grade 1 shortness of breath (with moderate exertion) and Grade 1 fatigue (relieved by rest). They survived for a further 35 months with zero toxicity reported at subsequent follow up appointments.

For patient 3 (92 years, male), the tumour is located in the apical right lung, upper lobe, but the lungs are close to average volume so the $NTCP_{LUNG}$ is less affected by the change in fractionation. However, the PTV overlaps with the chest wall structure, which gives rise to the high doses in the DVH and the pronounced effect when reducing fractionation observed in Figure 9. This patient reported mild chest wall pain and fatigue during treatment (Grade 1) but subsequently had no reported toxicity at follow up, prior to passing away four years later.

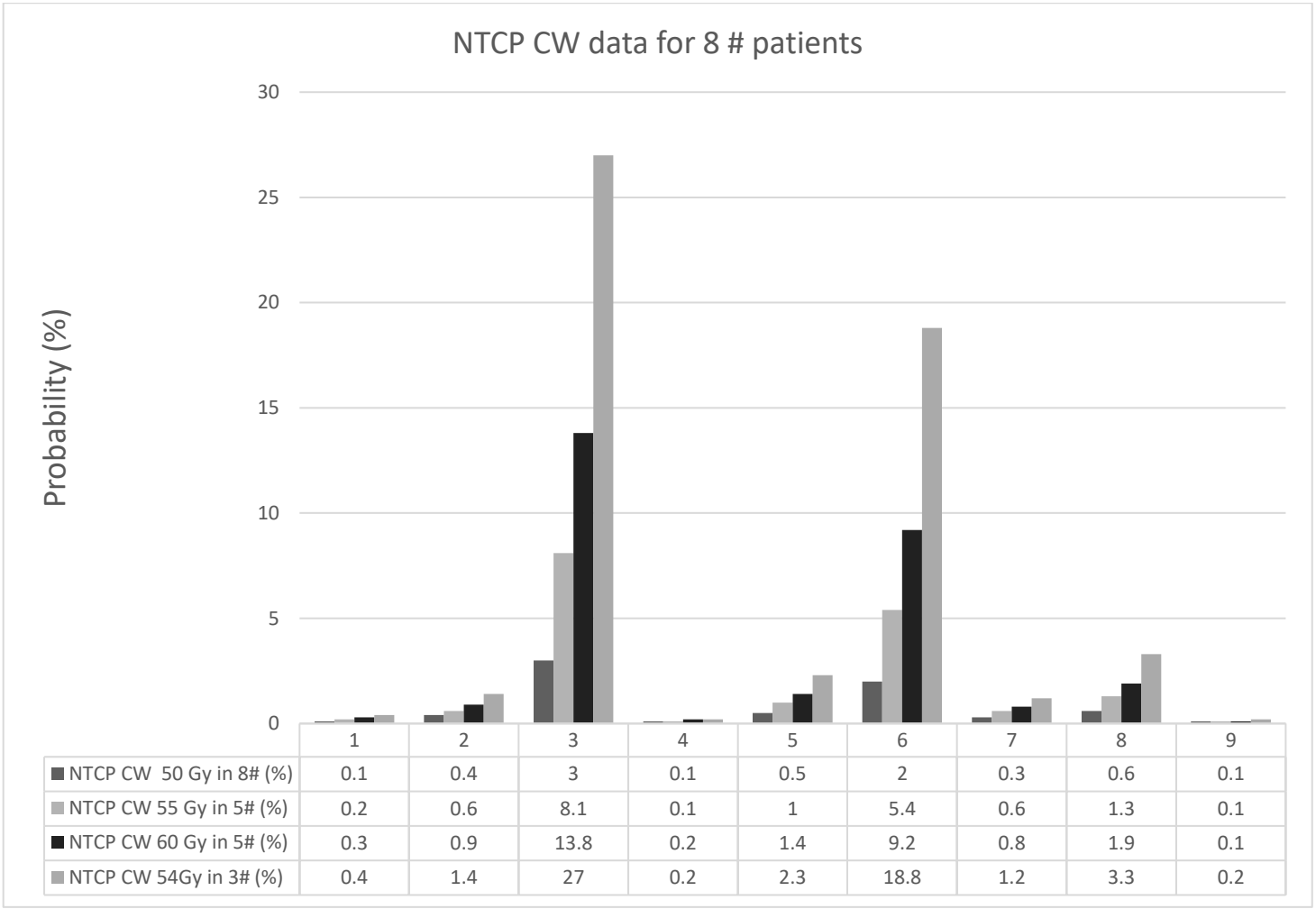
For patient 6 (58 years, female), both the $NTCP_{LUNG}$ and $NTCP_{CW}$ increase with shortening regimens with the resultant $NTCP_{LUNG}$ at 3 # being 13.4% and the $NTCP_{CW}$ rising from a 2.0% to 18.8% probability of side effects. On investigation, patient 6 had the largest PTV in the studied group, which is at the maximum limit of allowable lung SABR volumes (assuming a 'tumour' volume of 5cm x 5cm x 5cm). The SABR consortium exclusion criteria do not allow tumours greater than 5cm to be treated but the guidance does not specify if this applies to the GTV or the PTV. Many centres take this limit to apply to the GTV because PTV margins may be centre specific and therefore vary. The plan quality metrics for PTVs greater than 90 cc are the maximum tabulated suggesting that larger tumours are less suitable for SABR. This tumour was not only large but also highly incident to the left chest wall with the PTV overlapping the ribs. The recorded toxicity at the time of SABR treatment showed Grade 2 shortness of breath, fatigue and oesophagitis and Grade 1 chest wall pain (mild). Unfortunately, they also developed brain metastases on treatment and subsequently passed away 2 months after radiotherapy, with no thoracic toxicity data recorded due to incomplete follow up.

Figure 8 (not included in the accepted journal publication). The data is given for individual patients treated with 8 fractions. NTCP values for nine 8 # regimen patients, plotted for each patient showing the change with fractionation. The probabilities for each patient are also given in the table below the figure. It can be seen that for patients 2 and 6 the fractionation change would have made a significant impact on the $NTCP_{LUNG}$ and potential lung toxicity.



	1	2	3	4	5	6	7	8	9
NTCP LUNG 50 Gy in 8# (%)	0.9	6.5	1.1	1.0	0.6	3.6	1.3	0.6	0.9
NTCP LUNG 55 Gy in 5# (%)	1.2	13.6	1.6	1.3	0.6	6.3	2	0.7	1
NTCP LUNG 60 Gy in 5# (%)	1.4	19.8	2	1.5	0.7	8.8	2.5	0.7	1.1
NTCP LUNG 54Gy in 3# (%)	1.8	31.4	2.7	1.9	0.8	13.4	3.5	0.8	1.3

Figure 9 (not included in the accepted journal publication). Supplementary $NTCP_{CW}$ (chest wall) data for the same nine 8 # regimen patients as shown in Figure 8. The probabilities for each patient are also given in the table below the figure, as they would vary with fractionation and dose. Here patients 3 and 6 show the greatest changes in probability with altered dose fractionation.

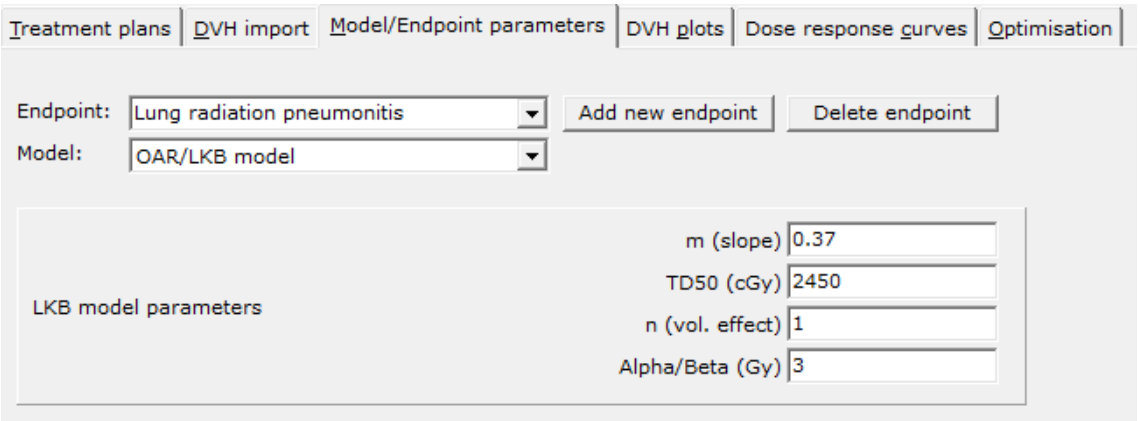


	1	2	3	4	5	6	7	8	9
NTCP CW 50 Gy in 8# (%)	0.1	0.4	3	0.1	0.5	2	0.3	0.6	0.1
NTCP CW 55 Gy in 5# (%)	0.2	0.6	8.1	0.1	1	5.4	0.6	1.3	0.1
NTCP CW 60 Gy in 5# (%)	0.3	0.9	13.8	0.2	1.4	9.2	0.8	1.9	0.1
NTCP CW 54Gy in 3# (%)	0.4	1.4	27	0.2	2.3	18.8	1.2	3.3	0.2

2.3.2. Biosuite NTCP model and Limitations

The probabilities presented are highly sensitive to the modelling parameters chosen and varying the parameters within Biosuite results in different NTCP values (Figure 8). The key parameters for use in the LKB NTCP model (Equation 1, Section 1.3) are the α/β ratio, n, m and the TD50, as described further below and shown in Figure 10.

Figure 10 Biosuite LKB model parameter interface. All parameters must be entered in the correct units in order to calculate the NTCP estimates.



The α/β ratio generally used for organs at risk is 3, however this is much discussed in the literature. Using patient 6 identified in the graphs above as an example, varying the α/β ratio for the lungs to typically given values of 2 and 4 in the literature,[90] instead of 3, results in probabilities of $NTCP_{LUNG}$ = 3.9% and $NTCP_{LUNG}$ = 3.5%. I have chosen the intermediate value of 3 for this study. Varying the α/β ratio for the chest wall in the same way results in probabilities of $NTCP_{CW}$ = 2.5% and $NTCP_{CW}$ = 1.7%. Thus, the effect is relatively small and this is representative of the group. The α/β ratio is used in Biosuite to convert doses and DVH doses to 2 Gy equivalent doses (EQD2) for the purposes of correcting for the large fraction sizes seen here using the LQ (linear quadratic) model, and similarly to correct the DVH dose bins for the TD_{50} as explained below.

The parameter n relates to the volume dependence of organ effects, and how the complication probability changes with the full or partial volume of the structure irradiated to a fixed dose. For the lungs, the parallel nature of the organs is clear and well known, and so n is set to unity. This means that lung function can be maintained even when a small area receives a high dose. For the chest wall (which includes the ribs and interconnecting tissue within the structure outlined) it can be argued that a similar situation exists in that a small area may receive a high dose (d_{max}) without compromising the integrity of the 'organ'. However, each

individual rib may exhibit some serial behaviour in that a very high dose to a single rib may cause a fracture, although not inhibit completely the ability to move the chest. Therefore, the location of the d_{max} is likely to be crucial. In this study the structure includes several ribs and the muscle and connective tissue between them and so the volume parameter has been set to unity. But, varying n will result in large changes to the resultant probability, for example changing n to 0.5 for patient 6 gives an NTCP of 10.5% for the chest wall. If the 'organ' was completely serial the NTCP values (using n = 0) would approach 100%. Using n = 0, would tend to predict higher chest wall toxicity than seen in the clinic locally.

The parameter m describes the NTCP versus dose curve, slope steepness. Both the structures investigated are relatively sensitive to this parameter, but much less than the volume dependence above. For patient 6, increasing the slope parameter, m, to unity raises the NTCP to approximately 25% for both lung and chest wall, whereas reducing m to 0.1 gives NTCP values of zero for both structures, which is unrealistic compared with the observed population side effects.

The TD_{50} is the uniform dose (Gy) that would result in a 50% complication probability of the 'normal' tissue in 5 years. The doses used for these parameters are gathered from historical data tracing back many decades[62] and they are usually presented in absolute physical dose in 2 Gy fractions (EQD2). In order to alter the DVH (which represents subvolumes irradiated non-uniformly) into usable data it is reduced[91] to an 'effective fractional volume', uniformly irradiated to the dose which would give rise to the same probability of complication.[92] Some publications present the TD_{50} in EUD which can lead to confusion if the units of the parameters are not appropriate for the tool or application. For example in Stam et al., the TD_{50} values appear ten times larger as they use EUD nomenclature.[84] The EQD2 values used in Biosuite for lung (2450 cGy, whole volume) and the chest wall (6500 cGy) are both taken directly from Emami et al.,[62] The smaller the dose for this parameter the larger the likely complication probability. For patient 6, reducing the TD50 from 2450 to 1450 cGy for the lung changes the NTCP from 3.6% to 12.1%. Reducing the TD_{50} from 6500 to 5500 cGy for the chest wall changes the NTCP from 2.0% to 3.4%. It is worth reiterating here that treatment planning algorithms have changed over this historical data collection and therefore affect the result of using 'doses', regardless of the unit definition.

Clearly, the results presented here are only comparable between regimes when all parameters are kept consistent between repeated calculations for each scenario. Different sets of parameters are required for different normal tissue complication endpoints. Also, as the

models only use a selection of parameters in order to reduce the complexity of the calculations, there are many assumptions being made which are important to consider as potential confounding factors. These include dose units, as previously mentioned, voluming accuracy, treatment planning algorithm (A, B, C or Monte Carlo, for example) and calculation matrix, and also patient population characteristics which may not be consistent between different studies. The use of the LQ model as a basis for NTCP or TCP calculations has not been validated in this work. Theoretically, there are discrepancies which cannot be accounted for with such few parameters, for example, the two types of mechanism responsible for cell death cannot occur independently from each other. If cells are killed with 'single hit' α there are fewer that can be exposed to the potentially repairable β kill mechanisms requiring two 'hits' as cells within a volume are finite. There are clearly more factors at work, however, experimentally the LQ model still fits plenty of tumour control data including those where fraction sizes are between 18-20 Gy.[45] In this thesis the LQ model has been used in a comparative way under the assumption that the empirical modelling is still valid at these high fraction sizes, which could still be a limitation of this work. The treatment NTCP or TCP calculated from set parameters has been compared with other scenarios, rather than trying to obtain absolute cell death for the organ.

Whilst probabilities are quoted here and in the literature as percentages in almost absolute terms, these differing factors will have an effect on the usefulness of these values. It should also be noted that even a small probability of complication, if doubled, could give rise to a significant number of patient toxicities. It may be useful in future work and when looking at previous studies, to band together ranges of typically expected toxicity (for example, less than 5% or 5 – 20%) in order to be able to relate these findings between different centres.

2.4. UK SABR Consortium Meeting 2019 Poster and Proffered Talk

A poster and a proffered talk were submitted to the annual UK SABR Consortium meeting in 2019. Both these submissions were peer reviewed by the meeting organising committee and accepted. The poster was an outline of the expectations of the entire doctoral project (not shown), and the talk was based on the analysis of the data captured for the main project with the data outcomes sex disaggregated in terms of outcome (overall survival). The talk entitled, 'Are Women Invisible in SABR Research?' was well received and although not part of the original research aims, the work was an interesting addition in that it showed that there was little gender bias in the local clinical service. The slides are given here as they were presented at the conference.

Published programme: https://www.sabr.org.uk/wp-content/uploads/2019/11/UK-SABR-Conf-programme-for-publish2019.pdf

Additional Notes on Slides:
Slide 8 – A Chi-square test was used to assess the difference in survival between men and women using IBM's SPSS Statistics 25 package. The confidence intervals are of interest because although they mostly overlap, the upper boundary for the men is much greater than for women. This is explored further on the next slide.

Slide 9 – Failure rates were equally split except in the case where the patient had distant metastases, in which case men had much increased rates than women.

Slide 10 - the first bar in the graph, which is unlabelled, shows tumour stage data that were 'Unknown'. This highlights the issues of missing clinical data from the records.

Slide 11 – Location of tumours for men (blue) and women (red). No statistical testing has been applied. This data was obtained as part of local auditing of 4D CT scans using scripting tools. The script took the position of the tumour relative to an arbitrary central point in the lungs for each patient, and then plotted it on a standardised central point in an 'average lung', for the purposes of mapping the general distribution of tumours at our radiotherapy centre. Labelling can also be applied to show locations of tumours where the motion was greater than 1cm.

Slide 12 – The absolute numbers for the 60 Gy row are 2 men, 9 women out of eleven.

Slide 13 - It should be noted that the term, 'Equity of Service' refers to the overall survival and toxicity rates and does not infer access equivalence, or any other equivalence between groups.

There is a risk of bias in patient selection prior to SABR treatment which may influence these results.

Are women invisible in SABR research? (Abstract as submitted)

Jenny Marsden

Aims

Evidence based cancer treatments are based on averages. Research done (occasionally even in randomised controlled trials) intentionally aims to remove the range and distribution of participants to avoid bias. However, are these outcomes really then applicable to all? Are there some 'invisible women' lurking in our data?

Content of Presentation

There may be a problem with our healthcare evidence base. But it's okay. It probably only affects about 50% of our data points. Taking instruction from Caroline Criado Perez [1][93] we decided to re-analyse our previously published SABR lung outcomes as sex disaggregated data.

Sex disaggregation may be particularly important for the SABR evidence base where clinical data and small trials are prevalent. As healthcare professionals, are we presenting what suits the average without fully appreciating how men and women are impacted differently? For elderly patients with different comorbidities, is it reasonable to consider these differences could affect access, ease of radiotherapy treatment planning and even survival outcomes?

Relevance/Impact

As we move towards big data analysis for various aspects of healthcare, we cannot afford to assume our results apply to all; and the sex divide is purely the start of assessing data gaps. For SABR studies and reporting of clinical outcomes, sex disaggregation is the first step to understanding potential differences in our results.

Outcomes

Median overall survival for men was 41.0 months (95% CI 30.1-51.9) and for women, 36.0 months (95% CI 27.0-44.9), ($n = 200$, $p >> 0.05$ so not significant). Further data will be presented.

[1] C. Criado Perez, *Invisible Women: Exposing Data Bias in a World Designed for Men*. Chatto & Windus, 2019, p. 432.

Figure 11. Proffered Talk Slides SABR Consortium Meeting November 2019 for the abstract above.

NHS
Hull University Teaching Hospitals

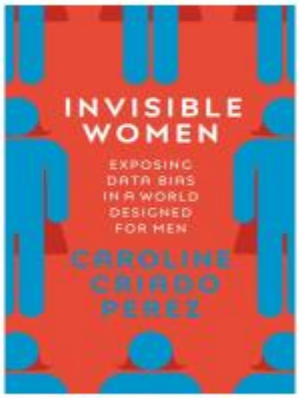
Are women invisible in SABR research?

Jenny Marsden

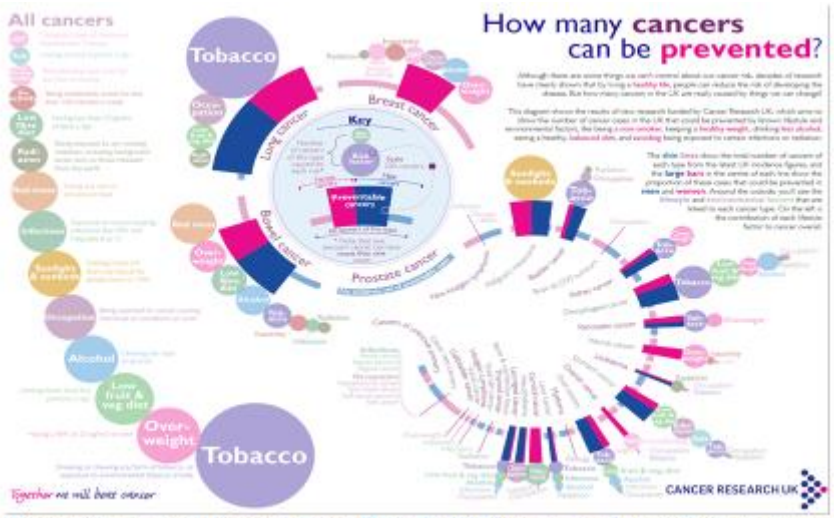
Radiotherapy Physics

Remarkable people. Extraordinary place. 1

NHS
Hull University Teaching Hospitals



Remarkable people. Extraordinary place. 2



https://scienceblog.cancerresearchuk.org/2011/12/07/the-causes-of-cancer-you-can-control/

Table 1. Summary population attributable fractions

	All cancers excluding	
	England	
	PAF (%)	Attrib. cases
Males		
Cancer incidence	152,891	
Tobacco smoking	17.3	26,375
Overweight and obesity	5.2	7,960
Occupation	4.9	7,458
Radiation—UV	3.9	5,899
Insufficient fibre	3.1	4,713
Alcohol	3.0	4,634
Infections	3.0	4,539
Processed meat	2.0	3,096
Radiation—ionising	1.7	2,675
Air pollution	1.1	1,636
Insufficient physical activity	0.5	794
All of the above	38.0	58,141
Females		
Cancer incidence	146,862	
Tobacco smoking	12.1	17,738
Overweight and obesity	7.5	11,036
Infections	4.0	6,083
Radiation—UV	3.8	5,541
Alcohol	3.5	5,202
Insufficient fibre	3.3	4,917
Occupation	2.4	3,528
Radiation—ionising	2.1	3,128
Not breastfeeding	1.4	2,117
Air pollution	1.0	1,442
Processed meat	0.9	1,330
Postmenopausal hormones	0.7	1,089
Insufficient physical activity	0.5	801
Oral contraceptives	0.5	667
All of the above	36.4	53,480

The fraction of cancer attributable to modifiable risk factors in England, Wales, Scotland, Northern Ireland, and the United Kingdom in 2015.

Why should we care about sex disaggregated data?

- Patient demographics, included sex, are usually (but not always) recorded in SABR research
- BUT
  - Outcomes and other variables are **rarely then separated by sex**
  - The outcomes may be pooled across the patient cohort because it is assumed there are no differences
  - This can lead to a 'Gender Gap' in the research conclusions
  - Evidence based research (hopefully) drives guidance and good practice, and ultimately funds health policy
  - Based on what could be poor multivariate analysis of the data

Was the question asked?

- Good examples:
- Timmerman et al., 2006. n = 70, 34M, 36F. No difference in overall survival or toxicity between men and women.
- Zhao et al., 2016: No difference in lung toxicity rates between male and female patients over 88 pooled studies (although there were twice as many men studied)
- Klement et al., 2016: sex was not a factor in predicting early death post SABR
- Murray et al., 2015 (UK lung SABR outcomes): No difference in overall survival or toxicity between UK men and women. Toxicity differences...?

Poor examples:

- Chang et al., 2015 (STARS and ROSEL trials)

	SABR group (N=31)	Surgery group (N=37)	p-value
Sex			0.73
Male	14 (45%)	15 (41%)	
Female	17 (55%)	22 (59%)	

- Navarro-Marin et al., 2016 (no comment on the bias)

Table 1. Patients Characteristics (N=38)

Variable	n	%
Sex		
Men	36	94.7
Women	2	5.3

- Shaverdian et al., 2016 (No data presented at all!)

Was the question asked?

- Good examples:
- Timmerman et al., 2006. n = 70, 34M, 36F. No difference in overall survival or toxicity between men and women.
- Zhao et al., 2016: No difference in lung toxicity rates between male and female patients over 88 pooled studies (although there were twice as many men studied)
- Klement et al., 2016: sex was not a factor in predicting early death post SABR
- Murray et al., 2015 (UK lung SABR outcomes): No difference in overall survival or toxicity between UK men and women. Toxicity differences...?

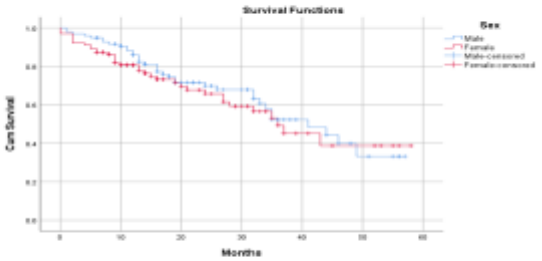
Example: KiTEC draft report on SABR for oligomets – outcomes were not disaggregated

(Thanks to Anastasia Chalkidou who may elaborate on why this might be on Friday)

Sex		
Male - N (%)	947	66.6%
Female - N (%)	475	33.4%

Hull Lung SABR Data

- n = 200, 50% women, 50% men
- Overall median survival:
  - 37 months (95% C.I. 30-44)
- Men median survival:
  - 41 months (95% C.I. 30-55)
- Women median survival:
  - 36 months (95% C.I. 27-44)



But, p>>0.05, so not significant (χ^2 test)
But, those confidence intervals look interesting...

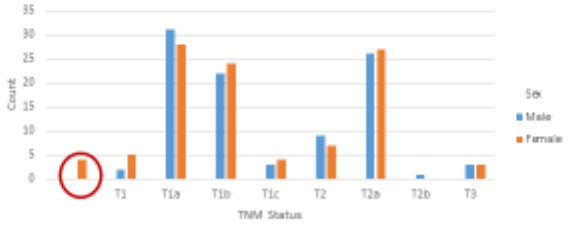
The joys of automated data

- Maybe the men are younger than the women?
- Maybe men have smaller tumours than the women?
- But, women's lungs might be smaller than men's anyway, so it could be a relative effect?
- And, what about toxicity?
- Failure rates?

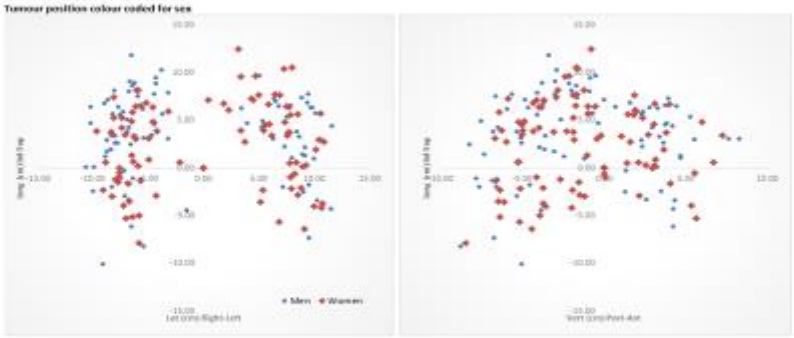
- No: Men older by 3.4 years (p<0.05)
- No: Male PTVs larger by 7.6 cc (p<0.05)
- Okay, so lets take a ratio of the lung volume to the PTV, and use that to standardise.
  No: Ratios the same (p = 0.2).
- 71% of all patients reported no side effects, 76% of women reported none, 67% of men reported none, p>>0.05
- 50:50 split M:F between local and regional failures. 75:20 M:F for distant mets

The joys of automated data

- Maybe the men have less advanced tumour staging than women?
- No
(but possibly some missing data?)



Was it location of tumour?



Doesn't look like it...but not statistically tested yet...

Thanks to Carl Horsfield

The problems of missing data

- Maybe the performance status for women was worse?
- Using choice of prescription dose (conservative or very conservative) as a proxy..

Total Dose (Gy)	Men	Women
50	44.4%	55.6%
54	56.4%	43.6%
55	42.0%	58.0%
60	18.2%	81.8%

$p < 0.05$, so this is **significant**! (χ^2 test)

So, are women invisible in SABR research?

- Not invisible! There are some excellent SABR research studies that perform multivariate analysis of endpoints, and state them explicitly in their conclusions
- But, some researchers have not explicitly compared the endpoints between men and women.
- In the local data I have presented:
  - There are no significant differences in Overall survival and Toxicity rates for men and women. EQUITY OF SERVICE!
  - There appears to be some inequity in the patients receiving conservative or very conservative dose fractionations.

So, are women invisible in SABR research?

- My request:
  - **For you to reflect and report on the absence or presence of any sex disaggregated differences in your outcomes.**
  - **For peer reviewers to question if the patient sample may create a 'Gender gap' which ought to be considered and commented on.**

A few more interesting things I learned from Caroline:

- Pre-clinical studies often don't report which sex is used, or use all one sex (e.g. 80% of pain studies used only male mice).
- Aspirin may not work to prevent heart attacks in women.
- Pain pathways in men and women are different
- TB kills more women globally than any other maternal mortality cause
- There is no requirement for a female crash test dummy to be used in the driver's seat of EU cars.
- Flu vaccines for each sex have been proposed as women develop higher antibody responses than men.
- Valium was never tests in RCTs on women.
- Average phone screen size: 14 cm; too large for the average woman's (and many men's) hands!

3. Critical Appraisal, Discussion and Conclusions

3.1 Introduction

The work set out in this thesis demonstrates that prospective radiobiological calculations can be used for personalising lung SABR to reduce the personal burden of treatment attendances on patients themselves. Baseline data for the TCP and the NTCP plans meeting the UK SABR Consortium guidelines have been presented for the PTV, lungs and chest wall. This is a valuable addition to the literature and can form the basis of further quality improvement studies. Whilst the TCP stays relatively high with varying fractionation, the NTCP estimates can more than double when using fewer fractions, even though they remain relatively small for the population as compared with standard radiotherapy. The service evaluation using the questionnaire shows that typical patients in this cohort are willing to have personalised radiotherapy, and are not deterred from moving away from standard of care, generally following health care professionals' guidance on the matter.

The work was carried out from August 2018 until August 2021 as part of the taught doctorate and HSST training programme. This time period covered the COVID-19 worldwide pandemic which saw many customary processes in health care necessitating urgent review and alteration. A significant change in the world of radiotherapy was the move towards reduced fractionations, for example for breast radiotherapy from fifteen to five following the FAST FORWARD trial.[94] This trial showed the shorter regime to be non-inferior and was brought in clinically prior to the evidence being formally published in order to reduce footfall within cancer hospitals. Reduced footfall in hospitals and other public spaces was the main strategy employed by the UK government to reduce pressure on the NHS in order to provide sufficient emergency care for admitted COVID-19 patients. Many centres looked towards hypofractionation of regimens using radiobiological calculations such as the LQ model and as a result professional practice for medical physicists changed.[95] Many centres investigated implementing single fraction SABR treatments for lung; although locally in Hull (the author's centre) we did not due to the risks of an increase in potential side effects and our capability to adequately manage patient social distancing and logistics within our building. Typically treating lung SABR with a single fraction of 30-34 Gy, as recommended by altered UK consensus[76] would result in an increase in toxicity compared with three fractions, however in order to reduce this likelihood the patient inclusion criteria were narrowed to those with tumours < 2cm and > 1cm from the chest wall, away from the central 'no-fly' zone'. Examples taken from this cohort show that for such patients the TCP for a single fraction can be maintained close to

100% without increasing toxicity over 3-4% (e.g., for a 30cc tumour, TCP = 100%, $NTCP_{CW}$ = 3.0%, $NTCP_{LUNG}$ = 2.6% using the same parameters as described earlier in this thesis). Individual patients were also *prospectively* managed to provide treatment before important dates where this was possible in the schedule, for example to allow ten days isolation before further cancer surgery (which still continued during the pandemic), national lockdowns and family or support system availability and closure of transport services or travel restrictions. Some centres implemented these shorter fractionations for the period of lockdown, others erred on the side of caution and continued to treat with existing schema under other policies such as social distancing, testing of cancer patients for COVID-19 prior to radiotherapy, and enhanced barrier nursing/care. Thus, although the patients themselves did not request shortening or alternative fractionations, the impetus to shorten radiotherapy treatments was nevertheless present with the pandemic being the primary motivator. Interestingly, reduction of fractionation to other dose and fractionation schedules was not generally observed. However, there would be no reason why five fractions could not be marginally reduced to four, and similarly for the other schemes, provided that the equivalent radiobiological doses were maintained. There may have been reluctance to do this because of the monitors and measures placed on services which aim for homogenisation of protocols. Outlying centres can be identified from the data returns provided by RTDS (RadioTherapy Data Set) and protocol variance would need to be justified.

Evidence from Bertholet et al., suggests that physicists welcomed the increased use of hypofractionation suggesting that, at least from a professional view point, it may be a long lasting change for a range of sites.[95] The authors also reported that the implementation, or increased use, of hypofractionation was the most widely implemented change (47% of respondents), indicating that the pandemic forced and supported these measures. The radiotherapy climate has therefore shifted towards radiobiological adjustments of fractionation during the period of the author's research.

This section critically reviews the methods presented in this thesis and appraises some of the literature which was latterly published and is similar to this work. Following this discussion, the conclusions of the research are presented.

3.2 Current evidence of tumour control and toxicity

As detailed in Chapter 1, the huge technological advances in radiotherapy mean that evidence based data on tumour control and toxicity needs to be carefully placed within the period of data collection. This knowledge will also impinge on reported TCP and NTCP values, the expectation being that improvements to tumour control are made with advancing time,

together with a reduction in toxicities. In this research TCP values are, or approach, 100% for all the regimens investigated, and the NTCP was low (< 5%).

Rib fracture incidence has been clinically reported at between 2 and 40%[96] where the upper incidence may be a result of poor plan quality and a non-risk adapted schedule, or simply patient cohort choice and tumour location near the ribs. Similarly, for radiation induced pneumonitis the occurrence rates can be between 9 - 40%. Chest wall pain and difficulty in breathing can be a symptom of both rib fracture and radiation pneumonitis, whereas a dry, unproductive cough is more symptomatic of radiation pneumonitis alone. Obviously these are all also symptoms of the underlying lung cancer, which is why asymptomatic diagnosis is important. Clinicians need to be able to prescribe the correct therapy to either cure side effects or address the cancer again. The wide range of incidences may also reflect the period of data collection. It is important to implement radiotherapy with the most up to date, evidence based, techniques available whilst measuring patient outcomes so that incidence rates reflect what patients are more likely to experience. The 2015 study by Aoki et al.,[97] reported rib fracture clinical incidences of between 12.9% and 55.7% depending on dose and fractionation, however they reported that none of these fractures was 'clinically significant'. The study population was, however, small, 70% male, and utilised 3D treatment planning and delivery before the advent of 4D CT in their centre, thereby demonstrating that even the literature in the last five years may not be representative or applicable for current radiotherapy patients.

Rib fractures may be symptomatic or asymptomatic and as treatment is limited, it is questionable whether asymptomatic rib fractures as seen on follow up imaging need to be considered at all as a patient toxicity. There is limited data on the underlying effects of irradiating bone,[98,99] and studies have been inconclusive as to the relationship between bone strength, mineral content and the vascular changes which affect osteopenia (low bone density for age). Thibault et al.,[96] identified osteoporosis as a potential characteristic of interest in their paper on chest wall toxicity and found that the condition predicted rib fracture ($p < 0.001$) in addition to female sex ($p = 0.024$). This was a medium sized study (50 rib fractures were observed) but there appears to be few works investigating this further, and it has not been highlighted in the guidance or standard protocols. Although the incidences of rib fracture in the patient cohort studied here were low, recent data has come to light over the last few months that six further patients were found to have rib fractures, five of whom were women. It would therefore be highly beneficial to study this further as it may be that osteoporosis (as a comorbidity) should be an indicator of extending the fractionation of lung SABR to avoid this

side effect. As long term toxicity data is not recorded well and cannot be easily data mined, a more robust method of capturing rib fractures with times and dates post treatment would be advantageous for this type of research.

In the paper by Hopewell[99] the radiation dose fractionation data for rib-fracture in breast cancer patients suggests that an α/β ratio of between 1.8 – 2.8 Gy may be more appropriate, so it would be interesting to repeat this work using this range. The value used here was $\alpha/\beta = 3$ Gy, which is standard for late responding tissue effects, however values of 2 and 4 were briefly investigated (Section 2.3.2). Shortness of breath, chest pain and cough may be significant side effects to contend with for elderly and infirm patients with additional health concerns. Although these effects are most likely to be short lived and acute, some may persist and become chronic. For Grade 2 pneumonitis, patients are treated with high dose steroids such as prednisolone but do not usually need to be admitted and the irritation usually subsides with time. This is the lung end point investigated in this work. Hospitalisation with oxygen therapy is required to treat Grade 3 pneumonitis but this is very rare and only usually occurs in SABR patients when other co-morbidities and/or low functional reserve are present. Fatal pneumonitis was observed in early IMRT studies for the treatment of mesothelioma, and this prompted the author's centre to introduce an additional tolerance dose for the combined lungs ($V_5 < 60$Gy) which is still used for all lung planning including SABR.[100] Rib fractures occurring from radiotherapy are often asymptomatic, but if there is pain, analgesics are prescribed to be taken at home with the symptoms expected to recede in a few months. It is incumbent on individual institutions to audit their outcomes and toxicities in the UK, but there is no mandated requirement to report these specific values and no national UK database. There are some recent moves to address this, with the introduction (or mandate) of NHS wide software, 'ProKnow' (Elekta, EKTA-B.ST), which is intended to be a repository for treatment planning data (the RT DICOM dataset) across England to allow collective data analysis. It will also be possible to map related toxicity data. However, there is still a lack of good quality clinical outcome and toxicity data which would need to be captured and linked to the radiotherapy treatment plans to enable meaningful results. The author recommends that a UK national registry is considered in addition to the ProKnow work programme.

More technically advanced methods of treatment planning such as dose 'painting', utilisation of standard planning models (e.g., 'Rapidplan', Varian) and careful adherence to plan quality metrics are now expected. The planning technique for patient data used in this thesis was consistent throughout, using two half arcs with the Acuros dose calculation as per local clinical

procedure. Although this adds strength to the study outcomes, it is important to understand that for different planning and treatment techniques, for example full arcs or static fields, the TCP and NTCP baseline ranges presented may not be comparable.

In the Dutch study by Stam et al.,[84] all patients received a standard 3 x 18 = 54 Gy regimen which resulted in 13.7% of patients receiving a rib fracture. Their model was subsequently set to keep the risk of rib fracture below 5%, but this could have potentially been achieved by considering the chest wall as an organ at risk during initial treatment planning and adjusting the plan accordingly. Longer alternative fractionation for those patients where the chest wall did not meet tolerances could then be employed, as is standard practice in the UK. Based on regional data collected by the author for three neighbouring cancer centres in the UK, typical toxicity rates for rib fracture and pneumonitis are less than 5% (author's correspondence based on attendance at the Yorkshire Regional Strategic Cancer Network meeting, 2018: Leeds Cancer Centre quoted symptomatic rib fracture at 5.5%, and grade 3 pneumonitis at <1%). There is no additional information available to understand why these rates are present, and looking at the comparative dose fractionations used in Leeds there appears to be a larger proportion of longer schemes than in the data presented here, which one might presume would give rise to fewer observed toxicities. It may be that as Leeds began SABR earlier, the techniques used (static beams, or IMRT, rather than arcs) contributed to the raised level of rib fractures. Only 1 rib fracture in the 200 patient sample was observed in the Hull patient cohort, to date. In critically analysing this sample, a further 100 patients were reviewed up to summer 2021 and two additional symptomatic rib fractures were reported via the clinical oncologists, giving an approximate rate of 1% locally. The occurrence of rib fractures in the UK appears smaller than that of other studies in other countries, which may be due to the use of tolerances at treatment planning as advised in the Consortium guidance. However onset time to rib fracture is relatively long at 16 months (Thibault et al., for 48 – 60 Gy in 4 #)[96] to 22 months (Stam et al., for 54 Gy in 3 #).[84] The median follow up time for patients in this research was 16 months as of January 2019, which means some rib fracture may yet present.

Indeed, after the first submission of this thesis, six patients were identified by Clinical Oncologists as having rib fractures outside of the original patient cohort. Five of these patients were, notably, women. One patient treatment plan was analysed and found to have an $NTCP_{CW}$ of 58.4%, indicating that had this analysis been performed prior to stratification, the patient may have been offered 5 or 8 fractions instead of 3. Further research is recommended to test

the hypothesis that osteoporotic patients should be categorised as higher risk and offered longer regimens.

Arbitrarily shortening regimens for this cohort of patients could increase the occurrence of rib fracture to rates above those currently seen in the UK, and therefore must be tackled in a patient specific way. Simply, rib fracture from SABR is predicted by the tumour being closely located to the chest wall, with Nambu et al., suggesting greater than 1.6-2cm to be the measure of 'close-ness'.[101] The question of whether to compromise the PTV if it is co-located with the chest wall is interesting because it relates to the importance of side effects compared with the efficacy of treatment. Whilst halting the progression of lung cancer is the primary purpose of radiotherapy, for the elderly and infirm patient subjecting themselves to potential side effects all for a small, asymptomatic tumour might not be in the patient's best interests. Fortunately, rib fracture, chest wall pain and radiation pneumonitis are not very common (≤ 1/10) side effects.[102] However, patients must be fully consented and understand the possibility and extent of likely treatment side effects.

Extending the overall treatment time reduces the risk of OAR toxicity, which should remain a factor for clinicians offering patients alternative regimens, exactly as the radiobiology would suggest. The nature of treatment delivery also needs to be considered. In the study by Jain et al.,[103] patients were treated on consecutive days in the shorter fractionation scheme whereas UK (and local) practice would be to leave a one day gap for normal tissue recovery and treat every other day where possible. Radiobiologically, one may expect to see higher acute, short term toxicities but better tumour control in this scenario.

Patient related factors may also give rise to incidental rib fractures, such as osteoporosis particularly in women over 65, and these cannot be identified distinctly as SABR induced rib fracture. Many rib fractures may be symptomless, and only show up because of the high intensity of CT follow up carried out for these patients. During the pandemic a local agreement was made, similar to other UK institutions, to reduce the frequency of CT scan follow up for SABR patients which is likely to affect the proportion of asymptomatic rib fractures discovered in future. As stated previously, there is no specific treatment for single rib fracture so diagnosing itself may be moot.

One weakness of this study is that only chest wall and normal lung tissues have been considered in the complication probabilities. There are several other OARs in the thorax which could have been included and give rise to potential side effects. These include the brachial

plexus for apical tumours (muscle pain and stiffness of the shoulder), the heart (pericarditis), the trachea and bronchus (stenosis or fistula), and the great blood vessels (aneurysm). The risks of these toxicities are discussed further within the latest SABR Consortium guidelines, and are not as prevalent as the lung and chest wall side effects. This work looks directly at the most widely reported toxicities. It is also worth noting that fatigue, whilst not related to any particular organ within the radiation treatment, is very common though 'self limiting'.

Another weakness of this study is the use of a single model for the assessment of both TCP and NTCP, in particular for the organs at risk. The LKB model is one of the most widely known, but modern volumetric techniques require alternative representations which are voxel based rather than a single reported probability. Such 'atlases' can give 3D information based on both the heterogeneous nature of the dose distribution and also the inhomogeneous susceptibility of the organ of interest to radiation.[104] However, to tie together both modern radiotherapy delivery with toxicity estimates and observations it is often vital to have some sort of transferrable 'currency' between historical and contemporary data. For proton radiation, rib fracture increases for breast cancer have been reported[105] and these need additional parameters to take into account relative biological effectiveness to modify the dose distribution and give a 3D depiction of fracture risk rather than a single probability or purely a physical dose representation.

Analysis of this thesis data shows that 8 fraction treatments for peripheral tumours could be delivered in 5 with no significant detriment when considering TCP and NTCP. However, the numbers in the 8 fraction treatment group were low (8 patients). In earlier versions of the guidance (version 5 and lower) this was known as a 'Very Conservative Dose Fractionation', to be used when the planning dose constraints could not be met. It is significant that during the period of study from 2014 to 2019, the recommended regimens altered from the originally conservative proposals to encompass non-peripheral tumours and shorter regimens (see Section 1.1.3). The 8 fraction schema suggested for centrally located tumours was only recommended in the recent 2019, version 6.1 guidance and the conclusions of this study should not affect this in any way, as they are only valid for peripheral tumours.

3.3 Critical review of similar research

The Lu et al., paper,[48] 'Calculating the individualized fraction regime in stereotactic body radiotherapy for non-small cell lung cancer based on uncomplicated tumour control probability function', retrospectively calculates radiobiological probabilities for tumour control and normal tissue complication of a cohort of 33 previously treated patients in China. It is similar to the author's research as it covers the same disease site and uses radiobiological modelling to hypothesise different potential number of SABR fractions. Consequently, this chapter contains a critical review of the work.

There are a number of differences to note, as shown in Table 6. Firstly, the cohort of patients is much smaller, with an unequal sex bias and statistically lower mean age ($p<0.01$, Independent T test performed on the raw data in the paper), and includes metastatic tumours. The PTV mean volumes are statistically different ($p<0.01$, Independent T test) although the range of volumes studied is similar. The planning and delivery techniques were essentially the same, but the dose calculation models were different within the Eclipse treatment planning system (Varian Medical System, Inc., Palo Alto, CA). The author's work uses the Acuros algorithm which provides a pseudo Monte Carlo approach and models lung/tissue/bone interfaces differently as explained in the Introduction. This is likely to be relevant in the case of lung tumour treatment planning and may translate to different outcomes in the studies.

The Chinese combined different NTCP models for rib fracture, pneumonitis and chest wall pain with the TCP to create a conglomerate model of 'uncomplicated tumour control probability' using in-house code. This is presented as a method by which an individual's fractionation regime can by optimised, although the possible regimens were then restricted to either 3 fractions or 4 fractions in the results, altering the dose per fraction to maximise the therapeutic gain for each individual. The stated reasons for optimisation did not include patient choice, or minimising hospital attendances.

Table 6 Differences between the Lu et al., 2019 paper and this research

	Lu et al., (2019)	**Author's work**
Patient cohort **Mean Age** (Independent Samples T-test, performed by thesis author, p<0.01) **Tumour status**	33 (21% Female) 66.2 years (51-77) T1: 61%, T2: 18%, Metastatic Lung: 21%	198 (50% Female) 75.2 years (54-93) T1: 60%, T2: 36%, T3: 3%, Missing:1%
Mean PTV volume (Independent Samples T-test, performed by thesis author, p<0.01)	50.9 cc (13.5 -128.9)	34.7cc (5.0 – 133.4)
Planning technique **Algorithm**	4D CT, 10 bins, Eclipse TPS with +5mm ITV to PTV expansion, 2 partial arcs. AAA (1mm grid)	4D CT, 10 bins, Eclipse TPS with +5mm ITV to PTV expansion, 2 partial arcs. Acuros (2mm grid)
Dose Regimen actually treated	4 x 12 = 48 Gy (100%) (3 fraction data was not shown in the paper)	3 x 18 = 54 Gy (55%) 5 x 11 = 55 Gy (35%) 5 x 12 = 60 Gy (6%) 8 x 7.5 = 50 Gy (4%) Risk adapted on PTV location as per the UK SABR Consortium Guidelines Vs 4.1 to 6
TCP prediction	Isocentre dose (>100%)	Prescribed dose (100%)
Tumour Control Probability a/b = 10	GTV DVH used 'All patient > 92%' but < 98% Regrowth LQ TCP model	PTV DVH used 3 fraction = All 100% 5 fraction = All 100% 8 fraction =All > 92% (Range 92-99%) LQ Marsden TCP model

The TCP demonstrated in this thesis is 100% for the 3 and 5 fraction schedules which make up the majority (96%) of clinically treated schedules, compared with the slightly lower values ranging between 92% and 98% in the Chinese data. Their TCP data is displayed in a bar chart and thus cannot be compared meaningfully with this author's study, other than to give the range of 92 – 98%. However, generally these values of TCP (from both studies) can be considered extremely high compared to other types and sites of radiotherapy, and therefore demonstrate why excellent clinical results can be observed for patients undergoing lung SABR treatment. It is unclear why none of the Chinese plans reached a TCP of 100%, but it may be related to the slightly different calculation model, the treatment planning algorithm, the different plan quality metrics or the OAR constraints used. Given that the GTV (gross tumour volume) Dose Volume Histogram (DVH) data was used in Lu et al., one might expect higher TCP values because GTVs are inherently smaller volumes than PTVs (which is a GTV plus 0.5cm isotropic margin, as described in Section 2.1.2). This is because the GTVs are situated within

the centre of the PTV where the dose is highest. It is interesting to note that there is no recommended 4 x 12 Gy regimen in the UK, and it is not stated if this represents the most commonly used fractionation scheme in China.

Because the UK already risk adapts schemes based on tumour location to OARs and the ability to meet tight OAR constraints and plan quality metrics, the toxicity seen in the UK is much lower than suggested in the Chinese paper, although they use published references and not data from their own patient cohort. Interestingly in the results section, patients were discussed in groups related to adjacency to chest wall and lung-GTV volume, which are plan quality metrics used in the UK to decide which fractionation scheme to use. In this area, the data validates the existing SABR consortium metrics that have been used in the UK for over ten years.

The hypothesis in this thesis is related to tailoring individual treatment courses for patient need and the ability to comply with daily attendances because the cohort has comorbidities and is quite elderly, more so than the Chinese cohort. Whilst obtaining an adequate TCP and NTCP is important, the purpose here is not to optimise or maximise the therapeutic gain but to offer patient choice as to the number of attendances, as found to be acceptable to patients in the qualitative survey results. It would seem that compared to the Lu et al., paper the 5 fraction regimens in the UK are already obtaining a higher TCP than the Chinese data and moving to a 5 fraction regimen would not result in detriment.

Sood et al.,[49] retrospectively modelled TCP and NTCP with Monte Carlo (XVMC) where they found a correlation between the 2-year actuarial local control rates and the modelled TCP. The rib fracture incidences were predicted at 13% and observed at 10%, and the lung pneumonitis was predicted at 3% and observed at 1%. The TCP estimates were size adjusted, and they studied both primary and metastatic tumours, for 3 to 5 fraction regimes. This publication was not about personalisation but more about correlation of the model probabilities and the outcomes seen clinically with particular emphasis on tumour control. The authors intend to further evaluate NTCP for lung and rib toxicity using Monte Carlo methods, as this was estimated using the Lyman NTCP model, although the parameters and an explanation of its use are missing from the publication.

In concluding this section, the presence of the Lu et al., paper in the literature supports the postulated idea of using radiobiological modelling in lung SABR treatment to tailor treatments. There are some critical differences between the works, as described above, but a key point to

consider is the lower TCP values seen in the data (92 - 98% for 3 and 4 fractions compared with almost all 100% in this thesis for 3 and 5 fractions). The lower values may be due to different calculation models, the use of different normalisation doses or plan quality metrics or the algorithm used. The consequences of this are that the detriment to the UK Lung SABR patients of changing fractionation regimes would be less of an issue than with the Chinese cohort. The Sood et al., data relates to population outcomes but is interesting because it gives more evidence to support the use of radiobiological models as predictors of outcome and toxicity.

3.4 Radiobiological parameters and the use of Biosuite

There are inherent uncertainties related to all the parameters within the TCP model (Section 2.1.2) which are related to several factors including the accuracy of the data, how closely the data represents the individual patient (for example the α/β values and other parameters as discussed in Section 2.3.1), the individual variations of cell survival and the patient specific recovery mechanisms as expressed by the individual's DNA repair mechanisms. Biological studies on cell lines to elicit typical α/β values are expensive, time consuming and whilst necessary, not patient specific. It is well known that tumour behaviour changes as cancer progresses, with cells becoming resistant to chemotherapy drugs and radiotherapy itself, for example. No one model, or one set of static parameters, is able to accurately assess these individual elements specific to each patient. Temporal tumour parameters identifying change with time are starting to be used to predict outcomes, e.g., texture analysis.[106]

The parameters chosen for this study for use in the LQ Poisson 'Marsden' TCP model were taken from the Nahum et al., publication[43] used in the original Biosuite paper.[47] Because the TCP values are being compared relatively between the treated regimens and possible alternative fractionation schemes, this is acceptable. This is also the case for the parameters used to calculate NTCP taken from other publications. Biosuite software was used to evaluate the probabilities in this research. This software is not validated for prospective use on clinical patients but is a useful tool to demonstrate the principle. Medical Device Regulations[107] for software use in a clinical context would need to be adhered to, or else there would need to be a transference of risk to the healthcare professionals utilising such tools.

3.4 Patient Survey

The service evaluation was conducted to obtain a patient perspective of the issues related to attending for treatment. The use of a paper and online survey was planned, although the timing during the pandemic could not have been anticipated and many people experienced

the move to online systems of working in their day-to-day lives. Face to face interviews, to obtain richer data could not be carried out during the lockdowns. The return rate of 50% was adequate compared to other postal surveys. It may have been possible to chase surveys up for patients undertaking telephone or video conferencing follow up appointments, however the surveys were anonymous and this would have broken the anonymity. Consequently the surveys returned could not be mapped to individuals and therefore outstanding questionnaires could not be followed up.

The surveys did not specifically ask about rib fractures and chest pain, and so did not elicit what patients' acceptable level of toxicity is. This is likely to be very personal, related to individuals' perceptions of dealing with side effects and how they affect their quality of life. The circumstances of the individual, for example caring responsibilities or living alone, are likely to be pertinent.

It is well known that people responding to questionnaires can be less than truthful so qualitative data does not always represent the choices that are actually made or would be made, and researchers therefore commit an 'attitudinal fallacy'.[108] In this circumstance, the only way to support the author's claims of what patients would do, would be to observe patients' behaviour directly when offering them fewer fractions in reality. This is problematic because patients are rarely offered a true choice between radiotherapy regimes. This could be an interesting future study for SABR patients; do they really opt for fewer appointments when faced with the real life decision?

The importance of anxiety, depression and quality of life factors for SABR lung patients is discussed by Rutkowski et al.,[109] where the results confirm that SABR is indeed well tolerated by elderly, non-operable lung cancer patients. This prospective survey was interesting because it collected baseline quality of life metrics before SABR, showing that all metrics in the QLQ-C30 and QLQ-LC13 EORTC validated questionnaires stayed the same or improved weeks after treatment. Metrics included chest pain and coughing relevant to this research, but also emotional and social functioning to assess the effect on patients more holistically. 66% of participants in the Rutkowski et al., study were male, so it would be fascinating to repeat this study using a larger and more gender balanced selection. The conclusions confirmed clinical and mental benefit for patients undergoing SABR.

3.5 Conclusions

The work presented here records baseline values for the radiobiological parameters of TCP and NTCP for a peripheral lung SABR service following the UK SABR Consortium guidelines. This baseline data is generalisable to other centres where the technique is similar. The data can be used as a comparator, contributing to the field of lung SABR research, and backing up the clinical experience that SABR is a well-tolerated and effective treatment for early stage lung cancer.

This data suggests that the 8 fraction regimen for peripheral lung cancers is not significantly different to the 5 fraction schedules in terms of the average TCP and NTCP, and that patients could be offered a similar treatment outcome whilst reducing the number of visits. This positively supports the changes in the guidance between version 5.1 and 6.1 of the SABR Consortium Guidelines, which exclude the 8 fraction regimen for general peripheral lung cancers, although some groups may still benefit from prolonged fractionation. As shown, the average TCP and NTCP does not necessarily reflect the individual's situation and so additional calculations of risk, varying or flexing the relevant parameters should give more information on which to base these clinical decisions. The patients surveyed using the questionnaire were generally happy with the SABR lung service they received and accepting of potential changes to the scheduled radiotherapy they had experienced. As such they are likely to be accepting and compliant with fractionation changes. The presence of a respiratory disease pandemic on the uptake of hypofraction by patients and health care professionals should also not be dismissed, as this has created a fundamental adjustment to the use of prospective radiobiological calculations which did not exist when this research began. The desire to reduce the risk of hospital acquired infections has become more important during this time and therefore reducing footfall by just a few visits may prove beneficial. This may be significant for the elderly, poor performance status, patients who may take up SABR rather than surgery for early stage lung cancer and for whom reduced hospital interactions could benefit in a myriad of ways.

4. Appendices

4.1. Appendix 1: Table of Papers from Original Literature Review

Table of references from the literature search utilising the PRISMA approach as depicted in Figure 1 of the main thesis. 17 articles originally identified; however further literature was researched during the course of study (see 5. References).

	Reference	Title	Relevance	Section Number in Thesis:
1	Hadziahmetovic et al., 2010[3]	Stereotactic body radiation therapy (stereotactic ablative radiotherapy) for stage I non-small cell lung cancer--updates of radiobiology, techniques, and clinical outcomes.	Overview, including a good summary of the radiobiological issues relating to the LQ mode overestimating the ablative range effects.	1
2	Nahum et al., 2012[44]	(Radio)biological optimization of external-beam radiotherapy	Introduces Biosuite as a tool for biological optimisation with a lung NSCLC illustration	1.3, 2.1.1
3	Uzan et al., 2012[47]	Radiobiologically guided optimisation of the prescription dose and fractionation scheme in radiotherapy using BioSuite	Demonstration of Biosuite as a tool for calculating TCP and NTCP.	2.1.1, 2.3
4	Soldà et. al., 2013[4]	Stereotactic radiotherapy (SABR) for the treatment of primary non-small cell lung cancer; Systematic	Survival outcomes similar between surgery and SABR for lung – retrospective study.	1.1.1

	Reference	Title	Relevance	Section Number in Thesis:
		review and comparison with a surgical cohort		
5	Brown et al., 2014[53]	The Tumor Radiobiology of SRS and SBRT: Are More Than the 5 Rs Involved?	Discusses if the LQ model needs to change in view of the SRS/SBRT outcomes above the 5 classics R's. Uses preclinical and clinical data to probe validity of LQ including for hypoxia and anti-tumour immunity.	1.4
6	Nahum, 2015[45]	The Radiobiology of Hypofractionation.	Discussion on use and validity of LQ for lung SABR and the theoretical reasons why LQ might not hold.	1.4,
7	Stam et al., 2015[86]	Validation of automatic segmentation of ribs for NTCP modeling	Technical validation of the automatic segmentation tools used to create the structure of the ribs (as opposed to manual voluming) for the purposes of NTCP calculation.	2.3
8	Abbas et al., 2016[110]	Stereotactic Body Radiotherapy and Ablative Therapies for Lung Cancer.	General discussion on lung SABR for primary and oligometastatic disease.	Not discussed explicitly.
9	Giglioli et al., 2016[111]	Lung stereotactic ablative body radiotherapy: A large scale multi-institutional planning comparison for interpreting results of multi-institutional studies.	Discussion on 'normalising' doses to Equivalent Uniform Dose to provide a comparator for multi-institutional studies related to planned and delivered dose. Retrospective analysis of the same planning data sent to various institutions. Includes detailed analysis of rib showing centres did not always respect the dose constraints.	Not discussed explicitly.
10	Stam et al., 2017[84]	Dose–effect analysis of radiation induced rib fractures after thoracic SBRT	NTCP presented for rib fracture for lung SABR using LQ model with parameters elicited from own plan data. Rib fracture risk at 24 months FU was 14% (high) when using 54 Gy in 3#.	2.3.2
11	Mancosu et al., 2018[112]	Editorial: The role of medical physics in Lung SBRT.	Short editorial on value of medical physics in lung SBRT. General interest/relevance.	Not discussed explicitly.

	Reference	Title	Relevance	Section Number in Thesis:
12	Dunne et al., 2018[113]	Stereotactic body radiation therapy for lung, spine and oligometastatic disease: current evidence and future directions.	This paper provides a critical review of recent developments in each of these areas particularly highlighting the challenges facing clinicians and discusses potential areas for future research.	Not discussed explicitly.
13	D'Andrea et al., 2018[42]	Radiobiological optimization in lung stereotactic body radiation therapy: Are we ready to apply radiobiological models?	Key paper discussing practical use of radiobiological modelling, specifically for lung SABR. Multiple models discussed.	1.3, 1.4
14	Lu et al., 2019[114]	Comparison of three radiobiological models in stereotactic body radiotherapy for non-small cell lung cancer	Applied LQ models to lung SABR and produced BED and TCP data based on 20 patients. Highly relevant to thesis in terms of choice of TCP model.	1.2, 2.3
15	Alaswad et al., 2019[82]	Optimal tumour control for early-stage non-small-cell lung cancer: A radiobiological modelling perspective	Summary of 16 publications of data reanalysed using various TCP models.	2.1
16	Lu et al., 2019[48]	Calculating the individualized fraction regime in stereotactic body radiotherapy for non-small cell lung cancer based on uncomplicated tumor control probability function.	Similar study to thesis. A smaller group of patients (n=33) was used, unevenly distributed between men and women, with a different fractionation and dose typical for China but not the UK. A different tumour control probability model as compared to this thesis was also used in subsequent analysis.	1.2, 3.3 Critical Analysis and reanalysis of data as compared with this thesis performed.

	Reference	Title	Relevance	Section Number in Thesis:
17	Sood et al., 2020[49]	Correlation of clinical outcome, radiobiological modeling of tumor control, normal tissue complication probability in lung cancer patients treated with SBRT using Monte Carlo calculation algorithm	Studied clinical outcome correlations albeit using Monte-Carlo based TCP and NTCP calculations for 100 patients.	1.2, 3.3

4.2. Appendix 2: List of Units and Assignments on D.Clin.Sci

This is a list of the AMBS 'A' and Medical Physics 'B' units and assignments I have undertaken during the D.Clin.Sci on the HSST programme. The professional portfolio on the OneFile system of sixty pieces of work commensurate with the role of Consultant Scientist has been submitted and positively assessed (May 2021).

AMBS – A Units		
Unit title	**Credits**	**Assignment wordcount**
A1: Professionalism and professional development in the healthcare environment	30	A1 – assignment 1 – 2500 words Group work/presentation – 10 minutes (10%) A1 – assignment 2 – 3000 words
A2: Theoretical foundations of leadership	20	A2 – assignment 1 – 3000 words A2 – assignment 2 – 3000 words
A3: Personal and professional development to enhance performance	30	A3 – assignment 1 – 1500 words A3 – assignment 2 – 4000 words
A4: Leadership and quality improvement in the clinical and scientific environment	20	A4 – assignment 1 – 3000 words A4 – assignment 2 – 3000 words
A5: Research and innovation in health and social care	20	A5 – Group work/presentation – 15 minutes (25%) A5 – assignment – 4000 words
Medical Physics – B Units		
B1: Medical Equipment Management	10	Group presentation 1500 word assignment
B2: Clinical and Scientific Computing	10	Group presentation 1500 word assignment
B3: Dosimetry	10	Group presentation 1500 word assignment
B4: Optimisation in Radiotherapy and Imaging	10	Group presentation 1500 word assignment
B6: Medical statistics in medical physics	10	3000 word assignment
B8: Health technology assessment	10	3000 word assignment
B9: Clinical applications of medical imaging technologies in radiotherapy physics	20	Group presentation 2000 word assignment
B10a: Advanced Radiobiology	10	Virtual experiment/1500 word report
B10d: Advanced Brachytherapy	10	1500 word report
B10i: Ionising radiations instrumentation specialisation	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

4.3. Appendix 3: Participant Information and Survey for Personalisation of Radiotherapy Treatment

NHS
Hull University Teaching Hospitals
NHS Trust
Queens Centre, Castle Hill Hospital
Castle Road, Cottingham
HU16 5JQ

Participant Information and Survey for Personalisation of Radiotherapy Treatment

As a previous patient of our **lung** radiotherapy service, we would like to invite you to help us evaluate the quality of the service we provide to our patients. The purpose of this study is to learn about your feelings about the number of individual radiotherapy treatments you had. This information will be used to find out if a personalised number of radiotherapy treatments is something that people want in the future.

If you would like to take part, please answer the questions and return the survey in the stamped addressed envelope included. If you would like to complete the survey electronically online instead, please visit: https://forms.gle/fY2s25hqWbcbeMAcA.

The survey should take approximately 5 minutes and your responses will be confidential and anonymous. By completing it, you will be permitting the information you give to be used.

You do not have to take part and it will not affect the quality of your hospital care in any way. We hope it will enable us to understand what patients want from the radiotherapy service and benefit future patients.

Any information you provide will be collated, analysed and confidentially stored within the hospital. The outcomes of this evaluation may be shared at radiotherapy conferences and in publications but participants will not be identifiable. Your individual responses will not be passed on to any third parties and all data will be managed according to the Trust Information Governance Confidentiality and Information Security Policy (CP134).

The person performing this survey is **Jenny Marsden**, Clinical Scientist (UK Health and Care Professions Council registration number CS03958), Hull University Teaching Hospitals NHS Trust.

Please contact Jenny on jenny.marsden@hey.nhs.uk or 01482 461384 if you have any queries, or if you would like to receive information on the outcomes of this study.

Thank you for your time.

Q1. How many radiotherapy treatments did you have? (Please circle one answer)

- 3
- 5
- 8
- Can't remember

Q2. Did you feel this was reasonably easy to cope with? (Please circle one answer)

- Yes
- No

If 'No', please explain what problems you (and/or your family or carers) had which made you feel that this was not manageable:

……

……

……

……

Q3. Would you have: (Please circle one or more answers)

- Preferred fewer treatment appointments?
- Accepted more treatment appointments?
- Attended as many as the doctor or healthcare professional recommended?

Q4. Did the number of treatments affect your decision to undergo radiotherapy? (Please circle one answer)

- Yes
- No

If 'Yes', please explain why:

……

……

……

……

Q5. In the future, it may be possible to tailor the number of radiotherapy treatments for individuals. This means that different people would get a different number of radiotherapy treatments. Please circle one answer and tell us, if this was part of our service, would you prefer to:

- Take advantage of the tailored, personalised service, even if it meant having fewer or more appointments?
- Have the standard number of radiotherapy treatment appointments?

Please leave any further comments here.

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……

Thank you for completing this survey!

4.4.Appendix 4: Patient Survey Raw Data

Participant Information and Survey for Personalisation of Radiotherapy Treatment

Questions Responses 50

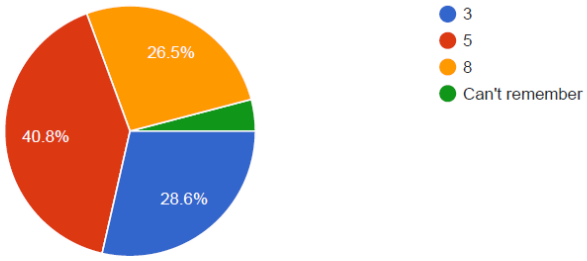
50 responses

Accepting responses

Summary Question Individual

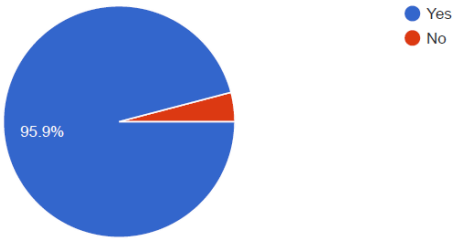
Q1. How many radiotherapy treatments did you have?

49 responses



Q2. Did you feel this was reasonably easy to cope with?

49 responses



Please explain what problems you (and/or your family or carers) had which made you feel that this was not manageable:

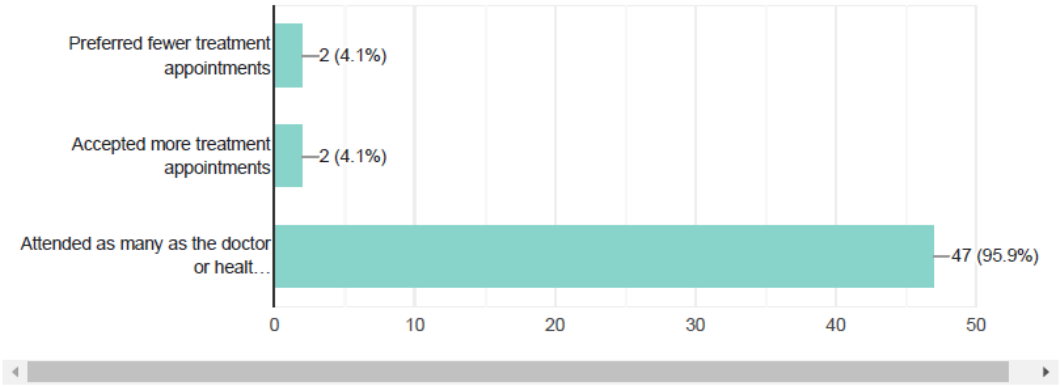
2 responses

LOSS OF WEIGHT, APPETITE, AND ENERGY

Feeling of claustrophobia but able to manage.

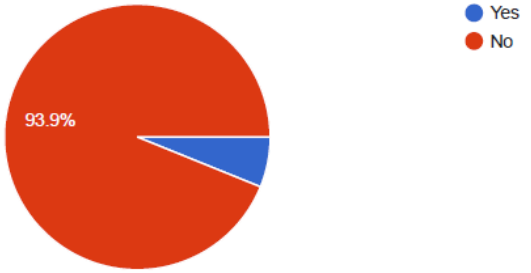
Q3. Would you have:

49 responses



Q4. Did the number of treatments affect your decision to undergo radiotherapy?

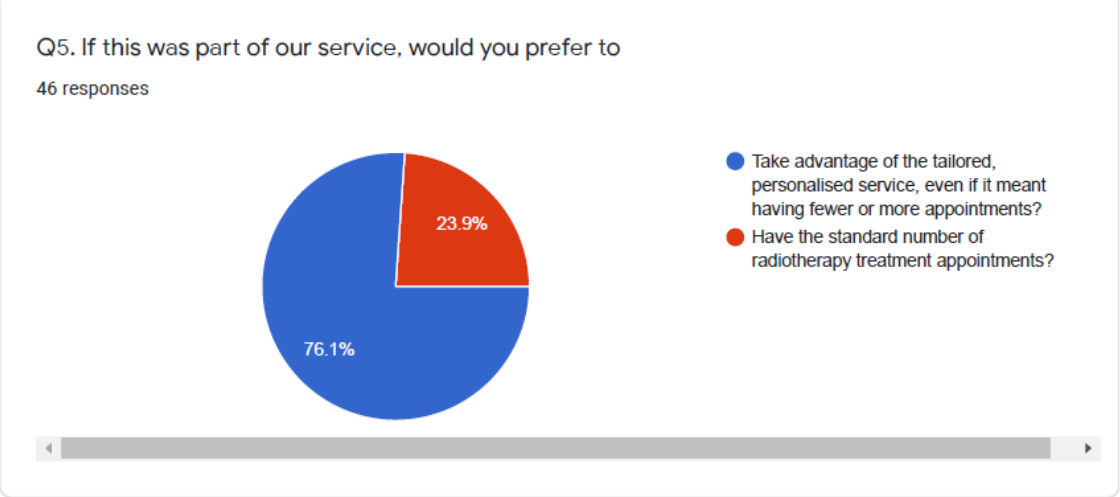
49 responses



Please explain why the number of appointments affected your decision to undergo radiotherapy treatment.

1 response

It was not everyday but spread over a week and a half.



Thank you for completing this survey!

Please leave any further comments here.

24 responses

Having been found to have lung cancer, and not being of the medical profession, I can only accept what the experts advise so would think that tailored treatments are the sensible way to go. What I can say though is from start to finish I could not have had better better treatment, the staff are just the best.....caring and considerate.....what more could you wish for.....Thank you.

Would do whatever Dr. Barton recommended. All scans were done. Had a small thing in the top right lung. I had 8 treatments and it was a new thing to have that many rather than 16. I am 95. Size had reduced a little after treatment.
Since then I occasionally get a jabbing pain (a minute or so) in my shoulder. It has progressed to going down my arm. And is now on my left. I have been told that nothing can be done next so I'll just have to live with it.
(Phone call - direct to Jenny on 30/11/2020 and transcribed into the online form. Patient left name but this has not been recorded for confidentiality).

Thes (sic) 3 I had, no problems

Worked well - No Car Charge very good

Always helpful - a delight to come to your Hospital

I was very happy with the treatment, staff and service.

EXCELLENT SERVICE FROM EVERYONE INVOLVED IN MY TREATMENT

I was well please (sic) with my treatment, Thank you.

The quality of service provided gave me confidence and assurance that I was getting the best treatment. Would definitely follow advice given.

VERY SATISFIED

Very pleased with the treatment I received in the past

MY WIFE AND (SIC) WERE BOTH TREATED THIS YEAR, WE CANNOT FAULT THE CARE AND DEDICATION OF THE STAFF AT CASTLE HILL. WE FEEL WE HAVE BEEN LUCKY TO HAVE HAD THE TREATMENT IN SUCH TROUBLED TIMES. THANK YOU.

Treatment was more than sufficient, staff were brilliant

Q4 - NOT AT THE TIME
THE NUMBER OF TREATMENTS SEVERELY COMPLICATED MY BOWEL OPERATION

I had no problems with the treatment, the staff were excellent and friendly. The only after effects I had were a few days tiredness. Everything greatly appreciated.

The treatment made me tired and sleepy.

Quiet (sic) like what I had. It work (sic) very well for me.

HAVING THE THERAPY WAS NO PROBLEM BUT THE TIME WAITING FOR IT WAS VERY FRUSTRATING LEADING TO STRESS. ALSO WOULD BE BETTER IF SOME FORM OF ENTERTAINMENT WAS THERE (i.e.) TELEVISION ON CHANNELS TO TAKE MIND OF WAITING. OUT OF 8 SESSIONS SPENT 2 DAYS WAITING.

WHICHEVER CONSULTANT RECOMMENDS

I would like to say a big thank you for the treatment I had.

Treatment was under 'lockdown' but could not have been better.

Q2 - Yes, but with some difficulties - sickness and severe back ache

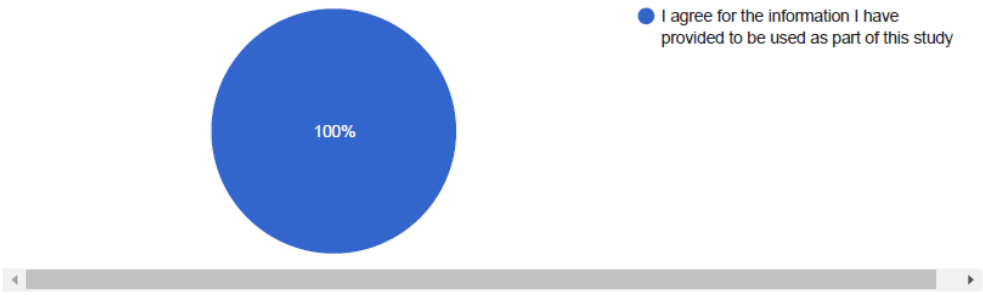
Took the Dr's advice that 8 was the Best for the seriousness of the position of the cancer on my lung. They couldn't have been nicer, plus the cheerfulness of the staff made me feel so much better. Thank you all.

I was happy with my service and the treatment I received. Everybody was really nice and helpful.

THE DECISION WAS PERSONAL IN THIS CASE AND THE TREATMENT WAS SUCCESSFUL FOR WHICH I AM DULY GRATEFUL

Please click the option below to confirm you have given your permission for this information to be used in this study.

50 responses



4.5.Appendix 5: HSST Innovation Proposal on Implementing Personalised SABR Fractionation in the Hospital

Executive/Lay Summary: Personalised Radiotherapy for Lung Cancer

Stereotactic Ablative Radiotherapy (SABR) for peripheral lung cancer has been given to patients in three, five or eight treatment sessions following the UK SABR Consortium Guidelines, based on the scientific trial data on the 'average' patient. However, we know that for individual patients this radiation dose may have a different effect; it may be enough, too much or insufficient. Also, there may be other factors which affect patients' ability and willingness to undergo treatment. For example, getting to the hospital, the time waiting once there, their family or partners' health and their own wellbeing in general. As lung SABR is currently the treatment suggested for people who cannot be operated on, this often means they are elderly and already vulnerable. Looking at holistic factors in addition to the scientific evidence ensures that treatments are both effective and palatable for patients.

This proposal suggests that we look more carefully at personalising the number of treatment sessions and aim to achieve a course of treatment that fits best with the patients' needs, rather than that of the 'average' person. In a recent survey, 75% of people treated with SABR would accept having a tailored, bespoke service with non-standard fractionation. For some, this might mean fewer visits which in turn could mean a less stressful experience of radiotherapy, and possible savings for both the patient and the NHS, whilst maintaining a high quality of cancer care.

Introduction

The doctoral research project described in this thesis could be implemented in practice within a hospital trust as an innovation. Currently protocols for radiotherapy are recommended by professional bodies based on a systematic evidence base, and there are specific efforts towards harmonising clinical protocols within regional operational networks being made by NHS England as part of the Radiotherapy Service Specification.[19] The NHS Constitution[68] describes the rights that individuals can expect from health services, including the 'right to receive care and treatment that is appropriate to you, meets your needs and reflects your preferences'. There are therefore two subtly conflicting drives in place; one to standardise and ensure every patient gets the same level of quality care which has in practice meant offering identical dose and fractionation, and one to personalise the individual patient's radiotherapy. A move towards offering patient choice with fractionation is a move away from the 'standard of care' and in this respect it can be considered an innovation.

The costs and reimbursements for the work done in radiotherapy (scanning, planning and treatment, for example) are not necessarily aligned in a meaningful way, and savings for the overall NHS may be reflected as losses for individual Trusts. There are national package and individual costs for Radiotherapy as a specialised service as part of the 'radiotherapy tariff'. Therefore, any changes which may affect patient footfall and attendance must also be costed correctly to ensure that monetary losses

(or gains) are explicit for the hospital Trust, and manageable within the financial basis. Care should be taken to ensure that the move to fewer fractions is not driven by increased profit, but by demonstrable patient benefit.

Stakeholder involvement

Section 2.2 of the thesis describes the work performed to obtain the patient view of personalisation and a bespoke fractionation service. The outcome of the service evaluation was that 75% of patients would be interested in taking advantage of a bespoke, tailored service. It was not possible to perform face-to-face interviews during the pandemic. Whilst the questionnaire didn't go into detail as to what personalisation would look like in any depth further than the number of treatment appointments, it is clear that patients would be accepting of a move away from standardised care. There are some caveats to this, and it should be noted that 96% of patients surveyed would take any changes their healthcare provider suggested so if the healthcare provider offered multiple options it is not clear how patients would behave. The burden of responsibility to ensure what is best for the patient always, to some extent, is passed to the health care professionals and their multidisciplinary teams for them to explain and present to the individual.

It might be reasonably assumed that patients would choose fewer treatments if they achieved a similar outcome, but this cannot be ascertained from this research, and may be best determined after a period of implementation and audit. This is because it is a very individualistic choice for each patient.

In addition to patient views, Trust management and leaders would need to be appraised of the changes, using the local Technique Change policy via a concept paper (such as this) raised at the appropriate Board. Transport or ambulance services and outpatient services may be affected and would also need to be kept appraised.

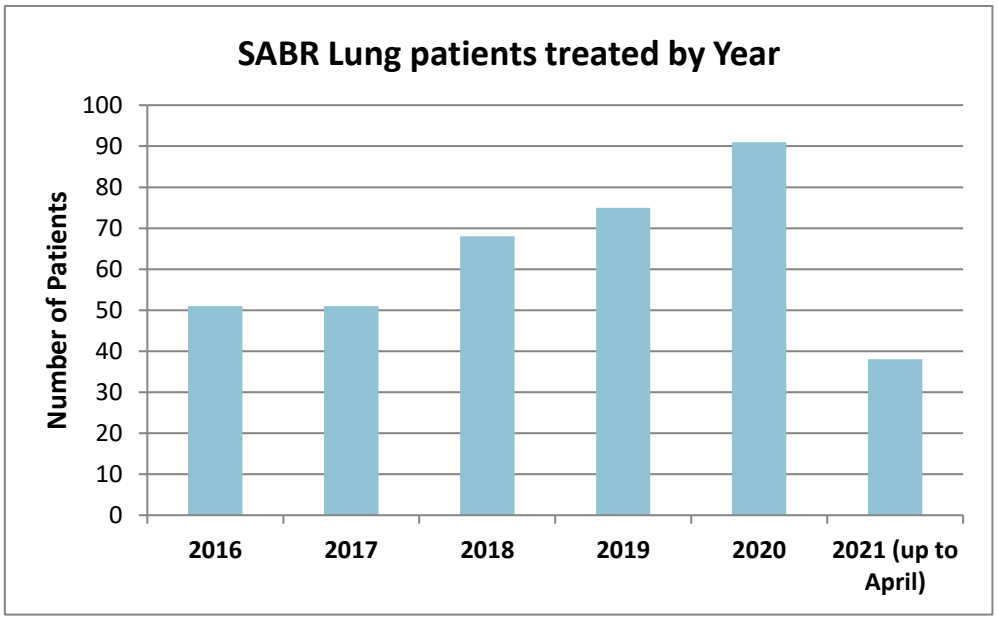
Background to Business case

Patients eligible for lung SABR are expected to rise significantly over the coming years exceeding the originally predicted 1000 patients per year.[8] Every radiotherapy provider in England is expected to provide a lung SABR service by 2022. In 2018 there were approximately 39,267 incidences of lung cancer (PHE CancerStats Data using ICD10 code C34, available from https://nww.cancerstats.nhs.uk/nlca). It is not therefore unreasonable, especially with the surgical backlog following the pandemic, that a significant number of cases could be expected in the coming years. This centre has treated between 50 and 90 patients per year over the last five calendar years, with numbers looking to increase further as routine lung cancer screening is rolled out nationally (Figure 1).

Although this business case will not discuss the overall cost effectiveness of surgery versus SABR (this can be found elsewhere in the literature[115-117]) the morbidity and mortality associated with surgery itself

has also led to SABR being chosen by patients who may otherwise be operable. This is another example of patient choice determining health care provision.

Figure 1 Local Lung SABR numbers by Calendar Year (Figure 1 in Appendix 4.4 [Thesis Figure 12]).



In the financial year 2020-2021, 101 lung SABR cases were treated by this Trust. Reimbursement for radiotherapy costs in England is governed by the 'tariff' which may or may not match the true 'cost' of delivering the radiotherapy in a centre. NHS England reimburse commissioned centres (only) following the tariff costs below. Centres which took part in, or are part of an agreed provider network who took part in, the Commissioning through Evaluation (CtE) programme were reimbursed with an uplift. This was provided by NHS England as an incentive using a £6 million 'research in practice' fund on potential applications of SABR. Any uncommissioned SABR services would attract the costs per patient in the final column in Table 1. This may not properly recompense for the original set up, commissioning, audit and quality assurance of a new SABR service. Therefore, this business case is very specific to each individual Trust.

Table 1. NHS England Tariff Costs for Lung SABR, with CtE uplift compared to single fraction costs if unbundled from the 'package'. The tariff for SABR treatments is much more than the cost for the individual elements using the current tariff, reflecting the complexity of the treatment and the governance oversight required.
(Table 1 in Appendix 4.4 [Thesis Table 7])

	Tariff 'package' price for SABR (£)	**Tariff 'package' price for SABR if part of CtE (£)**	**Tariff *per fraction* if CtE (£)**	**Un-bundled package prices (n fractions + planning) (£)**
3 fractions	3,432	3,485	*1,162*	1,734 = (3x146)+1296
5 fractions	4,856	4,931	*986*	2,026 = (5x146)+1296
8 fractions	6,992	7,100	*888*	2, 464 = (8x146)+1296

The reduction of hospital visits is clearly not the only factor for patients and their health care professionals to consider when deciding on the most appropriate course of treatment. For elderly patients, overall survival in terms of decades may simply be unachievable and quality of life is likely to be a more important factor. A common way to formally assess health utilities is the use of the time trade-off (TTO) method. Here participants in cost effectiveness/quality of life research (not always patients actually suffering from lung cancer) chose between remaining in their current health state for 10 years compared to trading off fewer years of 'full health'. This metric is obviously not much use for octogenarians, whose quality of life considerations are not likely to match with those of younger generations. Side effects or toxicities of treatment and their effect on ability to do daily tasks are likely to be much larger factors. Cultural and geographical differences in health utilities also exist.[118]

Assumptions for Business Case Modelling

Using the income based on the financial year 2020-2021, as per Table 2, the *savings* to the **NHS** would be as follows:

- Savings by the NHS if all 8 fraction treatments reduce to 5 fractions: **£71,200.** This approximates to 1530 minutes of linac time saved annually.
- Savings by the NHS if all 8 and 5 fraction treatments reduce to 3 fractions: **£192,240.** This approximates to 3060 minutes of linac time saved annually.

Table 2. HUTH Trust Lung SABR 'Income' between 01/04/2020 and 19/03/2021

(Table 2 in Appendix 4.4 [Thesis Table 8])

Total #	Count of Income	Sum of Income (£)
3	16	54912
5	51	246232
8	34	237728
Grand Total	101	538872

Note that for the individual Trust these *savings* would appear as *losses* to income. The following costs have NOT been included and could influence the overall modelling and outcome:

- Trust reimbursed as per column 1, Table 1. and do not include the CtE uplifted tariff costs (column 3)
- Treatment machine (linac) minutes saved translated into parts, maintenance and servicing costs, and technical/treatment staff costs
- Additional Consultant/Patient appointment time in order to explain the new choices with the benefits and risks.
- Outpatient ancillary services costing that could be saved by reduced footfall such as nursing, dieticians, catering, etc.
- Transport/ambulance costs for the Trust and the individual.

Conclusion

The personalisation of lung SABR fractionation in conjunction with promoting fewer visits to the hospital for eligible lung cancer patients could save the NHS between £71, 200 and £192,240 per financial year for this Trust alone.

For patients undergoing lung SABR treatment, the ability to be more involved and have a say as to the preference of the number of visits may improve their experience of cancer care and perhaps their willingness to undergo treatment. This may have the effect of improving access to radiotherapy.

Overall, the move away from standardised care for the average patient to a more holistic, tailored service should improve the radiotherapy cancer experience for both staff and patients.

(References included in Section 5.)

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