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Statement of Search Strategies Used

We searched PubMed and Google Scholar in 2017 for relevant literature on patient selection,

normal tissue complication probability modelling, quality-adjusted life-years, markov modelling,

cost-benefit modelling and demand modelling for proton therapy.

Abstract

Proton beam therapy (PBT) is still relatively new in cancer treatment and the clinical evidence base is

relatively sparse. Mathematical modelling offers assistance when selecting patients for PBT and

predicting the demand for service. Discrete event simulation, normal tissue complication

probability, quality-adjusted life years and Markov Chain models are all mathematical and statistical

modelling techniques currently employed but none is dominant. As new evidence and outcome

data become available from PBT, comprehensive models will emerge that are less dependent on the

specific technologies of radiotherapy planning and delivery.

Keywords

Mathematical Modelling, Proton Therapy, Discrete Event Simulation, NTCP, Patient Selection

Introduction

In this paper, the mathematical modelling tools for patient selection and demand prediction for X-ray radiotherapy (RT), in general, and proton beam therapy (PBT), in particular, are presented and compared. The modelling frameworks vary considerably in their scale of scrutiny, from bottom-up descriptions of DNA damage at the molecular level, to patient population, or top-down, and statistical models. The latter depend heavily on the quality and granularity of the data and predictions available for populations (size, age and location), disease incidence and treatment effectiveness as well as the occurrence and severity of side effects. Patient selection is inevitably linked to cost and benefit and the evidence base for the cost of PBT is now developing rapidly, given the number of centres operating and the total number of patients treated. There are still significant gaps and uncertainties in this evidence base, including for rare tumours and the effects of retreatment, which will have to be spanned by mathematical and statistical modelling for the foreseeable future and, to paraphrase Box, "all models are wrong, but some may be useful" [1].

Cost of PBT

While the exact cost of building and operating a proton therapy facility will always be case dependent, the overall cost of new facilities often attracts political and press attention, although it should be noted that the cost of RT compares favourably with the cost of other cancer treatments. In the UK, the total cost of radiotherapy, including PBT, accounts for less than 10% of the cancer budget [2]. The Department of Health is paying £250m for two, 4 room, centres [3] and centres in the USA have reported capital costs of between $150m [4] and $200m [5]. In contrast, the capital cost of a new linear accelerator and associated buildings is approximately £2.5m [6] and the cost of a combined magnetic resonance and X-ray radiation therapy machine (MR Linac), for example the Elekta Unity machine, is in excess of £5m [7].

When comparing costs, it has to be remembered that a proton therapy facility typically has three to five gantries or treatment lines. More recently, smaller cyclotrons and compact gantries have

allowed cheaper, single treatment room facilities to be developed. Since 2010, 11 of the 38 centres that have opened and 16 of the 40 under construction have a single treatment room. The capital cost of a single treatment room facility is reported to be about $40m [8]. In addition, to the initial capital costs, the operating costs of a proton facility, including the treatment delivery costs, are also higher, estimated at around 2.4 [9] - 2.5 [10] times that of conventional X-ray therapy. However, with technology improvements and wider adoption this figure is expected to drop.

The high costs of PBT facilities means there is a greater requirement to ensure that the treatment capacity is filled efficiently to ensure value for money. While the cost effectiveness of proton therapy has been reported more recently [11], one of the first publications appeared in 2005 [10]. However, with the increasing popularity of proton therapy, and changes in the technology and operating procedures, older studies may no longer be relevant. The introduction of new X-ray technologies (e.g. MR Linac) and new treatment regimens (such as hypo-fraction) could also affect the validity of the older comparisons.

Proton therapy facilities have also provided little evidence of cost-effectiveness [12] and clinical-effectiveness [13], with the latter an important component when calculating the former. Without direct clinical evidence for improved treatment, it can be difficult to justify the large expenditure on PBT compared to other radiotherapy modalities.

Demand Modelling

Mathematical and statistical modelling for both patient selection and the demand for services is not new in radiotherapy (RT) service planning. Some of the currently published comprehensive demand models originate from CCORE in Australia [14], Canada [15] and Malthus in England [16, 17] and are solved by discrete event simulations (DES). Discrete event models (DEM) are starting to be used for health simulations [18, 19]. In Malthus, for instance, discrete events include sampling population and cancer incidence data to construct virtual patients with statistically representative age, sex,

home location and disease at presentation. Then each virtual patient is presented to an evidence-based decision tree aligned with the RCR fractionation guidelines [20]. Each virtual patient accumulates a virtual patient record of arbitrary complexity but typically including the type and number of fractions of radiotherapy received. At the end of a simulation, the virtual patient records are analysed statistically, partly to check that enough patients have been simulated to ensure reproducible results. Finally the whole process can be embedded in a Monte Carlo simulation to calculate the effects of the uncertainties in the parameters of the model from the population, incidence and clinical decision making events. The output is the probability densities for the number of fractions delivered, broken down by the type of RT, location, age, sex and disease type etc. To illustrate the decision tree structure, Figure 1 shows a section from the Malthus lung cancer clinical-decision tree.

These models, described above, are currently used to predict service demand without reference to service availability. They require comprehensive data to populate the clinical decision trees, linked with granular population and incidence data or projections to capture demand variations within a country over time [21]. Once such a model has been established and validated, it is not computationally expensive to modify parameters, re-run simulations and compare outputs, so that these models can be used to estimate the impact of introducing a new technology into an established health-care system, especially where specific target clinical indications are to be compared [22]. A DEM can be used to estimate the corresponding reduction in demand for existing services. These models can also be used to predict the likely patient availability for clinical trials [22], however it is not always possible to predict accurately the success rate in actual patient recruitment. Similarly, like many other modelling technologies, DEM struggles for precision when the event rate is low as is inevitably the case for rare cancers in small geographical regions.

The current level of available clinical evidence will not allow for prediction of demand for PBT that is directly comparable to the prediction of conventional radiotherapy demand.

Cost-Benefit Modelling

With evidence for specific indications, a cost-utility analysis can be carried out including the calculation of quality-adjusted life-years (QALY) [23]. A QALY takes into account a number of outcomes and side effects to describe a health state, or utility, with a score of 0-1 where 0 indicates death and 1 indicates perfect health. 1 QALY is representative of a single year lived in perfect health [24]. To calculate the overall QALY value of a specific intervention, the numbers of years spent, in each of several health states, are combined. The cost of the specific intervention is then used to calculate the cost per QALY gained. With PBT, the QALYs gained are often compared to X-ray therapy to check if PBT is cost-efficient. For the UK, the National Institute for Health and Care Excellent (NICE) set a value of £20,000 or less per QALY gained to be considered cost-effective [25, 26].

Temporal discounting is normally applied to QALY calculations when calculating the benefit in the future [23, 27]. Discounting is used to account for the fact that the major costs are incurred at treatment prescription but the health benefits occur later [28].

A systematic review by Amin *et al* [29] provides an overview of QALYs being used for cost-effective comparisons of prostate cancer treatment. QALYs are often used in conjunction with Markov Chains to compare different treatment options for a single disease site. Markov Chains are used to model a system with changing states such as 'diseased', 'treated', 'cured' etc. As a simulation proceeds in time, the different states can carry a health-utility score and the scores are combined, as mentioned above, to give the overall QALYs for each specific treatment pathway. A QALYs analysis for PBT in England has been conducted by the NHS as will be discussed further below.

Modelling Patient Selection

For both the overseas proton therapy programme of the UK National Health Service (NHS), and the service proposed for Manchester and London, patient selection criteria are based on a defined

clinical indication list [30, 31]. Since the NHS is publicly funded and free at the point of use, it cannot

spend £250m on a technology without prior evidence of its effectiveness. These criteria enable the

service to be offered to those patients where there is a clear, definable benefit for proton therapy at

a cost-effectiveness level that agrees with NICE's QALY guidelines. The Department of Health's

National Proton Beam Therapy Service Development Programme used a QALY/Markov Chain

method for the proposed case-mix to demonstrate cost effectiveness [30, 31]. It was estimated that

introducing proton therapy for 1,500 patients per year would generate 48,000 additional QALYs,

with a discounted benefit over conventional radiotherapy of £1bn. This equates to approximately

£20.8k per QALY gained. For comparison, a study on low-risk prostate cancer calculated the cost per

QALY gained for proton therapy over conventional radiotherapy at $169,867 [32].

In a resource limited service, but where there are no regulations to define which patients should

receive proton therapy, then a patient prioritisation method could be used to select patients. The

patients given the highest priority should be the same as in an indication regulated service (such as

the NHS), but the list will then extend to at least some other indications with decreasing priority. In

some cases, tumours would be ranked, and treated, with an 'expected benefit' where there is

absence of data on the actual outcomes. The Roberts Proton Therapy Center at the University of

Pennsylvania adopted the prioritisation method, developing the Proton Priority System (PROPS) and

reported on it after three years of treatment [33]. Unfortunately, during the study period of PROPS,

the capacity exceeded the demand for service and so no firm conclusions can be made about this

method yet.

PBT can be used to dose escalate the tumour at fixed risk of normal tissue complication, or, if the

probability of local control is acceptable, the risk of normal tissue complication can be reduced.

Both strategies assume that the dose-response for protons is broadly similar to, or can be scaled

from, the X-ray response, e.g. via the concept of relative biological effectiveness (RBE) [34, 35] .

However, there is a slowly gathering body of scientific and clinical evidence that fixed, constant

values of RBE may need to be replaced by plans which allow the dose to be biologically optimised to the tumour and its microenvironment [36] .

The scientific evidence comes from an improving understanding of how DNA damage profile varies with linear energy transfer (LET), how LET varies with position within a Bragg peak and hence within a PBT treatment plan. The clinical evidence suggests a range of toxicities, usually associated with the distal edge of the Bragg peak in some relatively rare circumstances.

Normal Tissue Complication Probability (NTCP) Modelling

The Netherlands has published their proposed methodology for patient selection [37, 38]. They will use a dual track approach: one track is a relatively non-controversial fixed indication list based on evidence at levels 1 and 2, but a second track, using a "ΔNTCP" approach will be run in parallel. The first track is not expected to exceed the capacity under installation in the Netherlands, so they anticipate some spare capacity to be available for their second track.

The ΔNTCP approach that has been proposed will work as follows: any patient can be referred to this track if they have a tumour that is not on the fixed indication list. At the PBT centre, optimised X-ray and proton plans will be produced. These plans will then be assessed for normal tissue complication probability (NTCP) and if the NTCP of most concern for the X-ray plan exceeds the equivalent NTCP for the proton plan by more than some nationally agreed difference (ΔNTCP) then the patient will be treated with protons. As time passes, the threshold ΔNTCP can be adjusted by a feedback mechanism so that supply and demand become broadly matched. If the ΔNTCP threshold increases over time, to manage demand, further capacity can be considered. Furthermore, it is proposed that patients who just fail to meet the ΔNTCP criteria may be eligible for an appropriate randomised clinical trial where capacity permits.

The ΔNTCP approach requires considerable infrastructure to develop the NTCP models of sufficient statistical quality and sophisticated technologies are being employed (see, for example [39-42]). The

intended major advantage of this system is to provide an efficient and transparent mechanism for both patients and clinicians to be able to understand and justify the chosen treatment pathway. However, the matched X-ray and PBT plans will have to be produced and compared quickly so as not to compromise clinical effectiveness.

The ΔNTCP method for selecting patients is potentially vulnerable to the general problem of the effect of observation delay time on feedback systems [43]. Some normal tissue complications may only become evident some years after treatment, especially in paediatric cases. Observation of these complications will be recorded and fed back into the NTCP models. At which point the corrected NTCP model may no longer indicate that PBT is the preferred modality. The large delay times before complications can be observed, can destabilise a feedback system. Furthermore, advances in the technology of both PBT and X-ray treatment may make the adjustment of the NTCP models challenging.

The applicability of NTCP models derived from X-ray data to PBT is also subject to doubt. Firstly, in a proton plan, RBE will vary with position, and proton dose will have to be converted to equivalent X-ray dose before NTCP is assessed. RBE and its relationship to linear energy transfer, DNA damage complexity and tissue type are active research topics and far from fully understood with any certainty [44, 45].

Secondly, in PBT beam angles can be used which would not be possible with X-rays because of the exit dose. For instance, where an X-ray plan may graze an organ at risk, delivering dose to a small number of functional subunits (FSU), a PBT plan may cover a critical number of FSUs with a dramatic increase in the resulting toxicity even if the dose to each FSU is lower. The equivalent uniform dose (EUD), introduced by Niemierko [46, 47], is intended to capture these concepts rooted in the functional biology of the organ at risk. An alternative solution to this type of problem is to use a combination of NTCP models based in percolation theory as proposed by Thames et al [48] and the

known biology of the functioning of the organs at risk. This idea is not new and is now an excellent candidate for a renewed research effort.

Models now exist which can describe in some 'bottom up' detail the processes of DNA damage and repair [49] and cell survival of complex cell populations but recently models which capture the mechanical properties of sheets of tissue have been developed [50, 51]. These vertex dynamics models seem to be an excellent basis for the description of symptoms such as haemorrhagic proctitis, but so far have been applied only to embryology. Obversely, a 'top down' approach to modelling is also possible; for instance, in glioblastoma [52] and more recently in lung cancer [53].

NTCP is not necessarily the only criterion on which to select patients and a more comprehensive model has been proposed which includes elements of tumour control probability and NTCP as well as the probability of induction of secondary malignancy [54].

Finally, it should be noted that NTCP modelling is intrinsically difficult even if the outcome data are not as scattered as those in the classic paper by Emami *et al* [55]. In one recent study of heart toxicity in lung cancer patients, it has been shown that dose to the base of the heart is the critical factor [56]. However, in a separate study in breast cancer, the volume of the left ventricle receiving more than 5 Gy has just been shown to be a good predictor of acute coronary events [41]. Clearly, the two patient cohorts in these studies are very different in age, sex, smoking history, surgical interventions etc., but the two methodologies applied are also different and it is to be hoped that the two groups will soon exchange either data sets or analysis techniques or both. What both these studies illustrate is the care that will have to be taken in selecting truly valid endpoints for NTCP modelling.

Data to Inform and Populate Models

A key issue with modelling patient selection and demand for PBT is the current lack of evidence for clinical effectiveness [57]. There are two main contributing factors for this: while the number of

patients treated with PBT is expanding, few centres have been open long enough to report outcomes. Additionally, the core indications for proton therapy, where the greatest benefits are expected to occur, are generally rare indications especially in paediatrics. The estimates for the UK (pop. 65m) are just under 1,500 patients per year for the defined indications list [31], of which 252 are estimated to be paediatric. In total, up to end of 2015, there have been 131,240 reported patients treated with proton therapy around the World since 1954 [58]. Comparatively, across the 2014/2015 financial year there were 134,171 reported radiotherapy episodes in England alone [59]. Due to the increasing number of facilities, the evidence base and outcomes data are slowly expanding [57, 60-62], including some longer term follow up from the oldest centres [63-66].

The gold standard for clinical evidence is the randomised control trial (RCT) and these have to be carefully designed with respect to equipoise. Each arm of the trial needs to be equivalent (in the mind of the clinician) for the prospect of cure or improvement of quality of life

Selection of endpoints is extremely important in trial development and for proton clinical trials survival may require many years of follow-up before there is significant data. Thus trials which also look at endpoints, such as neurocognitive effects, early toxicity etc. will provide an early indication of areas where further research and investigation is required. Similarly, because of improvements in both photon and proton treatment, trials need to be developed that quantify accurately small but significant changes in the data.

While evidence level and recommendation grades have been used in medicine for a number of years [67, 68], a modern system to categorise evidence for therapy is being developed at the Oxford Centre for Evidence-based Medicine(OCEBM) [69]. This system is used in documents such as the Royal College of Radiologists fractionation document [20]. As Table 1and Table 2 show, for the highest grade of recommendation there has to be consistent RCT evidence and ideally it is these high levels of evidence that should be prioritised to populate the model parameters.

Very rare tumours are especially problematic, even in large databases the evidence reporting may be skewed. For example, the US National SEER database only has a 28% coverage of the whole population [70]. Older models of radiotherapy demand used a hierarchy of epidemiological data to rank data sources, with preference being given towards national data from the relevant country of origin, however, the process of deciding these preferences was contentious [14, 71].

Technology Creep

Proton and X-ray technologies for radiotherapy are constantly evolving. As the cost of proton therapy is higher than radiotherapy using X-rays, any equivalent treatment through a different modality (except perhaps carbon ion treatment) that displays non-inferiority will have an instant bonus in cost-effectiveness. Recent developments include image-modulated RT, image-guided RT, stereotactic RT, volumetric modulated arc RT, 4D adaptive RT and magnetic resonance image-guided RT. These advances all attempt to improve local control, or reduce side effects, or both [72]. Imaging techniques are also improving for both diagnostics and on-board for treatment imaging, allowing an increase in targeting accuracy and precision [73].

DEM techniques can be used to explore the interaction of a new technology with a current healthcare system. Discrete events can be included to represent the additional staff, ancillary services and patient travel times. These are especially useful when combined with sub-national data to estimate the changes in demand if the PBT centres have large population catchment areas. Travel time has been investigated for X-rays but not yet for protons [74].

Conclusions

There are a number of different mathematical modelling methodologies that can be used to estimate patient numbers, demand for service and guide individual patient selection. There is no single, correct methodology and the different methods are used for different purposes. The key issue for PBT is still the dearth of direct clinical evidence and this affects the modelling. However, mathematical modelling can now be used to help to design the clinical trials that can help to provide

the evidence. For individual patient selection, NTCP can be used to compare proton and X-ray plans, but setting the threshold for PBT will be challenging, especially initially while the technology is developing rapidly. Recently, more sophisticated modelling has been demonstrated which considers both tumour control probability and the risk of secondary cancer induction as well as normal tissue effects. Ultimately, NTCP models which capture the underlying damage to the biology of the normal tissue and not just the gross statistics will be required.

For cost-benefit analysis, QALY and Markov Chain models should be used in the planning of any new centre especially where it is intended to accept patients from a fixed indication list. But again, these models suffer from the lack of long term outcome data, clinical evidence and health utility information.

Discrete event simulation is ideally placed for service demand modelling, but to use its full potential it requires an established evidence base and granular population and incidence data. DES is potentially very flexible and is the only technique explored in this paper that can act as a general framework for cohort, costing and demand simulations.

PBT modelling over the next 5-10 years will absorb new data to create more comprehensive models that are less dependent on the specific technologies of planning and delivery, and will allow a universal approach to patient selection for PBT and support the development of smarter clinical trials.

Acknowledgements

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Figure 1

Stage 3a 10% LUCADA Normalised	Surgery 10% [Non-bulky nodal disease]	N0-1	No Radiotherapy ECRIC 71%
		Positive Margin > N2	Radiotherapy 55/20#, 60 Gy/30# if +ve margin 50/20> N2 disease Lung ART 54/30#
	No surgery 90%	Definitive RT 40% Concurrent chemo-RT 60-66 Gy in 30-33#, 55 Gy/20# If unable to have chemoradiotherapy consider CHART 54 Gy/36#/12 otherwise 66/33# or 55/20# Superior sulcus tumour consider preop crt 45 Gy/25# then surgery	
		Palliative RT 60% High dose palliative 36 Gy/12#, 30 Gy/10# Poor performance status focus symptoms - palliative 20 Gy/5#, 16 Gy/2#, 10 Gy/1# Thoracic radiotherapy	

Figure 1. An excerpt from the Malthus lung cancer decision tree, showing the stages of the discrete event simulation events going left to right. The key events being the determination of disease site, stage distribution, initial therapy, patient factors, evidence-based indications for radiotherapy including the number of treatment fractions. Adapted from [21].

Table 1

Evidence Level	Data required
1a	Systematic review (with homogeneity) of RCTs
1b	Individual RCT (with narrow confidence intervals)
1c	All or none study
2a	Systematic review (with homogeneity) of cohort studies
2b	Individual Cohort study (including low quality RCT, e.g. <80% follow-up)
2c	"Outcomes" research; Ecological studies
3a	Systematic review (with homogeneity) of case-control studies
3b	Individual Case-control study
4	Case series (and poor quality cohort and case-control study
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"

Table 1. Levels of evidence for therapy, derived from [69]

Table 2

Grade of Recommendation	Evidence level required
A	consistent level 1 studies
B	consistent level 2 or 3 studies or extrapolations from level 1 studies
C	level 4 studies or extrapolations from level 2 or 3 studies
D	level 5 evidence or troublingly inconsistent or inconclusive studies of any level

Table 2. Grades of recommendation for therapy, derived from [69]