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Overview

Mathematical Modelling for Patient Selection in Proton Therapy

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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 used 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.

Key words: Discrete event simulation; mathematical modelling; NTCP; patient selection; proton therapy

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.

Introduction

In this overview, the mathematical modelling tools for patient selection and demand prediction for X-ray radiotherapy, 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 [1], 'all models are wrong, but some may be useful'.

Cost of Proton Beam Therapy

Although 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 radiotherapy 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

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budget [2]. The Department of Health is paying £250m for two, four room, centres [3] and centres in the USA have reported capital costs of between $150m [4] and $200m [5]. By 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 times [9] to 2.5 times [10] 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 mean there is a greater requirement to ensure that the treatment capacity is filled efficiently to ensure value for money. Whereas 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 hypofractionation) 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 with other radiotherapy modalities.

Demand Modelling

Mathematical and statistical modelling for both patient selection and the demand for services is not new in radiotherapy 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 Royal College of Radiologists' 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 radiotherapy, 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 these models can be used to estimate the impact of introducing a new technology into an

<table>
<tr><td rowspan="3">Stage 3a
10%
LUCADA
Normalised</td><td rowspan="2">Surgery 10%
[Non-bulky nodal disease]</td><td>N0-1</td><td>No Radiotherapy ECRIC 71%</td></tr>
<tr><td>Positive Margin > N2</td><td>Radiotherapy
55/20#, 60 Gy/30# if +ve margin
50/20> N2 disease Lung ART 54/30#</td></tr>
<tr><td>No surgery 90%</td><td colspan="2">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</td></tr>
<tr><td></td><td colspan="2">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</td></tr>
</table>

Fig 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].

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