
Article:
Spencer, KL orcid.org/0000-0002-6846-4341 and Tree, AC (2020) Commentary on Cost-Effectiveness of Metastasis-Directed Therapy in Oligorecurrent Hormone-Sensitive Prostate Cancer. International Journal of Radiation: Oncology - Biology - Physics. ISSN 0360-3016

https://doi.org/10.1016/j.ijrobp.2020.08.021

Commentary on Cost-effectiveness of metastasis-directed therapy in oligorecurrent hormone-sensitive prostate cancer

Dr K L Spencer[1] and Dr A C Tree[2]

1. Academic Unit of Health Economics, Leeds Institute of Health Sciences, University of Leeds, UK; Leeds Cancer Centre, Leeds Teaching Hospitals NHS Trust, UK.
2. The Royal Marsden NHS Foundation Trust, London, UK; The Institute of Cancer Research, London, UK.

Corresponding author:

Dr K L Spencer
Academic Unit of Health Economics,
Room 11.58, Level 11, Worsley Building,
Clarendon Way,
University of Leeds,
Leeds
LS2 9LU

Conflicts of interest:
Dr Spencer reports no conflicts of interest. Dr. Tree reports conference travel from Astellas, personal fees from Ferring, Janssen, and Genesis healthcare, grants and personal fees from Elekta and grants from Accuray and Varian outside of the submitted work .

Funding:
No specific funding was received.

As the cost of healthcare rises globally there is a pressing need to recognise that ever escalating treatment costs must be matched by improved outcomes; resources spent on care which delivers no benefit may deprive others of beneficial care. As such, we welcome the manuscript by xxx et al who seek to estimate the cost-effectiveness of stereotactic radiotherapy for oligo-metastatic prostate cancer.

The use of SABR/SBRT for oligometastases remains a subject of controversy, due to the lack of Phase III randomised controlled trial evidence of an overall survival benefit. Several phase II studies have, however, shown a PFS benefit with the data in prostate cancer leading the field(1–3). For many clinicians this is sufficient to recommend treatment, whilst others retain equipoise. It is therefore timely to understand the cost-effectiveness of this intervention in order to guide reimbursement decisions and, importantly, highlight areas of uncertainty. We would like to highlight a number of important issues raised by xxx et al's study which have relevance to these two goals.

Firstly, the cost-effectiveness model presented here has been developed from the perspective of the US payer. This journal has a global readership and it is important to recognise that cost-effectiveness results are, by their nature, jurisdiction specific. The willingness to pay threshold varies widely; in the US a threshold of $100,000 per quality adjusted life year (QALY) is frequently quoted, whilst in England the National Institute for Health and Care Excellence accepts a threshold in the range of $25,000-40,000/QALY. Further extensive variation is observed in the costs of care. Indeed, the authors carry out a number of valuable sensitivity analyses considering alternative costs for abiraterone acetate plus prednisone (AAP) and androgen deprivation therapy (ADT) and other second-generation anti-hormonal therapies. The base-case model incorporates the 3-monthly cost of generic Abiraterone at $4,047. As the authors highlight, where branded Abiraterone, Enzalutamide or Apalutamide are included the net-monetary benefit (NMB) is more strikingly in favour of MDT. We note, however, that limited cost is incorporated for monitoring visits and bloods tests whilst on AAP+ADT; inclusion of greater numbers of appointments might be expected to improve the incremental NMB of the MDT strategy whilst conversely, a lower cost of Abiraterone could markedly reduce the incremental NMB. Similar variations are likely to exist in the cost of routine care across jurisdictions. This can be easily demonstrated in radiotherapy. The cost of three fraction SBRT was assumed to be $7643 in the model, which contrasts markedly with the cost of SBRT in the UK, for example, where the cost is just over half of this.

The authors incorporate in the model the risk of death due to other causes. This is an important consideration in a disease where more than a third of men diagnosed are over the age of 75. Again, however, it is necessary to define this risk and inevitably assumptions are therefore required. Here the average risk for a 66 year old American man is incorporated, as per the age profile of the STAMPEDE trial (4). The median age in a non-clinical trial population will undoubtedly be higher and the potential consequences of incorporating a risk profile more aligned to the age of those in routine care requires consideration. The competing risk of mortality for this somewhat older population will be higher and the consequences of this for the estimated cost-effectiveness are difficult to quantify. The benefits gained from

AAP+ADT may be reduced, however, the cost of this strategy is similarly likely to fall. Formal incorporation of alternative model assumptions, to reflect differing populations, would help to provide clarification of the cost-effectiveness in a non-trial population.

The fall in the incremental NMB of MDT observed with greater follow-up in the model (extending the time-horizon) raises a key point about uncertainty in cost-effectiveness modelling. It is routine to extrapolate outcomes beyond the available observed data in such analyses, as failure to recognise future benefits and harms may impact on the quality adjusted life years gained and thus the estimated cost-effectiveness. This requires careful consideration of the optimal modelling strategy based upon the available data. The reticence in presenting a baseline analysis with a longer time-horizon here reflects a lack of long term outcome data on which to model. This uncertainty is critical. We do not currently know if MDT can effectively 'reset the stopwatch' on time to prostate cancer death, or whether it simply achieves local control with no measurable impact on overall survival. The impact of MDT upon subsequent responses to systemic therapy is similarly hard to predict, yet a longer time-horizon is highly relevant for this population with an expected median overall survival likely to exceed 5 years.

A final uncertainty present in this analysis results from the measurement and valuation of quality of life used to inform the current model. It appears likely, given the accumulating evidence, that the use of ablative radiotherapy will delay the need for further therapy, which may include androgen deprivation therapy, targeted therapy or chemotherapy in prostate cancer. It may have been, *a priori*, assumed that this will improve quality of life, but the evidence for this is lacking to date. Indeed, whilst the use of early ADT is associated with a reduction in sexual activity-related quality of life and an increase in hormone therapy-related side effects, overall quality of life has previously been found to be unaffected(5), a finding mirrored in the STOMP trial (2). This seems at odds with what is heard anecdotally from patients, week in week out, so either our interpretation of what patients say is wrong, or our tools are too blunt to pick up the changes they feel. How each individual experiences these outcomes gains greater importance when, as is seen here, two treatments (MDT and AAP+ADT) appear to offer similar cost-effectiveness. If this is the case, and given the significant uncertainties around the quality of life benefits achieved by delaying ADT, future work should not only aim to reduce the uncertainties seen in the presented model but to deliver these outcomes in a way which is meaningful to patients. In this way patients and clinicians can make informed decisions about the optimal strategy for each individual.

We congratulate the authors for documenting clearly and transparently the assumptions used to inform their model. No cost-effectiveness model is perfect and uncertainties are inevitable. Transparency allows these uncertainties to be carefully considered by the relevant decision-maker when reimbursement is considered. Taking transparency a step further, there is an increasing momentum in health economics towards open source models with the model code, assumptions, documentation and results all provided such that others can interrogate it and build upon it for greater understanding (6). We encourage the authors of this study to consider such an approach. This would allow modifications and further sensitivity analyses to

be carried out, expanding the impact of their model into other healthcare jurisdictions. Not only do the authors benefit from potentially productive future collaborations but research efficiency is increased, as each interested party is not forced to 'reinvent the wheel'. Such an approach could also support the use of this model for value of information and real option analysis (7). In this way the value of reducing uncertainty through future clinical trials can be assessed and uncertain parameters with significant influence over cost-effectiveness can be highlighted to guide the design of future studies.

The uncertainties in this model are significant with considerable overlap in the estimated NMB of the MDT and AAP+ADT strategies. Potential exists for marked changes in interpretation as further data accrues; the long-term consequences of MDT in oligometastatic prostate cancer remain uncertain. Despite this, MDT for oligometastatic prostate cancer is increasingly used in routine practice. Over the last few decades, radiotherapeutic advances has not faced the same scrutiny as new pharmaceuticals. The reasons for this are multiple and have been considered previously by van Loon et al (8). Crucially, they include the challenges of funding trials to measure late endpoints, particularly given that trial funding is already sparse in comparison to pharmaceutical research. As a consequence, we all too often find ourselves stuck in a "Catch 22", where insufficient evidence is available to prove better survival or QoL, but where trials cannot be conducted, either due to lack of equipoise or, importantly, lack of funding. As such, innovations we believe to be beneficial become routine practice with only a progression-free survival benefit, sometimes to the detriment of toxicity levels and/or QoL. This has been the case with prostate dose escalation and low-dose rate brachytherapy boost (9,10). Further examples are not hard to come by as small, frequently unquantified, incremental improvements in outcomes have been exchanged for modest cost increases.

Without concerted efforts, both within radiation oncology and by commissioners and research funders, practice will continue to change without Level one evidence, as no change is a guarantee of no improvement. The benefits and opportunity costs of this approach will, however, remain unquantified. As the incremental cost of novel treatments rises, there is now a pressing need to increase radiation research funding globally. Increased costs should be matched by increased benefits and the uncertainty in outcomes must be reduced if we are to confidently state that, within finite healthcare budgets, the opportunity costs of novel interventions are justified.

We congratulate the authors on bringing health economics into the ongoing MDT debate. Whilst MDT appears a promising, and potentially cost-effective strategy, until greater clinical certainty is available, from randomised studies, the clinical debate will rumble on.

References:

1. Palma DA, Olson R, Harrow S, Gaede S, Louie AV, Haasbeek C, et al. Stereotactic ablative radiotherapy versus standard of care palliative treatment in patients with oligometastatic cancers (SABR-COMET): a randomised, phase 2, open-label trial. The Lancet. 2019 May;393(10185):2051–8.

2. Ost P, Reynders D, Decaestecker K, Fonteyne V, Lumen N, De Bruycker A, et al. Surveillance or Metastasis-Directed Therapy for Oligometastatic Prostate Cancer Recurrence: A Prospective, Randomized, Multicenter Phase II Trial. J Clin Oncol. 2017 Dec 14;JCO.2017.75.485.

3. Phillips R, Shi WY, Deek M, Radwan N, Lim SJ, Antonarakis ES, et al. Outcomes of Observation vs Stereotactic Ablative Radiation for Oligometastatic Prostate Cancer: The ORIOLE Phase 2 Randomized Clinical Trial. JAMA Oncol. 2020 May 1;6(5):650.

4. James ND, de Bono JS, Spears MR, Clarke NW, Mason MD, Dearnaley DP, et al. Abiraterone for Prostate Cancer Not Previously Treated with Hormone Therapy. N Engl J Med. 2017 Jul 27;377(4):338–51.

5. Duchesne GM, Woo HH, King M, Bowe SJ, Stockler MR, Ames A, et al. Health-related quality of life for immediate versus delayed androgen-deprivation therapy in patients with asymptomatic, non-curable prostate cancer (TROG 03.06 and VCOG PR 01-03 [TOAD]): a randomised, multicentre, non-blinded, phase 3 trial. Lancet Oncol. 2017 Sep;18(9):1192–201.

6. Dunlop WCN, Mason N, Kenworthy J, Akehurst RL. Benefits, Challenges and Potential Strategies of Open Source Health Economic Models. Pharmacoeconomics. 2017;35(1):125–8.

7. Eckermann S, Willan AR. Expected value of information and decision making in HTA. Health Econ. 2007;16(2):195–209.

8. van Loon J, Grutters J, Macbeth F. Evaluation of novel radiotherapy technologies: what evidence is needed to assess their clinical and cost effectiveness, and how should we get it? Lancet Oncol. 2012 Apr;13(4):e169-77.

9. Creak A, Hall E, Horwich A, Eeles R, Khoo V, Huddart R, et al. Randomised pilot study of dose escalation using conformal radiotherapy in prostate cancer: long-term follow-up. Br J Cancer. 2013 Aug;109(3):651–7.

10. Morris WJ, Tyldesley S, Rodda S, Halperin R, Pai H, McKenzie M, et al. Androgen Suppression Combined with Elective Nodal and Dose Escalated Radiation Therapy (the ASCENDE-RT Trial): An Analysis of Survival Endpoints for a Randomized Trial Comparing a Low-Dose-Rate Brachytherapy Boost to a Dose-Escalated External Beam Boost for High- and Intermediate-risk Prostate Cancer. Int J Radiat Oncol. 2017 Jun 1;98(2):275–85.