

Magnetic Resonance-guided Radiotherapy - Can We Justify More Expensive Technology?

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The importance of delivering value-based healthcare is being acknowledged across the world, regardless of the underpinning funding strategy. In the UK, the National Institute for Health and Care Excellence is recognised for spearheading the integration of health economics into healthcare. The National Health Service spends a lower proportion of national income when compared to other developed countries such as France, Germany, Japan and, of course, the USA (1). The media is filled with reports of underfunding and under-resourcing across the NHS. When it comes to new advanced radiotherapy technology, there is a dilemma; with new drugs, the health service pays for them once the evidence has been acquired, however, with technology, the hospital has to invest in the hardware prior to the evidence being obtained.

How then can we make a case for potentially cost-intensive MR-guided radiotherapy?

This question is particularly important at a time of economic unpredictability where spending on new technology is likely to be open to heavy scrutiny.

Aside from the philosophical argument about the wisdom of putting the brakes on progress for fear of over-reaching, there are two counter arguments; firstly, the financial impact of an innovation is unknown until it has been tested, data collected and analysed; secondly we, as physicians, have a primary responsibility to our patients, and to the wider population to continue to improve clinical outcomes, rather than be concerned with the current political whims of healthcare funding. The NHS spent £5.68 billion on cancer in 2012/2013 and despite radiotherapy being responsible for 40% of cancer cures (2) it accounts for only 5% of the NHS cancer spend. Radiotherapy is good value for money for the NHS, yet we constantly lose the PR war to the latest pharma innovation achieving incremental gains, often at high cost.

A good example of technology leading to improved cost effective treatment is stereotactic body radiotherapy (SBRT). SBRT has allowed us to test fractionations that were hitherto thought too toxic to attempt e.g. 54 Gy in 3 fractions to the lung. This would have been inconceivable using 3D conformal radiotherapy and only been possible due to investment in advanced radiotherapy planning and motion management. Though this makes SBRT expensive, cost-effectiveness data already suggests a possible financial benefit (3)(4).

MR-guided radiotherapy is the latest technology holding promise for better patient outcomes. It is already being used internationally in some centres using the ViewRay or MRIdian systems (5). The UK will “go-live” with MR-guided radiotherapy in 2018 on two sites, the Royal Marsden/Institute of Cancer research and The Christie/Manchester Cancer Research Centre. Both will use the Elekta Unity, a 1.5T Phillips MRI scanner integrated with an Elekta 7MV Linac (6). This collaboration involves both the global MR-Linac consortium (7) and the ART-NET collaboration across the UK (8). Not only is this important for the UK’s international standing, but it will strengthen these, and other, close partnerships within UK radiotherapy community.

But what is the clinical driver to this expensive innovation? There are still too many cancers where we don’t achieve adequate local control. With better image guidance and daily adaptation further dose escalation, beyond that achievable with current platforms, may be possible. For some cancers e.g. lung and pancreas this could improve local control and reduce subsequent metastatic failure. For instance, early reports from centres using ViewRay report results that show promise for patients with pancreatic cancer (9). In contrast, there are some cancers e.g. prostate and breast, where the local control rate already exceeds 90% for most cases. Here the objective is not about improvements in local control but about treatment minimisation, either by reducing side effects or by further hypofractionation.

In prostate cancer there is now consensus that the α/β ratio of prostate cancer is <2 Gy (10). We know that 60 Gy in 20 fractions is comparable to 74 Gy in 37 or 78 Gy in 39 (11-13). The PACE trial is testing whether 5 fraction SBRT is equivalent to 62 Gy in 20 fractions, but already there is a body of Level II evidence suggesting effective outcomes in 5 fractions (14).

If 5 fractions are effective, could a single fraction could be used to treat prostate cancer? Single fraction high dose rate brachytherapy as monotherapy appears safe and effective (15)(16), so can we do the same with linac-based radiotherapy? Now with MR-guided adaptive radiotherapy (i.e. plan designed, or amended immediately before treatment) this hypothesis can be investigated. A number of challenges will need to be overcome. MR-guided adaptive radiotherapy will need fast adaptive re-planning, the ability to plan on MRI without CT electron density information, physician-less auto-contouring and fast dose delivery (17).

If single fraction curative treatment is possible for prostate, then it may be possible in breast, lung and other cancers with a low α/β ratio or a high dependency on total treatment time for cure. The implications of this for radiotherapy departments, and the wider NHS, are startling. The implementation of the CHHiP 20 fraction regimen in the UK is estimated to save the NHS in excess of £20 million per year, albeit by reducing the 'income' of radiotherapy departments. If further hypofractionation and MR-guidance is to become commonplace, we need to find ways of reimbursing departments effectively. The NHS savings with single fraction SBRT would be even more stark, despite the higher machine and treatment delivery costs.

But it may not stop there. Counter-intuitively, a rather strange twist to the argument would be in the developing world. It may seem odd to raise this in an article about expensive technology, likely out of reach of many developing countries (18)(19). It is to the shame of us all that 29 African nations have no radiotherapy services at all, and that the total number of radiotherapy machines across the entire continent is 277 (20). Clearly none of the academically interesting research mentioned above will impact on this appalling situation in the next 10 years, but for a population who may need to travel hundreds of miles for treatment, a short stay away from home is more socio-economically viable than a long stay and a machine delivering single fraction of curative radiotherapy can treat many more patients than one delivering over 30 fractions per treatment.

For now, from our ivory towers, it remains about the spirit of human endeavor, about trying to cure more people, with less side effects, in less time. MR-guided radiotherapy in the UK is about to begin.

References

1. Studies) GS (Institute of F. Briefing Note (BN201) UK health spending [Internet]. 2017. Available from: <https://www.ifs.org.uk/publications/9186%0D>
2. Tubiana M. The role of local treatment in the cure of cancer. *Eur J Cancer*. 1992;28(12):2061–9.
3. Hodges JC, Lotan Y, Boike TP, Benton R, Barrier A, Timmerman RD. Cost-effectiveness analysis of SBRT versus IMRT: an emerging initial radiation treatment option for organ-confined prostate cancer. *Am J Manag Care* [Internet]. 2012/06/15. 2012;18(5):e186-93. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/22694113>
4. Smith BD, Jiang J, Chang JY, Welsh J, Likhacheva A, Buchholz TA, et al. Cost-effectiveness of stereotactic radiation , sublobar resection , and lobectomy for early non-small cell lung cancers in older adults. *J Geriatr Oncol* [Internet]. 2015;6(4):324–31. Available from: <http://dx.doi.org/10.1016/j.jgo.2015.05.002>
5. Mutic S, Dempsey JF. The ViewRay System : Magnetic Resonance –. *Semin Radiat Oncol* [Internet]. 2014;24(3):196–9. Available from: <http://dx.doi.org/10.1016/j.semradonc.2014.02.008>
6. Lagendijk JJ, Raaymakers BW, van Vulpen M. The magnetic resonance imaging-linac system. *Semin Radiat Oncol* [Internet]. 2014;24(3):207–9. Available from:

- <http://www.ncbi.nlm.nih.gov/pubmed/24931095>
7. Kerkmeijer LGW, Fuller CD, Verkooijen HM, Verheij M, Choudhury A, Harrington KJ, et al. The MRI-Linear Accelerator Consortium: Evidence-Based Clinical Introduction of an Innovation in Radiation Oncology Connecting Researchers, Methodology, Data Collection, Quality Assurance, and Technical Development. *Front Oncol* [Internet]. 2016;6(October):1–6. Available from: <http://journal.frontiersin.org/article/10.3389/fonc.2016.00215/full>
 8. Harrington K, Hall E, Hawkins M, Henry A, MacKay R, Maughan T, et al. Introducing the Cancer Research UK Advanced Radiotherapy Technologies Network (ART-NET). *Clin Oncol*. 2017;29.
 9. Rudra S, Jiang N, Rosenberg S, Olsen JR, Parikh P, MF B, et al. High dose adaptive MRI guided radiation therapy improves overall survival of inoperable pancreatic cancer. In: ASTRO annual meeting. 2017. p. Abstract 2443.
 10. Dasu A, Toma-Dasu I. Prostate alpha/beta revisited -- an analysis of clinical results from 14 168 patients. *Acta Oncol* [Internet]. 2012;09/13. 2012;51(8):963–74. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/22966812>
 11. Dearnaley D, Syndikus I, Mossop H, Khoo V, Birtle A, Bloomfi D, et al. Conventional versus hypofractionated high-dose intensity-modulated radiotherapy for prostate cancer : 5-year outcomes of the randomised , non-inferiority , phase 3 CHHiP trial. *Lancet Oncol* [Internet]. 2016;2045(16):1–14. Available from: [http://dx.doi.org/10.1016/S1470-2045\(16\)30102-4](http://dx.doi.org/10.1016/S1470-2045(16)30102-4)
 12. Catton CN, Lukka H, Gu C-S, Martin JM, Supiot S, Chung PWM, et al. Randomized Trial of a Hypofractionated Radiation Regimen for the Treatment of Localized Prostate Cancer. *J Clin Oncol* [Internet]. 2017 Jun 10 [cited 2017 Jul 29];35(17):1884–90. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/28296582>
 13. Dearnaley D, Syndikus I, Gulliford S, Hall E. Hypofractionation for Prostate Cancer: Time to Change. *Clin Oncol* [Internet]. 2017;29(1):3–5. Available from: <http://dx.doi.org/10.1016/j.clon.2016.09.020>
 14. King CR, Freeman D, Kaplan I, Fuller D, Bolzicco G, Collins S, et al. Stereotactic body radiotherapy for localized prostate cancer: pooled analysis from a multi-institutional consortium of prospective phase II trials. *Radiother Oncol* [Internet]. 2013/09/26. 2013;109(2):217–21. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/24060175>
 15. Hoskin P, Rojas A, Ostler P, Hughes R, Alonzi R, Lowe G, et al. High-dose-rate brachytherapy alone given as two or one fraction to patients for locally advanced prostate cancer: Acute toxicity. *Radiother Oncol* [Internet]. 2014 Feb [cited 2017 Jul 29];110(2):268–71. Available from: <http://linkinghub.elsevier.com/retrieve/pii/S0167814013005173>
 16. Prada PJ, Cardenal J, Blanco AG, Anchuelo J, Ferri M, Fernández G, et al. High-dose-rate interstitial brachytherapy as monotherapy in one fraction for the treatment of favorable stage prostate cancer: Toxicity and long-term biochemical results Prostate HDR brachytherapy as monotherapy in one fraction. *Radiother Oncol* [Internet]. 2016;119(3):411–6. Available from: <http://dx.doi.org/10.1016/j.radonc.2016.04.006>
 17. Pathmanathan A, van As NJ, Kerkmeijer LGW, Christodouleas JP, Lawton C, Vesprini D, et al. MR-guided adaptive radiotherapy; a ‘game changer’ for prostate radiation therapy. *Int J Radiat Oncol Biol Phys*. 2017;in press.
 18. Barton MB, Zubizarreta E, Gospodarowicz M. Radiotherapy in Low- and Middle-income Countries . What Can We Do Differently ? *Clin Oncol* [Internet]. 2017;29(2):69–71. Available from: <http://dx.doi.org/10.1016/j.clon.2016.11.009>
 19. Yap ML, Hanna TP, Sha J, Ferlay J, Bray F, Delaney GP, et al. The Bene fi ts of Providing External Beam Radiotherapy in Low- and Middle-income Countries Statement of Search Strategies Used and Sources of Information. 2017;29.
 - 20.. Stefan DC. Cancer Care in Africa: An Overview of Resources. *J Glob Oncol* [Internet]. 2015;1(1):30–6. Available from: <http://jgo.ascopubs.org/content/1/1/30.full%5Cnhttp://jgo.ascopubs.org/cgi/doi/10.1200/JG>

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