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Proton beam therapy: the next disruptive innovation in healthcare?

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The term *disruptive innovation* was coined in the 1990s by Harvard Business School professor, Clayton Christensen, to describe technological innovations that transform current markets and quickly replace existing technology.¹ A commonly cited example relates to the development of the automobile in the early 1900s. Clearly, the automobile represented a revolutionary technological advancement for transportation, but it remained a luxury good of limited use until Henry Ford began production of the Model-T in 1908. The Model-T was by no means a superior product to previously produced automobiles. But Ford's assembly line mass production methods allowed the car to be produced at a significantly less cost and suddenly the automobile was affordable to the masses. In this case, more efficient mass production techniques represented a disruptive innovation in the transportation market.

Technology innovation within healthcare has been extraordinary and has undoubtedly resulted in improved patient outcomes over time. However, examples of truly disruptive technologies in healthcare are uncommon. Essential qualities of disruptive technologies are that they need to be convenient, affordable and accessible in order to foster rapid adoption. Instead, most innovations in healthcare technology are considered *sustaining innovations* in that they represent stepwise improvements of existing technology, but are also more costly and complex. Recent examples include the use of positron emission tomography (PET)/CT, robotic assisted surgery or molecular targeted cancer therapies.

The need for evidence development is clearly one reason why disruptive innovations in healthcare are rare. Healthcare is relatively unique in this regard when compared with other sectors of technological innovation, such as automotive manufacturing or telecommunications. Decisions in healthcare use have high stakes that can impact patient's lives, and the associated costs are often borne by society as a whole rather than the individual. Stakeholders in healthcare therefore rely on methods of evidence-based medicine, health technology assessment and comparative effectiveness research to assess the value and to decide on the most appropriate application of new and innovative technologies.

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The development of the home glucometer in the early 1980s to assist in the management of diabetes mellitus was an example of a disruptive technology in healthcare. Frequent visits to the physician's office previously required to monitor blood glucose levels were no longer needed. In addition, the glucometers facilitated closer monitoring of blood glucose levels that could potentially reduce acute and long-term complications of the disease. These simple devices could reduce costs, improve convenience and potentially enhance patient outcomes. Their use was rapidly adopted as they were promoted by relatively low cost, ease of use and studies demonstrating the accuracy of the measured test results.

Proton beam therapy, a recently developed approach to treating cancer, may be one of those technical innovations that have the potential to disrupt and so transform our approach to oncological treatment. Proton beam therapy is an advanced radiation treatment technology that reduces low and intermediate radiation dose to normal tissues when compared with existing photon-based radiation techniques. By reducing radiation dose to normal tissue, proton beam therapy may have the potential to improve the outcomes of patients with cancer by reducing treatment-related toxicities and/or allowing for safe escalation of radiation doses to enhance tumour control rates.

In its current state, proton beam therapy is more closely analogous to the automobile scenario prior to the development of the Model-T, rather than the home glucometer. There has been a global proliferation of proton treatment facilities over the past two decades, and some have suggested that proton beam therapy may at some point replace current radiation treatment techniques.²³ However, the promise and potential of proton beam therapy as a disruptive innovation in healthcare remains largely unrealised due to prohibitively high costs limiting patient access as well as a lack of evidence regarding its clinical effectiveness. In order for proton therapy to become a disruptive innovation and gain widespread adoption that would transform the treatment for patients with cancer, significant additional innovations are necessary to improve patient access by reducing costs of treatment, and evidence development must occur to mitigate clinical uncertainties regarding its use (figure 1).

Proton therapy is more costly than most other existing radiation treatment technologies. Construction of a proton therapy centre is expensive, ranging from US\$25 million to over US\$200 million depending on the size and capacity of the facility. The costs of treatment delivery from a payer perspective are generally two to three times greater than photon-based radiation treatments. Although previous advances in radiation therapy such as intensity modulated radiation therapy were more expensive than conventional treatments and have been widely adopted, proton beam therapy requires a much larger financial investment to provide for the necessary space, equipment and personnel. As a result, treatments are only available in selected centres, sometimes requiring patients and their families to relocate for several weeks or longer. The associated financial burdens such as costs of travel, temporary housing, childcare and lost wages will often fall on patients and their families. National healthcare systems as well as private payers have had to make difficult decisions regarding how and when to financially support patient access to proton therapy. Despite limited evidence to guide such decisions, strong opinions among patients, physicians and other stakeholders have resulted in a challenging medical–ethical dialogue.

Greater affordability alone though would not obviate the need for evidence development supporting the use of proton therapy. Delivery of proton therapy requires a centre to develop new technical expertise in treatment planning, equipment maintenance and quality assurance to provide for consistent, high quality and timely treatment of patients. In addition, there are many relevant clinical uncertainties with the use of proton therapy, and we must develop effective strategies to mitigate these uncertainties and develop further evidence regarding its effectiveness in real world clinical settings, irrespective of the costs of care.

A significant limitation of proton therapy is that the depth of tissue penetration for protons is sensitive to tissue density, and, therefore, changes in a patient's internal anatomy such as bowel gas or respiration can result in alterations of the dose distribution compared with the intended treatment plan.⁴⁵ This phenomenon is referred to as 'range uncertainty' and is a concern when treating patients for malignancies outside the central nervous system where targets and organs are mobile and dynamic. To ensure adequate dose coverage with proton therapy, radiation oncologists may compensate by treating more distal to the intended target with less conformal treatment. This results in more radiation dose to normal tissues than would otherwise be required. More recent advancements in proton therapy delivery techniques such as image guidance with cone-beam CT or pencil beam scanning technology may help to mitigate uncertainties related to dose delivery and further improve the conformality of proton therapy treatment relative to photon-based techniques. Advanced image guidance such as cone-beam CT may be particularly important to ensure accurate delivery of proton beam therapy given the sensitivity of protons to changes in internal anatomy and tissue density. However, our knowledge and understanding in this area continues to evolve and prospective randomised clinical trials as well as high quality observational studies are crucial to evaluate the strategies intended to mitigate the uncertainties inherent in proton therapy delivery.

There is also a persistent knowledge gap regarding the relative biological effectiveness (RBE) of proton therapy which varies along the path of a proton beam.⁶ RBE is defined as the ratio of biological effectiveness of one type of ionising radiation relative to another, given the same amount of absorbed energy. Proton RBE has not been well studied for many tumour types as well as for many normal organs. As a result, radiation dose prescriptions and dose limits for normal tissues are often borrowed from our experience with treatments based on X-rays instead of being derived through direct experiment. Further basic and clinical research is needed to improve our understanding of proton RBE, which will provide greater confidence in the safety and effectiveness of proton-based treatments.

Another concern relates to the potential for delays in patient treatment that may result from cumbersome coordination of care between physicians of different oncological specialties, primary care, treating health systems, patient relocation and payment authorisation procedures. Such delays may be clinically significant for certain malignancies and could compromise oncological outcomes. Development of efficient care pathways for patients receiving proton therapy that allow for timely initiation of treatment is required.

Evidence supporting the net health benefits of proton therapy remains insufficient, and traditional methods of health technology assessment fall short in our current evaluation of

proton therapy. Within the USA, the Washington State Health Technology Assessment Program (HTAP) recently conducted a systematic assessment of the value of proton therapy with regards to policy decisions related to payment, for the state's public healthcare payers.⁷ In their final report, they stated that 'comparative evidence was extremely limited for certain conditions and entirely absent for others'. The report identified six randomised controlled trials that included patients receiving proton therapy, but only two of these trials actually directly compared proton therapy with alternative radiation techniques.⁸⁹ Furthermore, the group expressed quality concerns with retrospective and observational studies that have been published, stating that cohorts under comparison were frequently non-contemporaneous or had substantial differences in baseline demographic and clinical characteristics. Based on available evidence, the group concluded that proton therapy provided at least incremental net health benefits for patients with ocular tumours, central nervous system tumours, paediatric cancers or tumours within previously irradiated areas of the body.⁹⁻¹⁴ In their final recommendations, treatment with proton therapy is recommended as a covered benefit for patients with these specific conditions, but not for others. With the exception of ocular tumours, these recommendations are not based upon randomised evidence but instead are based upon the lack of judged clinical equipoise in select patient groups which was deemed likely to prevent the conduct of prospective randomised trials.

The conclusions of the Washington State HTAP are understandable in the context of limited evidence and high costs associated with proton therapy. However, evidence development regarding proton therapy has faced several potential barriers which should be discussed. First, some of the potential benefits of proton therapy, such as reduced secondary malignancy rates or improvements in patient neurocognitive function, may take years or even decades of follow-up to be adequately measured. While prospective clinical trials are ongoing, observational studies have been limited by available data sources that lack details regarding radiation treatments delivered. Evidence development in this area should be enhanced through growth of novel data sources for observational studies which are designed to provide data specific to radiation therapy.

A second concern is the potential lack of clinical equipoise regarding proton therapy compared with conventional photon-based radiotherapy. Clinical equipoise requires genuine uncertainty in the expert medical community over whether a treatment will be beneficial.¹⁵ Some experts have argued that neither patients nor providers would prefer to have more healthy, normal tissue exposed to radiation and that the idea of requiring randomised controlled trials in any disease site to demonstrate the superiority of proton therapy is unethical.³ Some have expressed this sentiment by stating that 'we don't need a randomized controlled trial to prove the effectiveness of a parachute.'¹⁶ These arguments, however, oversimplify the evidence for and against equipoise vis a vis proton therapy and ignore the consequential complexities and uncertainties inherent to proton therapy delivery in its current state as well as the costs. Importantly, the persistent uncertainties discussed previously in this article establish the clinical equipoise necessary for the conduct of proton therapy research.

The ethical basis for proton therapy research was further supported by the findings from a recent series of workshops among international experts.¹⁷ In their final position statement,

they conclude that ‘overall there is a decided need for more basic scientific and clinical research on charged particle radiation therapy [proton therapy]’. The position statement also describes how the presence of clinical equipoise for research may vary among differing patient populations and therefore randomised and non-randomised clinical trials should be designed accordingly.

A third barrier to evidence development regarding proton therapy is the variable coverage policies of payers in healthcare which may deny payment for proton therapy based on the lack of supportive evidence. Such coverage decisions may slow the conduct of further research regarding the comparative effectiveness of this promising but unproven medical technology. Healthcare systems cannot afford to pay for expensive therapies without evidence of value; however, it is short-sighted to establish payment policies that slow evidence development for innovative treatments that could lead to better cancer outcomes.

Disruptive innovations in our society are occurring at an extraordinary and unprecedented pace. Within the last decade, the adoption of email and wireless mobile devices has transformed the work place for much of the world. However, disruptive innovations in healthcare technology are appropriately less frequent, due to the potentially higher stakes of technology adoption and the need to demonstrate clinical effectiveness and value for society. Proton therapy currently remains a highly promising health technology with the potential to reduce consequential side effects of treatment or in some cases enhance the cure rates in patients with cancer receiving radiotherapy. However, without further innovation to mitigate treatment uncertainties and improve affordability, the use of proton therapy will remain limited. The ‘promise’ held by proton therapy to improve outcomes for our patients demands that we have the will to engage in proton therapy research and innovation so that its real world value matches its great potential. A path for proton therapy towards disruptive innovation remains unseen at the moment; but the promise of the Bragg peak is likely to be a critical component in future radiation therapy.

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Figure 1.
Proton therapy: a pathway to disruptive innovation.