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COMMENTARY

The evaluation of innovation in radiation oncology – what can we do and what should we do?

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Due to multiple factors including population ageing and generalization of cancer screening, the incidence of cancer is rising in both developed and emerging countries [1]. More patients mean more health care spending, and in a context of economic stagnation this creates serious financial pressure for the society and the individuals. New technologies are almost invariably more expensive than older ones, because of development cost and also incentive cost related to their adoption [2]. However, since the introduction in the 1990s of computed tomography (CT) planning and multileaf collimation leading to intensity-modulated radiotherapy (IMRT), the pace of innovation in radiation oncology has accelerated and the adoption of new technology is rarely based on level 1 clinical evidences [3,4]. Currently two new technologies, namely, the MR-Linac and intensity-modulated proton therapy (IMPT) [5,6], are being introduced, inducing major changes in the radiation oncology practice and may also lead to ballooning costs especially for the later one. There have been repeated press releases questioning the need for expensive techniques like proton therapy, pointing out at the limited amount of evidences to justify their implementation, and recommending abandoning their development [7].

In this commentary we review three different strategies to demonstrate measurable, reproducible and meaningful patient benefits for new technologies to better justify their adoption and to be able to produce cost effectiveness measures.

Randomized clinical trial (RCT)

RCT is the gold standard

RCT remains the gold standard for the demonstration of a clinical benefit of a medical intervention [3]. Those trials compare the outcomes of an experimental procedure to the standard treatment in a randomized fashion. To become a level 1 evidence trials should be multicenter and double-blinded. They are easier to perform if the endpoint is easy to measure, occur frequently and early, and if the new technique effect is large. This leads to sample sizes of a couple of hundreds of patients making the trial affordable. Finally if the endpoint is important for the patient, e.g. a painful moist desquamation, the trial can accrue quickly. An example of fast accruing clinical is the Canadian multicenter randomized clinical comparing breast IMRT to standard two-dimensional (2D) compensation technique [8]. The primary endpoint was moist desquamation and the study accrued rapidly since this side effect occurs frequently and is feared by the patient.

Issues with RCT for new technologies

There are several problems using RCT to evaluate new technologies in radiation oncology. First, double blinding is often not possible for new technologies. Especially in the case of proton therapy patients will know which technique they receive. In such case, it is very important to have the assessors strictly blinded, asking the patient not to disclose the treatment arm, to avoid evaluation bias. The difficulty to blind patients to their treatment arm makes it unreliable to use self-reported measures like quality of life questionnaires.

The second issue is that several cancers have now optimal loco-regional control using radiotherapy, surgery, or a combination of those with medical treatment, such that there appears to be limited room for further improvements to be tested. For example,

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it is unlikely that for patients with early stage breast cancer, low- or intermediate-risk prostate cancer, or rectal cancer treated with mesorectal excision, improvements of the loco-regional control could be achieved [9]. A very large number of patients would be required to demonstrate an incremental disease free or survival benefit such that the cost and complexity of those trials make them difficult to realize.

The third concern is the very rapid pace of change in radiation techniques and treatment protocols, regarding target volume definition and dose fractionation scheme. Also longer patient's follow-ups are necessary to conclude on a benefit as patients have better outcomes. Typically, as the results of a study were mature, the field had often already adopted different treatment volumes and/or dose-fractionation. For example it is difficult today to define a gold standard for prostate radiotherapy in term of dose or fractionation.

A fourth concern is the ethical idea of clinical equipoise [10], meaning that there is a genuine uncertainty for the radiation oncologists whether one treatment arm is superior to the other. In other words a patient should not be randomized to receive a treatment known to be inferior. However, technology adoption often relies on dosimetry and radiobiology studies that show a clear advantage for the new technique compared to the older technique. This leads to challenging ethical issues for the realization of a randomized clinical trial.

The last concern is related to the potentially large anatomical differences in normal or tumor volumes between patients. This means that a new technology may not necessarily lead to a better dose distribution and the standard treatment may in some instance still be better. This makes the process of randomization relatively inefficient.

Model-based approach

The second strategy for the evaluation of new technology is the model-based approach proposed by Langendijk [11]. This strategy has been initially discussed for proton therapy, however, it could well be applied to any new radiotherapy technique. The model-based approach involves the parallel planning of a photon and proton treatments. For example radiation of a carcinoma of the tonsil will have a parallel calculation of a standard IMRT plan and of an IMPT plan. The plans are then analyzed using a normal tissue complication probability (NTCP)-model and a differential probability of toxicity (ΔNTCP) is calculated. In the present case the relevant toxicity would be the occurrence of a grade 3 xerostomia. In The Netherlands reduction thresholds of 10%, 5% and 2% for, respectively, grade 2, 3 and 4 NCI CTCAE side effects have been suggested to justify treating the patient with protons. This strategy needs a first phase of development and validation of NTCP models, and the realization of in silico dosimetry studies to estimate the benefit for a given group of patients. The second phase involves a reality check with clinical assessment using prospective observational studies.

The model-based approach circumvents most of the RCT drawbacks. Focusing on a known side effect, the new technology is only offered when a clear advantage is proved. There is no need to define a standard arm. There is no need of a clinical equipoise, as only the treatment that appears less toxic is offered after the planning comparison. The clear ethical advantage of the model-based approach is that all patients will be given the technique providing them the most clinical benefit. The patient's anatomical variations are also accounted for as photons and protons are compared.

However, it remains unclear what statistical approach should be used to demonstrate the clinical benefit or calculate sample size. Pair-matched analyses with historical controls have significant risk of selection bias. They would also need retrospective photon-proton plan comparison to ensure similar ΔNTCPs between cases for the matching. Another solution would be to compare the theoretical and observed complication rate on the same cohort, and use paired t-tests to assess the degree of significance. However those trials should accept a 2–3% equivalence threshold maximum and they will require about a thousand of patients. They are needed and important because most of the published NTCP models are theoretical, based on complex mathematical modeling of existing data [12]. There is currently no clinically validated NTCP model.

Biological surrogate of delayed outcomes

None of the design detailed above would be well suited to test the benefit of a new technology on rare and long-term, but dramatic endpoints. An example includes patients with an increased risk of cardiac morbidity that are eligible for adjuvant radiotherapy after left breast lumpectomy, and for whom a photon planning is unable to reduce the mean cardiac dose [13]. However, IMPT may be able to reduce significantly the cardiac exposure and hence reduce the occurrence of dramatic events. As cardiac failure is generally detected after several dozen of years, the true benefit of IMPT is difficult to prove.

A solution could be the use of a panel of early biological surrogates for the selected endpoint. A classical example is the use of PSA to assess prostate cancer treatment failure [14]. For the example cited above there has been several publications suggesting that cardiac biomarkers, including the N-terminal pro-B–type

natriuretic peptide (NT-pro-BNP), could be used to assess early signs of cardiovascular dysfunction. In a recent study from D'Errico there was a significant correlation between an elevated NT-pro-BNP and the volume of the heart receiving more than 3 Gy [15]. In another study reported by Wieshammer, patients with evidence of cardiac failure or significant heart exposure several decades ago also had increased NT-pro-BNP levels [16]. One could propose a RCT comparing photons to protons using biological surrogate markers.

The main challenge is to select a biomarker that is specific, sensitive and highly correlated to the long-term endpoint. This means that an extensive preliminary research on the predicting value, sensitivity and specificity of those surrogate biomarkers is needed and must be done on extensive cohorts of patients.

Discussion

There is an increased pressure to develop clinical trials for radiation oncology in the context of the rapid pace of technical development, narrowing of the patient benefit and increasing costs. It is less and less relevant to use traditional survival outcomes since tumor control and survival outcomes have been maximized. As cancer patients are living longer, the research and development goal should shift from ensuring the tumor control, toward the minimization of long-term side effects. Selecting a complication that is frequent and has great impact on the patient's quality of life is a logical clinical trial endpoint. On the other end of the spectrum there are still tumors like pancreatic cancers where an improvement of the loco-regional control is still needed.

The need to use RCT to provide level 1 evidence before adopting a new technology is often in direct conflict with the clinical equipoise and a culture shift is needed to accept new clinical trial strategies, such as the model-based approach. This is critical for a discipline that is transforming, expanding and taking an increasing place in anti-cancer treatment strategies. With more resources invested in the field, it is likely that more costly innovations will appears for which we need to create innovative clinical trial strategies to produce the necessary evidences justifying their adoption.

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