## Abstract

### *Purpose*

Randomized control trials (RCTs) are the cornerstone of delivering sustained improvements in cancer outcome. To inform radiotherapy research policy and prioritization, we analyze the radiotherapy RCT landscape including comparison with trials of systemic therapies over the same time period, with a specific focus on funding and disparities across income settings.

### *Methods and Materials*

This retrospective cohort study identified all phase three RCTs evaluating anticancer therapies published from 2014 to 2017. RCTs were classified according to anticancer modality and country of origin. Descriptive statistics were used to compare key characteristics of radiotherapy RCT studies according to study design characteristics, tumor types evaluated, types of intervention appraised, treatment intent and main funding sources.

### *Results*

The study cohort included 694 RCTs of which 64 were radiotherapy RCTs (9%) compared to 601 (87%) systemic therapy RCTs. 47% of all radiotherapy RCTs focused on two areas of evaluation; combining radiotherapy with systemic agents (25%) and changes in dose fractionation (22%). The most common cancers studied were head and neck (22%), lung (22%) and breast (14%) with cervical cancer trials only representing 3% of the cohort. 33% of radiotherapy RCTs met their primary end point. 62% of radiotherapy RCTs assessed interventions in the curative setting compared to 31% in systemic therapy RCTs. 77% of the radiotherapy RCTs were performed in high-income countries (HIC), 13% in low-and-middle-income countries (LMIC) and 11% in both HIC and LMICs. 17% of radiotherapy RCTs received funding from industry compared to 79% of systemic therapy RCTs.

### *Conclusion*

This study has highlighted the need for greater investment in radiotherapy RCTs and the disparities in conduct of RCTs globally. The study emphases the urgent need for more capacity building for cancer clinical trials in LMICs and more sustainable funding sources.

## Introduction

Cancer research is one of the most dynamic areas of scientific development and randomized controlled trials (RCTs) continue to be the most influential tool to alter clinical practice and improve outcomes. The important benefits of RCTs, compared to large observational studies, is that the act of randomization mitigates bias in assignment to the intervention and control groups, and ensures that the characteristics of patients are balanced [1]. Consequently, if RCTs are large enough, the efficacy of a treatment can be reliably assessed.

Whilst surgery, radiation therapy and systemic therapy are all components of the cancer treatment pathway, there is a discordance between research that is needed to progress cancer care and what is being undertaken given the relative contributions of these modalities to cancer control and cure [2].

Despite challenges in delivering radiotherapy RCTs, there are likely to be major gaps in the evidence base for radiotherapy given that radiotherapy RCTs represent only 9% [2] of all RCTs undertaken globally. This is a stark statistic given that 50% of cancer patients require radiotherapy during their treatment pathway [3]. In addition, the rapid evolution of radiotherapy practice with respect to different technologies, techniques and treatments would suggest that this figure should be significantly higher and could point to a lack of prioritisation by funding agencies.

In addition, there is a major global disparity in oncology research between high income countries (HICs) and low- and middle-income countries (LMICs). 75% [4] of global cancer deaths by 2030 will be in LMICs. However, patients participating in research trials do not represent the worldwide population. A review in 2013 highlighted that, of 12,340 clinical trials, 89% of trials and 82% of research participants were from HICs [5].

From a treatment access perspective, radiotherapy remains the primary modality for the management of several high burden cancers in LMICs (e.g., cervix, head and neck, and

lung). However, only 40 to 60% of cancer patients in middle income countries have access to it and in low-income countries (LICs) this figure is as low as 10% [6] .

To better inform national and international research policymakers we sought to describe the radiotherapy RCT landscape, including the extent to which areas of investigation correlate with global disease burden and how trial design, funding and the impact of trial outputs vary across economic settings. Within this, we compare the characteristics of radiotherapy RCTs with systemic therapy RCTs focusing on differences in funding, treatment intent (curative versus palliative) and statistical design. The purpose of this is to identify trends and highlight gaps to provide direction on research domains that should be prioritised to meet the present and imminent challenges.

## Methods and Materials

### *Study Design and Search Strategy*

We undertook a secondary analysis of a retrospective cohort of all oncology RCTs published globally between 2014 and 2017. Study design and identification of the cohort are described in detail by Wells et al and this secondary analysis uses the same dataset [2]. A structured PubMed literature search identified all phase 3 RCTs of cancer therapy (systemic, radiotherapy, surgery) published during this period. Studies were excluded if they reported only subset/pooled analyses, reported interim analyses, or assessed cancer screening/prevention. Studies of supportive and palliative care (i.e., anti-emetics, growth factors) or integrative medicine (i.e., yoga, vitamins) were excluded. Descriptive results were generated for the full study cohort, with secondary analyses restricted to radiotherapy RCTs.

### *Data Abstraction and Classification*

All eligible studies were reviewed using a standardized data abstraction form to capture information regarding authorship, funding, study design, results, and journal of publication. Data abstraction was performed independently by two authors. The senior author performed random duplicate abstraction throughout the process to ensure data abstraction was of high

quality. At completion of data collection, 30 studies were randomly chosen for double review; only 11/1020 variables (1%) were found to be discordant with the original assessment and a decision regarding inclusion was based on consensus.

Studies were classified into modality type (radiotherapy, systemic therapy, and surgery) and country of origin based on the first author's institution. Furthermore, we analysed the study sites for trials based on where patients were recruited. This information was extracted from the trial appendices and was available for 56 of the 64 trials (88%). The country of origin was used to further divide studies into income level classifications based on the World Bank income classification[7]. Because of a paucity of studies from lower-middle income countries, they were combined with upper-middle income countries and collectively referred to as LMICs. There were no RCTs from low-income countries.

***Classification of funding***

The RCT funding source for radiotherapy RCTs was identified by explicit statements in the manuscript or acknowledgement section. The funding classification was divided into Government (e.g., Federal/national government-level funding agency), Industry (e.g., Varian), Philanthropic (any charitable organisations e.g., Cancer Research UK), International Body (e.g., International Atomic Energy Agency or IAEA), hospital (if funded by single hospital) and none stated.

***Categorization***

The radiotherapy RCTs were categorized according to pre-specified framework designed by the research team and developed with reference to previous analyses [8]. The research domains and individual codes used for analysis were as follows; COMB (combination with another systemic treatment), FRAC (change to fractionation schedule), OMIT (omitting radiotherapy), TECH (new technique of radiotherapy e.g., stereotactic radiotherapy), INDI (new indication for radiotherapy e.g., prostate RT in metastatic disease), BRAC (brachytherapy trials), ESCA (dose escalation), SURG (combination with surgery) and SEQU (sequence change i.e., neo-adjuvant or adjuvant).

### *Outcomes*

The intent of radiotherapy RCTs (curative vs palliative), primary trial endpoints, and tumor types that the studies focused on were extracted and analysed. We assessed the concordance between the research commitment to each tumor type and the cancer control benefit from radiotherapy for that tumor type (defined by 5-year local control benefit and 5 year overall survival from radiotherapy) [3].

In addition, journal impact factor for each published RCT was analysed using the impact factor from 2016, as reported by the Journal Citation Reports Impact Factor [9]. Comparisons were made of the characteristics of studies led by HICs compared to those from LMICs. In addition, outcomes were compared between trials of systemic therapy and radiation therapy to identify trends.

## Results

In total, the search strategy identified 2275 publications. Reasons for exclusion were subset or pooled analysis (n=883), not phase III RCT (n=250), not anti-cancer intervention (n=217), protocol/interim analysis (n=134), or additional report of included study (n=97). The final study cohort included 694 RCTs. Of these, 64 (9.2%) were radiotherapy related RCTs (see consort diagram in Appendix 1). The baseline characteristics of the radiotherapy RCTs included are presented in Table 1.

### *Domains of radiotherapy RCT research*

Figure 1 demonstrates the different research output categories. Nearly half of all RCTs in radiation oncology focused on two main areas of evaluation. The first was trials combining radiotherapy with systemic agents (25% (n=16)), followed by RCTs evaluating the impact of changes in dose fractionation regimens (22% (n=14)). The other half of the trials focused on evaluating the omission of radiotherapy (11%), a new radiotherapy technique (9%), a new radiotherapy indication (8%), brachytherapy (8%), dose escalation (6%), combination with surgery (6%) and sequencing of treatment (11%)

***Country origin of RCT research in radiation oncology***

Table 1 demonstrates that most of the radiotherapy RCTs (n=49, 77%) were performed in a HIC and only 13% (n=8) in a single LMIC. The highest research output countries, by first author, were USA (n=11, 17%), UK (n=10, 16%), Netherlands (n=6, 9%) and China (n=5, 8%). A sub-analysis was undertaken to ascertain from which LMIC countries patients were recruited from. Of the 15 trials that recruited patients from LMICs, countries included China (n=6, 9%), India (n=5, 8%), Brazil (n=3, 5%), Serbia (n=3, 5%) and Egypt (n=2, 3%).

***Tumor types evaluated***

In total 13 tumor types were evaluated in the 64 radiotherapy RCTs. The most common cancers enrolled were head and neck 22% (n=14), lung 22% (n=14) and breast 14% (n=9). Figure 2 and 3 demonstrate the concordance between the top 10 cancers amenable to the greatest benefit from radiotherapy (both by 5-year local control (Figure 2) and 5-year overall survival (Figure 3)) and number of radiotherapy RCTs in each cancer type between 2014 and 2017. The results demonstrate that cervical cancer had the greatest ranked radiotherapy population 5-year local control and 5-year overall survival benefit but only ranked eighth according to number of RCTs undertaken by tumor type. Breast and prostate trials comprised 23% of all radiotherapy RCTs, yet neither tumor type feature in the top 10 cancers with 5-year overall survival benefit from radiotherapy.

***RCT funding***

58 radiotherapy RCTs (91%) reported funding, with 10 trials having more than one funding source. Most radiotherapy RCTs received funding from national government or federal sources (n=31, 48%) (Figure 4). 33% (n=21) received funding from philanthropic sources, 17% (n=11) from industry, 6% (n=4) from international bodies and 3% (n=2) from hospitals. This is in contrast with the RCTs of systemic therapy where 79% were industry funded and only 3% had no evidence of a funding source.

We further categorized funding based on whether the RCT was conducted in a HIC, LMIC or both a HIC and LMIC. Figure 5 highlights that in HICs, most of the RCT research has

funding contributions from government (47% (n=23)) or philanthropy (37% (n=18)) with 20% (n=10) receiving funding from industry. In comparison, 37.5% (n=3) of RCTs in LMICs declared no explicit funding, with 50% (n=4) receiving government funding and 12.5% (n=1) receiving philanthropy funding. There was no evidence of any funding from industry for RCTs undertaken in LMICs. Trials undertaken across both HIC and LMIC settings received most funding from international bodies (57% (n=4)) and government (57% (n=4)) with only 14% (n=1) funded by industry.

***Intention to treat, statistical design and primary end point***

A higher proportion of radiotherapy RCTs assessed interventions in the curative setting (62%) compared to trials of systemic therapies (31%) (see Table 1). A higher proportion of RCTs evaluating radiotherapy were non-inferiority studies (19%) compared to RCTs of systemic therapies (11%). Of note only 33% (n=21) of the radiotherapy RCTs met their primary end point.

***Journal impact factor of RCTs***

The average impact factor of the journal in which the RCT was published based on country of origin was assessed. Publications from RCTs undertaken in high income countries had a higher average impact factor (23) than those conducted in LMICs (9). When contrasting impact factors between radiotherapy and systemic therapy RCTs, the average impact factor for radiotherapy RCTs (20) was similar to systemic therapy RCTs (23).

## Discussion

This study of the global radiotherapy research landscape has highlighted several important findings. The first is that despite radiotherapy being a key modality of cancer control and cure, only 9% of oncology RCTs were devoted to this area, compared to 87% in systemic therapies. This has been observed before in specific tumor types, for example a paper by Aggarwal et al [10] highlighted the paucity of radiotherapy RCT research in lung cancer.

One of the reasons for this discrepancy is likely to be due to funding, for example, whilst RCTs of systemic therapies are predominantly funded by industry, radiotherapy RCTs are much more dependent on national or federal public sector funding sources. There are also differences in evidence requirements for market access. Whilst RCTs are still considered the optimum evidence to support licencing and market access for systemic therapies, the same evidence thresholds are presently not required for market access for radiotherapeutic options which need to demonstrate safety. Furthermore, there are structural challenges with setting up radiotherapy RCTs, as it requires high investment costs and, particularly for software modifications, can be subject to rapid changes over time which may result in the technology becoming obsolete [11, 12]. In addition to these structural factors, one also needs to consider whether as a clinical community we are demanding the right level of evidence of benefit for new innovations before adopting these into clinical practice.

Another major finding is that presently only a small proportion (13%) of RCTs are led by LMICs and mainly involve China or India. International bodies lead most of the RCTs undertaken across the combination LMIC and HIC settings, for example, the International Atomic Energy Agency (IAEA). In addition, RCTs undertaken in LMICs may face challenges in influencing global practices of care as we found that LMIC RCTs were published in journals that had far lower impact factors than HIC RCTs. This may be due to the fact that the results from trials performed in LMICs may not be broadly applicable to HIC settings due to differences in patient populations and radiotherapy infrastructure which necessitates alternative questions or innovation to evaluate within clinical studies [13].

In this setting, it is crucial to encourage collaboration and research capability in these regions. The commitment to cancer trials would help create and improve existing infrastructure to support the widening of access to local populations. It also enables diversification of the populations included in RCTs and therefore the generalisability of findings across clinical practice globally rather than a HIC to LMIC dissemination model. Additionally, RCTs remain important in LMICs to drive effective health technology

assessment (HTA) processes that can enable commitment to cost-effective novel technologies rather than employing technologies that have dubious value to the health care system [13].

Conducting research in LMICs has many barriers, which will also translate to radiotherapy-specific work, including reduced funding availability, significant clinical commitments resulting in less protected research time and inadequate research infrastructure (i.e. ethics and law, supervisory, data collection and analysis) [14-16]. In addition, there is little education of trainees in critical appraisal and research methodology which further reduces the number of investigator-initiated regional studies.

Whilst there is an increasing number of RCTs from large middle-income countries such as India and China [17, 18], worryingly no RCTs were being undertaken in sub-Saharan Africa, which is likely to relate to the paucity of research infrastructure and funding available. There is also a lack of availability of radiotherapy equipment and workforce in this setting which both limits access to treatment and is also is a barrier to research being conducted in these regions [19, 20]. In particular, the large difference between availability and demand for radiotherapy in these regions will make it difficult to protect the radiotherapy machines for research time. However, it is important to build research capacity to enable the development and testing of innovations to address these infrastructure gaps. For instance, research trials involving alternative fractionation schedules or automation of the pathway, which would in turn reduce treatment time and allow more patients to be treated, may be an important strategy.

Our findings also suggest a bias towards tumors of higher burden in HICs than in LMICs. For example, cervical cancer which ranked first for 5-year local control and 5-year overall survival benefit from radiotherapy, only ranked eight for volume of radiotherapy RCTs undertaken (Figure 2 and 3). Conversely, head and neck cancer which, like cervical cancer, necessitates radiotherapy for cancer control ranked first according to the number of radiotherapy RCTs conducted. The paucity of RCTs focusing on cervical cancer is likely to

relate to the fact that cervical cancer has far higher incidence in low income countries than HICs, with amongst the greatest burden in sub-Saharan Africa [21] where no radiotherapy RCTs were identified. The finding is particular relevant given the advent of the WHO strategy [22] to accelerate the eradication of cervical cancer as a public health issue by improving access to radiotherapy [23]. Greater investment in RCTs would be a major stepping stone to achieving this goal by supporting the continued optimization of cervical cancer treatments (morbidity remains a major issue) as well as continue to provide innovative advances in the practical delivery and scheduling.

The study also finds that the funding of RCTs in radiotherapy is quite different to systemic therapy RCT funding. Industry funded only 17% of all radiotherapy RCTs, compared to 79% of systemic RCTs. 9% of radiotherapy RCTs had no funding stated compared to 3% of systemic therapy trials. These results are corroborated by a study by Jairam et al [24], which demonstrated that industry is more likely to fund RCTs in targeted therapies than in radiation or multimodality treatment.

We also identified key differences in funding sources for HIC and LMIC RCTs. Industry funded 20% of all HIC RCTs but no RCTs undertaken purely in a LMIC setting. The potential reasons for this have been outlined by Wells et al [2] and include that industry may be reluctant to sponsor regions with limited research infrastructure. Furthermore, universal health coverage is limited for many patients living in LMICs and the prices of even standard treatment may mean that companies are reluctant to run studies in these countries as they do not represent viable markets for high-cost technologies. There may also be differences in the way systemic therapies are compensated by health systems compared to radiotherapy treatments which make systemic therapies more profitable for industry. The market is also larger for pharmaceuticals given the population size in many LMICs as well as the proportion of patients presenting with more advanced incurable disease.

Following on from this work, it is essential from a research policy standpoint to identify why industry is not funding as many RCTs in radiotherapy in LMICs. At present 38% of RCTs in

LMICs receive no explicit funding which is a stark statistic when we consider the growing cancer burden in LMICs. A sustainable research funding infrastructure is going to be imperative going forward especially in low-income countries. In this regard the IAEA, and other international organisations may need to play a greater role in supporting this.

Finally, the patterns seen with respect to the domains of radiotherapy RCTs are interesting as they demonstrate that trials involving combination with a systemic therapy or change in dose fractionation are the most common radiotherapy RCT categories. It would be intriguing to understand why more trials are not being conducted in new techniques or technologies for radiotherapy, for example stereotactic ablative radiotherapy, as a new and evolving treatment modality in radiotherapy. The findings corroborate those by Aggarwal et al [6], which found that most studies were performed in multi-modality therapy (i.e., combination of RT with systemic therapy) and different dose fractionation schedules. This is likely to be a legacy of the preclinical research performed during the 1980s and 1990s, which had more of a biological emphasis, with research focusing on dose per fraction, hypoxia, and drug–radiation interactions.

The limitations of this study are that a contemporary four-year study period was chosen between 2014 and 2017 across all treatment modalities. Whilst we expect this to be consistent with subsequent years, it could be subject to change. A further limitation is with regard to allocation of country of origin for RCTs. This was selected based on country of first author affiliation but we ran a sensitivity analysis with last author and found negligible differences in the proportion of RCTs allocated to HICs and LMIC.

## Conclusion

This study has highlighted the need for greater investment in radiotherapy RCTs and the disparities in conduct of RCTs globally. The study emphases the urgent need for more capacity building for cancer clinical trials in LMICs and more sustainable funding sources.

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## Figure captions

***Fig 1.*** *Type of radiotherapy trials*

*Notes: COMB (combination with another systemic treatment), FRAC (change to fractionation schedule), OMIT (omitting radiotherapy), TECH (new technique of radiotherapy), INDI (new indication for radiotherapy), BRAC (brachytherapy trials), ESCA (dose escalation), SURG (combination with surgery) and SEQU (sequence change)*

***Fig. 2.*** *Top 10 Cancers by Radiotherapy Population 5-year local control benefit [3] and Top 10 Cancers by Proportion of Phase 3 Radiotherapy Randomized Clinical Trials (RCTs)*

*Notes: The number of studies associated with each tumor type is labelled in brackets on the right*

***Fig. 3.*** *Top 10 Cancers by Radiotherapy Population 5-year overall survival benefit [3] and Top 10 Cancers by Proportion of Phase 3 Radiotherapy Randomized Clinical Trials (RCTs)*

*Notes: The number of studies associated with each tumor type is labelled in brackets on the right*

***Fig. 4.*** *Distribution of funding for all radiotherapy RCTs*

*Notes: The number of studies receiving funding from each source is labelled on the graph*

***Fig. 5.*** *Funding based on LMIC, HIC or combination*