Is Clinical Research Serving the Needs of the Global Cancer Burden?

An Analysis of Contemporary Worldwide Randomized Controlled Trials

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KEY POINTS

Question: To what extent do oncology RCTs match the global cancer burden?

Findings: This review of all RCTs published globally during 2014-2017 (n=694) demonstrates that trials are dominated by high-income countries and study cancers that do not match the global burden of disease. Despite being more likely to new treatments that benefit patients, RCTs from LMICs are published in much lower impact journals.

Meaning: Policy-makers, research funders and journals need to urgently address these challenges with a range of measures including building capacity and capability in RCTs.

ABSTRACT

Importance: The burden of cancer falls disproportionally on low-middle income countries. It is not well known how novel therapies are tests in current clinical trials and the extent to which they match global disease burden.

Objective: To describe design, results, and publication of all oncology randomized controlled trials (RCTs) published globally

Design: Retrospective cohort study

Setting/Participants/Exposure: A literature search identified all RCTs evaluating anti-cancer therapies published during 2014-2017. RCTs were classified based on the World Bank economic classification; low-middle/upper-middle income countries (LMICs) and high-income countries (HICs). Descriptive statistics were used to compare RCT design and results from HICs and LMICs.

Main Outcome: Differences in design, results, and output of RCTs between HICs and LMICs.

Results: The study cohort included 694 RCTs; 636 (92%) led by HICs and 58 (8%) led by LMICs. Eighty-seven percent (601/694) tested systemic therapy; 13% (88/694) tested radiotherapy or surgery. The proportion of RCTs relative to global deaths is higher for breast cancer (17% RCTs/7% deaths) but lower for gastroesophageal (6%/14%), liver (2%/8%), pancreas (2%/5%), and cervical (1%/3%) cancers. RCTs in HICs were more likely to be funded by industry (73% vs 41%, $p<0.001$). LMIC studies were smaller (median n=220 vs n=474 participants, $p<0.001$) and more likely to meet their primary endpoints (66% vs 44%, $p=0.002$). The observed effect size was larger in LMICs compared to HICs (median HR 0.62 vs HR 0.84, $p<0.001$). Studies from LMICs were published in journals with lower impact factors (IF) (median IF 7 vs 21, $p<0.001$). Publication bias persisted when adjusted for whether a trial was

positive or negative: median IF LMIC negative trial=5 vs HIC negative trial=18; LMIC positive trial=9 vs HIC positive trial= 25 ($p<0.001$).

Conclusions and Relevance: Oncology RCTs are dominated by HICs and do not match the global burden of cancer. RCTs from LMICs are more likely to identify effective therapies and with a larger effect size than HICs. There is a substantial funding and publication bias against RCTs led by LMICs. Policy-makers, research funders and journals need to urgently address this with a range of measures including building capacity and capability in RCTs.

BACKGROUND

Low and middle-income countries (LMICs) will account for 75% of global cancer deaths by 2030 [1]. In this context, there is an urgent need for building collaboration and capacity in these regions. Randomized controlled trials (RCTs) remain the most powerful tool to change clinical practice and improve outcomes. RCT are increasingly multi-national, funded by industry, and more likely to use surrogate endpoints and identify modest effect size [2-5]. Despite this, only a minority of new cancer drugs offer substantial clinical benefit for patients [6-9]. This body of work supports the assertion that research priorities are shaped by the pharmaceutical industry in high-income countries (HICs) rather than population and context-specific needs.

There is increasing recognition that the global cancer research ecosystem needs re-calibration to address imbalances across disease settings and between pre-clinical and clinical efforts [10-12]. Patients enrolled in clinical trials often do not adequatelyrepresent the diversity of the global population. A 2013 Cochrane review of 12,340 clinical trials found that 89% of trials and 82% of participants were from HICs [13]. Whilst bibliometric analysis has exposed the dominance of HICs in global cancer research there are very limited data regarding the extent to which RCT design and results vary based on the economic setting in which they are conducted. It is also unknown whether the current trends of "mega-trials" and marginal effect sizes apply to RCTs from low resource settings. In this study we analyse all oncology RCTs conducted globally during 2014-2017. The objectives were to understand: 1) the extent to which trials match global disease burden; and 2) how trial methodology and results differ across economic settings.

METHODS

Study Design and Search Strategy

We performed a retrospective cohort study to evaluate characteristics of all oncology RCTs published globally during 2014-2017. A structured PUBMED literature search used the following terms: ("Neoplasms/drug therapy" [Mesh] OR "Neoplasms/radiotherapy"[Mesh] OR "Neoplasms/surgery" [Mesh] OR "Neoplasms/therapy"[Mesh] OR "Neoplasms/transplantation"[Mesh]) Sort by: Best Match Filters: Clinical Trial, Phase III). Studies were included if they were: English-language reports of a phase III study of any cancer and tested a cancer-directed therapy. There was no minimum sample size. Studies were excluded if they reported only subset/pooled analyses, reported interim analyses, or assessed cancer screening/prevention. Studies of supportive care (i.e. anti-emetics, growth factors) or integrative medicine (i.e. yoga, vitamins) were excluded.

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 (J.C.W. and S.S.). The senior author (C.M.B.) 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. Another author (J.D.P.) with extensive experience using the European Society of Medical Oncology-Magnitude of Clinical Benefit Results Scale (ESMO-MCBS) derived grades for all superiority studies of systemic therapy that met their primary endpoint.

Studies were classified into country of origin based on the institutional affiliation of the first author. The country of origin was used to further divide studies into income level classifications based on the World Bank income classification [14]. There were no RCTs from low income countries. Because of a paucity of studies from lower-middle income countries (n=7), they were combined with upper-middle income countries (n=51) and collectively referred to as LMICs; these trials are compared to those from HICs.

Outcomes and Statistical Analysis

Descriptive results were generated for the full study cohort. Comparisons were made between studies led by HICs and those from LMIC. Journal impact factor (IF) was also compared using the impact factor from 2016, as reported by the Journal Citation Reports Impact Factor [15]. We also compared the primary endpoint effect size (i.e. Hazard Ratio) of "positive" superiority RCTs between HICs and LMICs. Version 1.1 of the ESMO-MCBS was used to derive a grade based on the positive endpoint for systemic therapy [16]. Grades of A and B (curative setting) and 5 and 4 (palliative setting) were considered to be "substantial" benefit.

Statistical analysis was conducted using IBM SPSS version 26.0 for Windows (Armonk, New York, 2019). Outcomes were compared using the Pearson Chi Square or Fisher's Exact test, and independent samples t-tests or the Mann-Whitney U as appropriate. P values less than 0.05 were considered significant; no adjustments for multiple comparisons were made.

RESULTS

Results of the search strategy

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) (Supplemental eFigure 1). The final study cohort included 694 RCTs.

Design characteristics of global RCTs

The majority of RCTs were led by HICs (92%, 636/694); 58 were led by LMICs (8%). Eighty-one percent (565/694) of all RCTs reported countries that enrolled patients: 42% (238/565) enrolled patients from LMICs. Among trials led by HICs, 36% (182/509) enrolled participants from LMICs. Among HICs, the most common leading countries were US (27%, 174/636), France (10%, 64/636), Germany (10%, 62/636), Japan (9%, 59/636), and UK (9%, 57/636). The most common leading countries among LMICs were China (42/58, 72%) and India (6/58, 10%).

Characteristics of the study cohort are presented in Table 1. The most common cancers enrolled were breast (17%, 121/694), lung (15%, 104/694) and colorectal (8%, 58/694). The extent to which cancers studied in RCTs align with global cancer mortality is shown in Figure 1. There is general alignment between the proportion of all global cancer deaths and the proportion of all global RCTs for lung (15% RCTs, 18% deaths), colorectal (8% RCTs, 9% deaths), and prostate cancers (5% RCTs, 4% deaths). The proportion of oncology RCTs relative to global cancer deaths is substantially higher for breast cancer (17% RCTs, 7% deaths), leukemia (7% RCTs, 3% deaths), and lymphoma (6% RCTs, 3% deaths); the proportion of RCTs is

substantially lower for gastroesophageal (6% RCTs, 14% deaths), liver (2% RCTs, 8% deaths), pancreas (2% RCTs, 5% deaths), and cervical (1% RCTs, 3% deaths) cancers.

Two thirds (448/694, 65%) of RCTs were conducted in the palliative setting. Eight-seven percent (601/694) of trials tested systemic therapy (34% cytotoxic, 19% TKI, 8% monoclonal antibody, 6% hormone, 23% multi-agent, 10% other) and 13% (88/694) tested radiotherapy or surgery. Sixty percent (416/694) of RCTs tested palliative systemic therapies. The most common primary endpoints were progression-free survival (PFS) (32%, 220/694), overall survival (OS) (31%, 215/694), and disease/event/relapse-free survival (DFS/EFS/RFS) (22%, 149/694). Seventy percent (488/694) of RCTs were supported by industry.

Comparisons of RCT design between HICs and LMICs are presented in Table 1. Primary endpoint of DFS/EFS/RFS was more common in HICs than LMICs (22% vs 12%, p=0.069); response rate was a more common primary endpoint in LMICs than HICs (16% vs 6%, p=0.003). Trials conducted by HICs were more likely than LMICs to be industry funded (73% vs 41%, p<0.001).

Results of global RCTs

Details regarding the conduct and results of RCTs are shown in Table 2. The median number of participants across all RCTs was 443 (IQR 246-718). The median time of accrual was 36 (IQR 24-60) months. Forty-four percent (306/694) of all trials met their primary endpoint. Primary endpoint results were reported for 607/610 (99%) of superiority trials. Forty-three percent (262/607) of superiority trials met their primary endpoint (i.e. p<0.05 for primary endpoint); among these trials the median (IQR) HR was 0.63 (0.51-0.74). Among the 166 positive superiority trials of systemic therapy for which an ESMO-MCBS grade could be calculated 33% (55/166) met the threshold for substantial benefit.

LMIC studies were smaller than HIC trials (median n=219 vs n=474 participants, p<0.001) and were more likely to meet their primary endpoints (64% vs 43%, p=0.002). Among superiority trials, the effect size was larger in LMICs compared to HICs (all RCTs median HR 0.62 vs 0.84, p<0.001; "positive" trials median HR 0.59 vs 0.65, p=0.022). The proportion of trials identifying treatments with substantial clinical benefit (ESMO MCBS 4/5/A/B) was 48% (LMICs) and 31% (HICs, p=0.131).

Journal impact factor of global RCTs

Ninety-nine percent (686/694) of RCTs were published in journals with impact factors (IF). The median IF for all RCTs was 21 (IQR 7-27). Studies from LMIC were published in journals with lower IF than HICs [median IF 7 (IQR 4-21) vs 21 (IQR 7-34), p<0.001] (Figure 2). This publication bias persisted when adjusted for whether a trial was positive or negative: median IF of positive LMIC trial=9 vs positive HIC trial=25; median IF of negative LMIC trial=5 vs negative HIC trial=18 (p<0.001).

DISCUSSION

This is the first systematic overview of the global RCT cancer ecosystem. A number of important findings have emerged. First, the RCT landscape is dominated by investigators in HICs and the diseases studied do not match the global burden of cancer. Gastroesophageal, liver, pancreas, and cervical cancers are substantially under-represented in RCTs. Second, most RCTs are funded by the high income-based pharmaceutical industry and focused disproportionally on systemic therapies in the palliative setting. Third, RCTs testing new approaches in surgery and radiotherapy account for only 13% of all RCTs. Fourth, use of surrogate endpoints is pervasive. Fifth, only one third of positive trials identify a new treatment that is associated with substantial clinical benefit. Sixth, compared to HICs, RCTs from LMIC are more likely to be positive and identify a larger magnitude of benefit. Finally, we have identified a very substantial publication bias; despite being more likely to be "positive" and having a larger magnitude of benefit, RCTs from LMICs are published in journals with far lower impact factors than trials from HICs.

Our study identifies a striking imbalance in the number of RCTs conducted in HICs and LMICs; we also describe substantial discordance in the cancers studies compared to the global burden of disease. These results are consistent with prior work [11, 17, 18]. This imbalance reflects a historical colonial approach to global health and is perpetuated by substantial structural barriers to conducting clinical research in low resource settings. These barriers are compounded by the global cancer funding paradox whereby 5% of global resources for cancer are spent in LMICs, where 64% of global deaths as a result of cancer occur [19, 20].

Our results demonstrate that the global research agenda is dominated by the pharmaceutical industry in high-income countries; this is not unexpected given that the primary goal of industry is to maximize profit. There is an urgent need for philanthropic and government

funding agencies to re-calibrate this imbalance. The marked difference in rates of industry funding may also reflect a reluctance of industry to sponsor studies in countries with less established research infrastructure**.** A related theme is the practice of investigators from HICs leading a drug registration trial that predominantly enrolls patients in LMICs where the treatment would have no chance of being available after the clinical trial; this in itself represents a distinct form of research parachutism [21-23].

There are substantial barriers to conducting cancer research in LMICs. These include limited research infrastructure (i.e. research staff, ethics, regulatory, legal/contracts, data capture/analysis, pharmacy/laboratory accreditation), limited funding opportunities, and the remarkable clinical workloads which make "protected time for research" non-existent in most parts of the world [24-26]. Because patients in many LMICs do not have access to universal health coverage the prohibitive costs of even standard of care preclude participation in research studies. In many LMICs, trainees receive very limited teaching in principles of critical appraisal or research methodology; this makes it even more difficult to launch investigator-initiated local studies. Despite these barriers, there are encouraging signs that things are improving. For example, the National Cancer Grid (NCG) in India leads a highly successful week-long intensive research methodology workshop for emerging leaders in academic medicine [27]. The NCG has also leveraged substantial funding to support Indian-led clinical research and is establishing "research hubs" across the country to provide logistic and methodologic support.

Despite barriers to research in LMICs, a series of recently published high-profile RCTs from LMICs have changed clinical practice globally [28-30]. Data from the current study suggest that RCTs led by researchers in LMICs may be less prone to one of the greatest pitfalls of contemporary oncology: the over-powered "mega-trial" that detects marginal improvements in

outcome. Our data show that RCTs from LMIC are smaller, more likely to be "positive" and are associated with a larger magnitude of benefit. This likely reflects a level of pragmatism in the design of RCTs in LMICs that has been lost in HICs where it is commonplace to adopt a $100,000/year cancer treatment which extends median survival by a few weeks.

While the primary objective of our study was to compare and contrast RCTs conducted in HICs and LMICs, a number of important findings have emerged about the overall state of oncology RCTs. Consistent with other reports [2-5], RCTs are largely funded by industry, testing palliative systemic therapy, using surrogate endpoints (requiring frequent imaging studies which may not be feasible in many settings), and are associated with marginal therapeutic benefits. This is not an encouraging portrait for the global cancer research ecosystem. With the growing interest in high-value cancer care it is imperative that clinical trials raise the bar so that patients have access to new treatments that lead to meaningful improvements in outcome and are of broad value to health systems.

Our data demonstrate that since the initial report of negative publication bias in oncology in 2003 [31] this phenomenon remains a problem in our field. However, the most striking result of our study is the observation of a strong publication bias against studies led by LMICs. Notably, positive trials from LMICs were published in substantially lower impact journals than negative trials from HICs. The bias against non-oncology studies from LMICs has been previously described in general medicine [32, 33]; however, this is the first study to our knowledge to identify this phenomenon in oncology. These observations highlight an important form of bias within the current system. This "publication prejudice" needs to be recognized and addressed to ensure a fair and equitable research ecosystem that leads to improvements in health for all global citizens. The American Society of Oncology's Journal of Global Oncology (JGO)

has provided an important venue for research from LMICs. The recent announcement by *e*Cancer [34] that it will only publish work from LMICs will also mitigate some of this bias. However, one of the unintended consequences of having dedicated global cancer journals is that it may relegate any paper from a non-HIC to one of these lower impact journals. As investigators who work extensively in global oncology, our perception is that many cancer journals are reluctant to publish anything that is not from a HIC; editors of these journals may feel that JGO and *e*Cancer offer the mainstream journals an opportunity to reject papers from LMICs. It will be important that the major cancer journals be mindful of their role in supporting research from all countries and ensuring that they publish reports based on scientific merit and human health impact regardless of where the study was conducted.

This is the first study to systematically study oncology RCTs from a global perspective and offers insights that can guide future policy and research. However, our results should be interpreted in light of methodologic limitations. The study was restricted to RCTs and therefore may not reflect the entire research ecosystem; however, RCTs shape policy and practice and for that reason the findings from this study are highly relevant to patient care. Studies were classified based on country of the first author; however this was found to highly correlate with country of the last author (data not shown). Our study did not include reports in languages other than English and our search strategy would also have missed RCTs published in non-indexed journals. However, to ascertain the validity of the search strategy process for RCTs in LMICs we queried ClinicalTrials.gov for phase III trials completed during 2014-2017. Twelve LMICs were randomly selected; 90% (104/114) of studies identified in our ClinicalTrials.gov were captured by our search strategy suggesting that our cohort is likely very representative of the overall body of RCTs. Finally, given the paucity of RCTs from low-middle income countries, they were

grouped with upper-middle income countries; policy issues may vary widely across the economic continuum.

Our results offer policy-relevant insights into the cancer research enterprise that require attention in the next 5 years. First, there is an urgent need to correct the global research funding paradox; philanthropic and government funding agencies should uphold their moral and scientific duty to support research in LMICs. Second, initiatives to build research infrastructure and human capacity in low resource settings must be promoted and supported with a particular emphasis on creating networks of countries with similar context-specific needs (i.e. South-South partnerships). Third, the pressing clinical volumes in LMICs need to be recognized and supported with additional care providers to allow clinical investigators to develop their own independent research programmes. This should be an integral component of health systems strengthening. Fourth, our finding of a striking publication bias against RCTs from LMICs cannot be ignored. Oncology journals need to recognize their role in promoting and disseminating high quality research regardless of country of origin. Increasing LMIC representation on Editorial Boards is one important first step in this regard. Global oncology specific journals also play an important role but do not absolve other journals from the responsibility to ensure that high-quality work is published. Fifth, sustained effort is needed to increase RCTs that address new surgical and RT techniques. Finally, we make an urgent plea to oncologists and investigators worldwide to recognize the importance and synergies that can emerge from global research efforts that are truly collaborative in spirit, bi-directional, and mutually beneficial. Living and working in very different contexts provides a unique opportunity for clinicians and health systems to learn from each other. With appropriate support,

investigators in LMICs may in fact be better positioned than colleagues in HICs to answer fundamental research questions that can substantially improve patient outcomes globally.

In summary, oncology RCTs are predominantly led by HICs, funded by high-income based pharmaceutical industry, focus on palliative systemic therapy, and study cancers that do not match the global burden of disease. RCTs from LMICs more likely to identify new treatments that benefit patients. Finally, we identify evidence of a substantial publication bias against RCTs from LMICs. Cancer is now recognized as a global disease; these data support the call for capacity-building and research support directed at cancer clinical trials in LMICs that are context relevant.

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Dr. Booth had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Ms. Wilma Hopman conducted data analysis for this study.

DISCLOSURES

The authors report no conflicts of interest.

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Table 1. Characteristics of all oncology RCTs published globally 2014-2017.

	All RCTs	**Country of First Author**	
	n=694	**HIC (n=636)**	**LMIC (n=58)**
	n (%)	n (%)	
Disease site			
Breast	121 (17%)	115 (18%)	6 (10%)
Lung	104 (15%)	84 (13%)	20 (35%)
Colorectal	58 (8%)	55 (9%)	3 (5%)
Head and Neck	34 (5%)	24 (4%)	10 (17%)
Gastroesophageal	38 (6%)	33 (5%)	5 (9%)
Leukemia/Lymphoma	90 (13%)	87(14%)	3 (5%)
Other^	249 (36%)	238 (37%)	11(19%)
Treatment intent*			
Palliative	448 (65%)	411 (65%)	37 (64%)
Curative	68 (10%)	61 (10%)	7 (12%)
Neoadjuvant/adjuvant	176 (25%)	162 (26%)	14 (24%)
Experimental arm			
Systemic	601 (87%)	556 (87%)	45 (78%)
Radiation	38 (6%)	34 (5%)	4 (7%)
Surgery	16 (2%)	15 (2%)	1 (2%)
Other^	39 (6%)	31 (5%)	8 (14%)
Study design			
Superiority	610 (88%)	559 (88%)	51 (88%)
Non-inferiority/equivalence	84 (12%)	77 (12%)	7 (12%)
Primary EP			
OS	215 (31%)	198 (31%)	17 (29%)
DFS/EFS/RFS	149 (22%)	142 (22%)	7 (12%)
PFS/TTF	232 (33%)	213 (34%)	19 (33%)
Other[#]	98 (14%)	83 (13%)	15 (26%)
Industry funding			
Yes	488 (70%)	464 (73%)	24 (41%)
No	173 (25%)	149 (23%)	24 (41%)
Unstated	33 (5%)	23 (4%)	10 (17%)

Column totals add to 694 (100%) unless otherwise noted by * due to missing data.

^Other interventions included systemic-RT (n=29), systemic-surgical (n=5) hyperthermia plus RT (n=2), photodynamic therapy, stem cell transplant, tumour treating field

[#]Other primary endpoints include QOL/toxicity (n=21), response rate (n=44), and other (n=33)

Table 2. Results of all oncology randomized controlled trials published globally 2014-2017.

	All RCTs	Country of First Author		P-value
	n=694	**HIC (n=636)**	**LMIC (n=58)**	
	n (%)	n (%)		
Total sample size				
Median (IQR)	443 (246-718)	474 (262-743)	219 (137-363)	<0.001
Primary endpoint met				0.001
Yes	325 (47%)	286 (45%)	39 (67%)	
No	369 (53%)	350 (55%)	19 (33%)	
P<0.05 for primary endpoint^				<0.001
Yes	262 (43%)	229 (41%)	33 (65%)	
No	345 (56%)	328 (59%)	17 (33%)	
HR for all superiority RCTs^				
Median (IQR)	0.82 (0.65-0.96)	0.84 (0.67-0.97)	0.62 (0.54-0.76)	<0.001
HR for + superiority RCTs*				
Median (IQR)	0.63 (0.51-0.74)	0.65 (0.52-0.75)	0.59 (0.43-0.66)	0.022
ESMO-MCBS grade#	n=166	n=145	n=21	0.131
Substantial benefit (A,B,4,5)	55 (33%)	45 (31%)	10 (48%)	
Not substantial benefit (C,1,2,3)	111 (67%)	100 (69%)	11 (52%)	

^Only reported for n=610 superiority trials, data not available for n=3

*Only reported for n=262 positive superiority trials; #Only reported for 166/262 positive superiority trials