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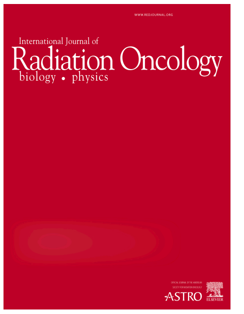


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# Radiation therapy research: a global analysis 2001-2015

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**Conflicts of Interest**

There are no conflicts of interest to declare

## Abstract

**Introduction**

Radiotherapy is a core modality of cancer treatment, however concerns have been expressed regarding its underutilization and its lack of prioritisation as a research domain relative to other cancer treatment modalities in spite of its rapid technical evolution. It is therefore important to understand from a public policy perspective, the evolution of global radiotherapy research, to identify strengths, weaknesses and opportunities.

**Materials and Methods**

The study utilised a bibliometric approach to undertake a quantitative analysis of global radiotherapy research published between 2001-2015 and available in the Web of Science (Wos) database, with particular focus on the 25 leading research-active countries.

**Results**

62,550 radiotherapy research articles from 127 countries, published in 2531 international journals were analysed. The United States was responsible for 32.3% of these outputs, followed by Japan (8.0%) and Germany (7.7%). Nearly half of all publications related to preparation and delivery of radiotherapy, combined modality regimens and dose fractionation studies. Health services research, palliative care, and quality of life studies represented only 2%, 5% and 4% of all research outputs. Countries varied significantly in their commitment to different research domains and trial related publications represented only 5.1% of total output. Research impact was analysed according to three different citation scores with research outputs from Denmark, The Netherlands, and The United States consistently the highest ranked.

**Conclusions**

Globally, radiotherapy publication outputs continue to increase but lag behind other spheres of cancer management. The types of radiotherapy research undertaken appears to be regionally patterned and there is a clear disconcordance between the volume of research output from individual countries and its citation impact. Greater support for radiotherapy research in low- and middle-income countries is required including international collaboration. The study findings are expected to provide the requisite knowledge to guide future radiation therapy research programs.

**Key words:** Bibliometrics; Health policy; Radiation therapy; Research

## INTRODUCTION

Cancer research is one of the most globally active domains of science, with more than $14 billion per annum in public and private expenditure (1). Research is integral to improving outcomes from cancer, be it through an improved understanding of the etiology of disease, identifying new treatment targets or modalities, or by the provision of information on how best to coordinate cancer services to deliver affordable and equitable cancer care.

Radiotherapy is one of the main modalities of control, cure and palliation for cancer with approximately 50% of cancer patients requiring radiotherapy during their disease course (2-4). Given the outcomes it can deliver with respect to survival and quality of life, its under-utilization as a clinical modality (3) and the lack of prioritization it has been given as a research domain within the cancer spectrum, remain major concerns. A recent study within lung cancer has found that only 8% of lung cancer research is devoted to radiotherapy research compared to 20% for genetics, 17% for systemic therapies and 16% for prognostic biomarkers (5). This undoubtedly will influence patterns of care for particular disease entities and the potential for new developments that will ultimately improve patient outcomes.

It is therefore important to understand from a public policy perspective how, why, and which particular research domains evolve and have an impact on outcomes. For example, how do different countries influence the radiotherapy research agenda either through the volume of research they publish, the citation impact of their papers or their commitment to particular research domains (e.g. basic science, health services research).

It will also highlight gaps and provide direction as to which research areas should be prioritized to meet current and future challenges. For example, there is currently an ongoing debate (6) as to whether the increasing focus on technological innovation within radiotherapy to improve the therapeutic ratio has been at the cost of not developing a greater understanding of the potential role for radiotherapy in exploiting cancer weaknesses based on the biological hallmarks of cancer. It is thought that further research into these areas could unlock new and more cost-effective opportunities for radiotherapy to improve outcomes from cancer. In addition, it would help to ensure that radiotherapy continues to be relevant and that research in this area prioritized in an era of precision medicine, which is increasingly drug-focused (7, 8).

Using a bibliometric approach, we present an analysis of global research on cancer radiotherapy between 2001 and 2015. This type of analysis is now used routinely in public policy analysis to study research domains (9, 10). We examine the growth in research output from 25 leading countries, the volume of research produced relative to their wealth, the main radiotherapy research domains these countries prioritise, and the citation impact of radiotherapy research stratified according to country and research domain.

**METHODS**

We performed a bibliometric analysis of radiotherapy research outputs during 2001-15, based on articles and reviews in the Web of Science (WoS) database. This contains full bibliographic information about the papers, including all addresses as well as the numbers of citations received by each paper in each year. Of note, the use of additional biomedical databases does not significantly increase the yield of relevant journals.

We used filters (macro algorithms based on logic functions) developed by an expert bibliometrician (GL) in conjunction with the team's expertise in radiotherapy and radiation research, to identify relevant papers in the WoS. The search for radiotherapy papers included papers in ANY journal, including general medical and basic science journals, provided that they had a title term indicative of cancer (composed of 323 words and short phrases (11)) AND had the word "radiation or radiotherapy" including wildcard "rad*", OR contained one of the 12 radiotherapy specific title words, such as "brachytherapy" (See supplementary appendix 1). It also included papers in seven specialist cancer radiotherapy journals identified by the study authors (supplementary appendix 1) and in 185 specialist cancer journals, provided that papers in the latter contained one of the radiotherapy filter terms. In addition, there were 20 more journals identified by the authors that also covered both cancer and non-cancer radiation topics (supplementary appendix 1). Papers in these journals were retained ONLY if they had one of the 323 cancer filter terms.

All these filters were developed through iterative rounds which involved creating datasets and having these manually coded by clinical experts as to their relevance to the research fields being sought (using methods previously described (12)). This process resulted in both a precision or specificity and a recall or sensitivity for identifying radiotherapy research papers of 0.95, which is considered very high (11).

There were 127 countries that contributed to these radiotherapy papers. However, the results presented in this study will primarily focus on the 25 leading research-active countries that are responsible for 97% of the total.

The counts of the numbers of publications per year were obtained as both integer and fractional counts using the paper's addresses. For example, if a paper has two addresses in Germany and one in France it would be counted as 1 for each on an integer count basis, but as 0.67 and 0.33 respectively on a fractional count basis. Fractional counts sum to less than the total partly because of the outputs of the other countries, and partly because some papers had no addresses. Integer counts summed to more than the total because of international co-authorship. Unless otherwise mentioned, our analysis is based on fractional counts, which give a much better impression than integer counts of the relative research effort by each country (13, 14).

*Volume of research*

For each of the 25 leading countries, we analysed the numbers of published radiotherapy research papers for each year from 2001 to 2015, and calculated the annual average percentage growth rate (AAPG) and the ratio of outputs between 2011-15 and 2001-05. We also calculated the commitment of the 25 countries to radiotherapy research relative to their output of cancer research overall. For example, between 2001 and 2015, Canada published 3956 papers out of a world total of 62,550 (6.3%). In the same time-period, Canada contributed to 4.2% of all oncology research outputs worldwide. Canada's relative commitment to radiotherapy research was therefore 6.3 / 4.2 = 1.50. For selected high- and middle- income countries we also analysed the association between radiotherapy research output and each country's GDP [Gross Domestic Product). The GDP is a measure of a country's economy and is the total market value of all consumer goods and services produced by all the people and companies in the country in a period of time (quarterly or yearly).

*Radiotherapy research domains*

Radiotherapy research publications were categorised into ten research domains. These were defined using sub-filters that contained a set of title words and strings to categorise relevant papers into particular domains. These sub-filters were all developed as part of an iterative process by AA and YL in collaboration with GL, with additional terms being added to each of the sub-filters in order to capture many of the papers not yet classified. We also used a complex logic process as the individual sub-filters were applied to the spreadsheet, so that some papers were classified if they were identified by particular sub-filters but NOT by others.

The research domains and individual codes used for analysis were as follows: BIOL ((Radio)biology); PHYS (physics); ASSU (Quality Assurance); FRAC (dose fractionation and sequencing studies); COMB (multimodality studies involving radiotherapy); PRED (preparation and delivery of radiotherapy); PALL (palliative care); QUAL (quality of life); HESR (health services research); REVS (review papers). Of note, the PRED domain also included studies evaluating particle therapy in the clinical setting. The domains were not mutually exclusive and therefore papers reviewing quality of life in relation to clinical dose fractionation studies would be included in both categories, i.e. QUAL and FRAC. In addition, papers classified solely within either BIOL, PHYS or ASSU were treated as non-clinical basic science studies. PRED, FRAC and COMB domains included studies that measured clinical endpoints such as morbidity. Eventually, all but 6465 papers were classified into one or more of these categories (10.3%).

Fractional counts were calculated for each country and research type, and the results compared with the world totals so as to show whether a country was over- or under-represented relative to the world average for each research domain. We also analysed the number of papers describing radiotherapy trials (phases 1-4) and the fractional counts of these papers for each country.

*Citation impact by country and research domain*

The citation counts for each paper from 2001-11, year by year, were downloaded from the WoS. The five-year citation counts (Actual Citation Impact, ACI) beginning in the publication year were calculated. A five-year window was used as a compromise between the need for immediacy (i.e., citations to recent papers) and stability (i.e., inclusion of the peak year for citations, usually the second or third year after publication). It is best determined for a country based on fractional counts, because many of the most cited papers are multi-national. Altogether, citation counts were determined for 32,162 papers.

For each country we calculated an arithmetic mean citation score as a measure of the impact of their radiotherapy-related research. This was based on the ACI of each of their papers during the study period. To calculate this, the citation score for each paper was multiplied by the country's fractional contribution to that paper and the products summed, and the total divided by the sum of the country's fractional counts for the relevant years. For example, for Germany, the top-cited paper, with 1360 cites, had a German presence among the addresses of 0.133. Germany was therefore credited with 1360 x 0.1333 = 181.3 cites. All the products for individual papers were summed, to give the fractional German citation total of 44,341.4 cites, which when divided by the German fractional count citable total of 3306.9 papers gives an arithmetic mean citation score of 13.41 cites per paper. A **geometric** mean was also calculated based on the logarithms of the actual citation counts. This value is considered to be a better indicator as it is less influenced by a few very high citation counts (15).

Another measure of citation impact is the number of a country's papers that receive enough citations to put them in the top 1%, 2% or 5% of all cited radiotherapy papers. During the time-period of analysis (2001-2011), a paper would have had to receive 93, 68 and 44 cites respectively to be in these centiles. A WorldScale (WS) value at a particular centile was calculated based on the ratio of the proportion of papers from a selected country in the top x% of cited papers compared to the proportion of all papers in that particular centile. So for Germany, with 3306.9 citable papers in the 11 years, as it published 136.5 papers with 44 or more citations, its WS value at 5% was (136.5/3306.9)/0.05 x100= 83. This value is lower than 100 and indicate it has fewer than the expected number of papers in this centile. The three WS values at 1%, 2% and 5% for each country were averaged to give a composite value for a country's highly cited papers – the WorldScale mean.

The 25 leading countries were ranked separately on these three citation indicators (arithmetic, geometric and WS means) and the rankings were then averaged. Using similar methods, we also determined the citation impacts for papers in the ten research domains.

Finally, an analysis of the proportion of publications that were open access between 2001-2015 was undertaken, as well as a comparative analysis of five-year citation scores for open access versus non–open access papers published between 2010-2012.

**RESULTS**

In total, 62,550 papers were identified from 2531 international journals and from 127 countries. Nearly all of the papers were in English (60,494 papers, 96.7%), but others were in 20 different languages, led by French (1193, 1.9%), German (598, 0.96%) and Spanish (76, 0.12%). A few were in Chinese, Japanese or Korean.

The 25 leading research-active countries, which accounted for 96.9% (or 60,673 papers) of the total in the file, included (in alphabetical order): Australia (AU), Austria (AT), Belgium (BE), Brazil (BE), Canada (CA), China (CN), Denmark (DK), France (FR), Germany (DE), Greece (GR), India (IN), Iran (IR) Italy (IT), Japan (JP), Netherlands (NL), Norway (NO), Poland (PL), Republic of Korea (KR), Spain (ES), Sweden (SE), Switzerland (CH), Taiwan (TW), Turkey (TR), the United Kingdom (UK) and the USA (US).

*Volume of research*

Between 2001 and 2015 the volume of radiotherapy research increased year on year, with a doubling in world outputs (Figure 1). The United States was responsible for 32.3% of these outputs (Table 1), followed by Japan (8.0%) and Germany (7.7%). However, there have been significant changes in the volume of research produced from some countries, with Iran, China, Brazil and South Korea showing the highest AAPG values and with output ratios between 2011-15 and 2001-05 of 19.3, 10.4, 4.8, and 4.5 respectively.

Most countries had a smaller percentage presence in radiotherapy research than they did in oncology overall (Table 1). The Netherlands, Canada and Belgium are notable exceptions. China, despite having a sustained and large increase in its volume of radiotherapy research over the 15-

year period, still had a smaller percentage presence in radiotherapy research than in all cancer. A similar pattern was observed for Brazil.

Figure 2 shows that the volume of radiotherapy research output is positively correlated with each country's GDP, with the spots for most of the selected high- and upper-middle income countries close to the least-squares regression line. Notable exceptions are the Netherlands, which published more than three times as much as the regression line predicts, and Taiwan, Canada and the USA whose output was double or almost double the amount predicted. On the other hand, upper-middle income countries, such as China and Brazil, published less than half the predicted amounts. Russia published less than one tenth of the amount predicted from the regression line. All these differences are highly statistically significant ($p < 0.001\%$ on the Poisson distribution with one degree of freedom).

*Research domains*

Figure 3 shows the distribution of research papers during the study period in nine of the research domains. Clinical research domains predominate, with studies focussing on (1) preparation and delivery of radiotherapy (PRED, 24%), (2) use of radiotherapy as part of combined modality management (COMB, 17%) and (3) evaluation of different dose and fractionation schedules (FRAC, 15%). These three domains accounted for nearly half of all published radiotherapy research.

Basic science represented a further third of research outputs, with radiobiological (BIOL) investigation accounting for 19% and physics (PHYS) for 13% of total outputs. Health services research (HESR) was very limited accounting for only 2% of the total. Palliative care (PALL) and quality of life studies (QUAL) in radiotherapy also made only small contributions to the literature, of 5% and 4% respectively.

Figure 3 shows that between 2001-2005 and 2011-2015 radiobiology research has had the most modest increase in volume of research output (AAPG = 4.8) compared with clinical domains such as preparation and delivery (AAPG = 9.0) and dose fractionation studies (AAPG = 9.3). Health services research has had sustained increases over the time period with an AAPG of 10.8.

Table 2 shows the relative commitment of different countries to the nine research domains. Whilst the US, France and Austria are well represented in all the domains, this is not so for other countries. For example, China's radiotherapy research is focussed on basic science, particularly on radiobiology. Canada has a focus on physics, palliative care and health services research. The Netherlands, Belgium, Denmark and Iran have a strong commitment to physics research, with the Netherlands also noticeable for its commitment to quality of life related research and Iran to quality assurance.

Australia, like Canada, and to a lesser extent the UK, is notable for its strong commitment to health services research; Norway excels in quality of life and palliative care research.

*Clinical trial outputs*

Of the 62,550 radiotherapy papers, only 3926 (6.3%) involved clinical trials. Of these, 34 described preparatory work, and 687 were secondary sources (meta-analyses, systematic reviews and other trials without specification of stage). The remaining 3205 (5.1%) papers described trials in the four established phases: 769 phase 1, 1065 phase 2, 1367 phase 3 and four described phase 4 trials. Table 3 demonstrates the variation in clinical trial outputs across the top 20 leading countries. The US, published the greatest number of outputs across Phase 1 to Phase 3 studies. Japan is notable for the high proportion of publications describing phase 1 studies relative to all other countries. With respect to Phase 2 trial outputs, Japan again features strongly as does Italy and China. Phase 3 trial outputs are dominated by the UK, Germany and The Netherlands after the US. An analysis of the ratio of phase 3 to Phase 2 trial outputs from each of the 25 countries showed significant international variation. The US for instance had a relatively low ratio of Phase 3 relative to Phase 2 outputs. This was also notable for countries such as Japan (0.50), Italy (0.58), Republic of Korea (0.60) and Spain (0.46). Conversely countries such as the UK (3.45), Netherlands (4.72), Sweden (4.14), and Poland (5.02) published over double the number of trial outputs of Phase 3 studies compared to Phase 2 studies in the study period. India, a middle income country, also had a strong commitment to Phase 3 studies (2.83).

*Citation counts and research impact*

Table 4 shows the 25 leading countries with their mean ACI values (arithmetic and geometric) and their mean WorldScale values. The latter is based on the numbers of their papers with enough citations to put them in the top 1% (≥93 citations), top 2% (≥68 citations), top 5% (≥44 citations) as described in the methods section. The countries are ranked according to the mean ranking across the three scales.

We find that Denmark, The Netherlands, the United States, Switzerland and Belgium are the only countries with consistently superior performance at all three WorldScale percentiles (*i.e.* values > 100). High research output countries such as China, Japan, and Germany rank in the lower half of the table. Conversely, Denmark, Switzerland, and Belgium appear to produce research with greater impact, despite the low volume of their research relative to that of the other countries.

Table 5 shows the citation impact of different radiotherapy research domains according to the mean WorldScale values. It shows that whilst review papers, and research focussing on combined modality treatment (*e.g*. radiation and drug therapies), are highly cited and potentially will have a greater impact on practices of care, research into quality assurance and health services research may have less impact with a small fraction of papers in the top centiles of cited radiotherapy papers.

*Open access papers*

Figure 5 presents a breakdown of the changing proportion of radiation therapy research papers available through the WoS, which are closed (i.e. behind a pay wall), gold open access (all freely available from the publisher), or green open access (available from the author's archive). The proportion of open access papers have continued to increase since 2001. Green open access papers are the best cited: the mean ACI for 2010-2012 papers was 19.7 cites in five years, compared with 15.7 cites for gold open access and 12.3 cites for closed papers.

**DISCUSSION**

This analysis of the global research landscape is the first to characterise the output of radiotherapy research globally and to identify trends in research priorities and contributions by individual countries. We found a doubling in overall research output over a 15-year period, consistent with trends observed in other disciplines (16). The globalization of research has been a major contributor to this increase in output. Although the USA was responsible for over a third of the radiotherapy research output between 2001 and 2015, there was only a 55% increase in research output in the USA during that period, compared to over 2000% in China.

Significant increases in research output were also seen in several other middle-income countries, including India, Brazil, Turkey, and Iran although their overall contribution to total worldwide radiotherapy research remained small. In this regard, it is important to acknowledge the issues related to access to radiotherapy in the majority of low- and middle-income countries (LMIC) (17), which undoubtedly will have important implications on their ability to influence the research portfolio.

Furthermore, when these countries' research output is compared with their GDP, they still lag some way behind the major high-income countries. This is likely to be influenced by differences in cancer research funding between LMICs and high-income countries. We know that only 2.7% of total global cancer research investment is directly relevant to LMICs (18). Of that investment, the majority of cancer research funding is directed to studies that focus on cancer biology and drug development rather than radiotherapy related research (19, 20).

It is important that LMICs are supported and encouraged to participate in research because of the need to continue to develop cost-effective treatment pathways, which can also meet key goals such as equity and efficiency within the constraints of their health system (21). The wider research community will also benefit from a more globally inclusive research base given inherent differences in cancer epidemiology and biology related to risk factor exposure. In the European Union for instance, limitations in the size (by population) and resources of individual countries is compensated by strong international collaboration, with the European Organisation for Research and Treatment of Cancer (EORTC), acting to coordinate radiation therapy research in the region.

It may be argued that with improved survival outcomes and more people living with cancer (22), there should be greater attention in research to the domains of quality-of-life, health services, and palliative care. However, these areas represent only 4%, 2%, and 5% of total radiotherapy research outputs respectively over the study period. This is in stark contrast to other clinical research domains such as preparation and delivery (24%) and dose fractionation studies (15%). Quality of life research appears particularly low given the dominance of clinical studies involving patients and the importance of this as a clinical end-point.

This discrepancy between the health needs of the population and current research priorities was also found in other cancer studies. In a bibliometric analysis, Sanson-Fisher et al found that there were four times as many publications on chemotherapy in 2005 as on quality of life research, despite steady increases in the latter over the preceding 20 years (23).

Health services research encompasses a broad multi-disciplinary area addressing issues related to access, equity and the value of health care. This branch of research helps to define new research priorities. It also aids effective implementation and sustainability of new innovative processes of care given the health system constraints, financial, political or geographic, of a particular country. However, despite its importance, this area of research still lags far behind more established clinical and basic science research domains. It may not be considered to have the same value or relevance as other domains, as shown by its relatively low citation impact. Furthermore, this is an interdisciplinary subject area and requires collaboration between radiation oncologists and social scientists such as health economists and epidemiologists.

However, this view may finally be changing because of growing fiscal constraints that affect both high-income and low-and-middle income countries and an increasing focus on value-based frameworks within medicine (24, 25). One example is the Health Economics in Radiation Oncology (HERO) project under the auspices of the European Society of Radiation Oncology (ESTRO) which seeks to address the short fall in applied research in this area (26).

The low commitment of several countries to palliative care research shown in Table 3 may be the result of the relative lack of senior academic appointments in this domain. This may limit opportunities for cross-sectoral research collaboration and for the attraction of research funding and the creation of research infrastructure (27). Norway demonstrated the strongest commitment to palliative care research, relative to other priorities. This is likely to reflect the country's strong support for palliative care at all levels of the public health care system (28).

The predominance of clinical research outputs in our study is also a likely reflection of the particular time-period in which these analyses were undertaken, where significant technical improvements have been made (IMRT, particle therapy, motion management) that have sought to reduce the morbidity associated with treatment. In addition, large clinical trials in this era such as those assessing multimodality therapy (29) and different dose fractionation schedules (30) have been a natural consequence of the pre-clinical research performed in the 1980's and 1990's, which had a much greater biological focus with studies addressing dose per fraction, hypoxia and drug radiation interactions.

Review papers were the most highly cited research domain, which suggests that evidence syntheses in the form of systematic reviews and meta-analyses have the potential to greatly influence practice, which is desirable. Research into multi-modality therapy involving radiotherapy is also highly cited, most likely because of the large investment made in such studies (especially those involving pharmaceuticals) and the importance that these outputs have across the entire cancer spectrum from basic science to medical, surgical and radiation oncology.

Clinical trial publications accounted for 5% of total research output during the study period. The low overall proportion of publications related to clinical trials also points to a more worrying trend within radiotherapy research. This concerns the level of evidence required to integrate new processes of care and technologies into treatment, which remains reliant on small-scale observational studies and, more recently, modelling studies (31, 32). Whilst there are constraints to conducting Phase 3 trials in radiotherapy, increasing concerns about the value of new innovations means that investment in trials is required (public or private) to ensure new modalities are evaluated with rigorous methods so as to enable cost-effectiveness analyses to support their widespread implementation (33). Of even greater concern is that once available in the market following Food and Drug Administration (FDA) and European Union (EU) approval, few phase 4 studies are subsequently undertaken, even within centres that are early adopters of a new technology (34). Pragmatic research designs such as multicentre observational cohort studies or nationally coordinated coverage with evidence development (CED) schemes are alternative approaches that have been considered for evaluating the effectiveness of treatment in the real world setting (32, 35).

A number of interesting observations are offered in Table 3, which looks more closely at phase 1 to 3 trial outputs from individual countries. European countries such as The UK, Netherlands, Sweden and Poland produce a much higher ratio of Phase 3 related trial outputs relative to Phase 2. India also demonstrated a greater commitment to Phase 3 relative to Phase 2 trials, compared to several high-income countries, where the reverse trend was observed. For example, the US, Japan and Italy had a significantly higher proportion of Phase 2 study outputs relative to Phase 3. It is not clear why such differences are apparent, but may relate to economic and cultural factors. For example, whether or not the necessary infrastructure or funding is available to conduct radiation therapy research trials, may be one factor influencing these figures. Countries may vary in the level of evidence required by health care reimbursement organisations before they will routinely fund new technologies or practices of care. In addition, organisations such as the FDA require demonstration of safety, rather than efficacy within phase 3 studies, before approving new technologies, which has a downstream effect on the types of research evidence likely to be generated prior to clinical adoption.

While the US was the largest contributor to randomised control trial (RCT) publications, the proportion of its total radiotherapy research output devoted to RCTs was significantly less than that in other countries such as India.  This may reflect the recent trend of pharmaceutical and medical technology companies to conduct trials in countries where the personnel costs are lower and where the large pool of potential research participants can accelerate recruitment (36).  There may be many benefits that accrue to these countries from clinical trials research such as the opportunity for international collaboration, investments in healthcare infrastructure, and the redirection of research priorities towards locally relevant and feasible interventions.  However, concerns have also been raised about whether there is adequate transparency and oversight of human subjects in these countries, which may have weak regulatory systems and limited experience in research (36).

In this study, we used three different citation scores based on actual citation counts to rank countries on the quality and importance of their published outputs.  While China, Japan, France and Germany were high output countries in terms of the number of research publications, their citation performance was significantly lower than that of several other countries that had lower research outputs (e.g. Denmark). This may be partly because their papers tended to be published in low-impact journals or related to the language in which they were published.  In that regard, a study of the impact of publication language on citation frequency in the scientific dental literature showed that papers published in English had a 6-7 times higher chance of being cited than articles published in German or French (37).

Furthermore, research papers from middle-income countries are poorly cited. It is unclear whether this relates to the perceived quality or level of interest in research from these countries or the low impact factor of the journals these studies are published in. This needs to improve to encourage middle-income countries to become more involved in radiotherapy research and influence practices of care. If not, practices of care may risk becoming regionally entrenched or influenced by a few select countries in North America and Europe, which could result in distinct knowledge gaps in the empirical literature.

International collaboration is one mechanism by which this situation can be improved and prevent unnecessary duplication of research to ensure the best available evidence is used to drive radiotherapy practice. One could consider a regional approach to identifying gaps in the evidence base and undertake relevant clinical and non-clinical studies, for example, through pre-existing regional alliances such as EMRO (Regional office for the East Mediterranean) and PAHO (Pan American Health Organisation). In addition, the IAEA (International Atomic Energy Association) continues to support and coordinate multinational clinical radiotherapy trials (http://www-naweb.iaea.org/nahu/ARBR/crp.html ), which have impacted on clinical practice (38).

Our analysis of open access papers demonstrates that they are steadily increasing over time representing nearly 40% of papers currently published in the WoS either as gold or green open access. Whilst the overall citation impact of more recent open access papers (2010-2012) is higher than closed papers, this varies depending on country of origin and the type of radiotherapy research undertaken.

*Limitations*

The present study must be considered in the context of its strengths and limitations. The analysis has been undertaken on an individual country basis and findings with respect to country outputs are potentially skewed depending on the size (by population) and resources of individual countries. However, this reflects the reality of their research strengths and weaknesses. Outputs relative to each individual country's GDP and research impact have also been presented. In addition, European countries which conduct a number of collaborative multinational studies, may appear to produce comparatively less trial outputs when using fractional counts compared to the US for instance. A regional based analysis may be one mechanism for addressing this in the future. We have used citation frequency as a proxy indicator for quality of research and dissemination of scientific findings. However, a true evaluation of the scientific quality of publications cannot be achieved without an independent and dedicated assessment of their merit. Furthermore, citation frequency cannot determine whether a publication changes practice and improves population health (16).

We have not provided a detailed analysis of the factors that have led to the observed trends and can only hypothesize potential reasons at this stage. The quantity of research outputs may be affected by publication bias, with failure of up to 20% to 30% of trials to report their results (39). Equally excellent research may not be published or published elsewhere. This will have an impact on country-level integer and fractional counts, as well as on potential under-representation of clinical research outputs.

We have selected publications available in the WoS for analysis, and it is therefore likely that some research output in national language journals has not been included, which could affect our results for country-level outputs. In addition, as with any bibliometric evaluation it is not possible to guarantee inclusion of all relevant papers. However, attempts to minimise this have been sought by undertaking several iterations to develop the precision of our search filters to ensure inclusion of papers which have a relevant title word or mesh terms specific for clinical and basic science papers in radiotherapy. Whilst the WoS has selection criteria for the inclusion of journals based on repute and citation, it is unknown what proportion of low-quality "predatory" open access papers that are included and the impact this has had on the estimations of total radiotherapy research output(40). Finally, although our coding scheme for research types was made as explicit as possible, it is possible that some publications were miscategorised or that not all publications could be categorised according to the selected domains.

**CONCLUSIONS**

To conclude, our findings provide a detailed analysis of trends in radiotherapy research since 2001. Whilst there has been a doubling of radiotherapy research outputs over the study period, significant variation exists in the research output of individual countries, with evidence that radiotherapy research output is falling behind that of other cancer related research domains. Although LMICs such as India, Iran, China and Brazil continue to increase their radiotherapy research output, this still lags behind what is expected given their economic strength. Greater support is required to develop the necessary infrastructure to support high quality research in LMICs that will contribute to the development of the speciality overall but allow the essential upscaling of radiotherapy resources in these countries.

When considering the radiotherapy research types, there is evidence of individual countries' being committed to particular domains that reflect national cultures and economies. A major concern remains the very low proportion of trial related publications within radiotherapy. This is an area which requires greater investment if we are to try and establish the relevant evidence base to promote the implementation of the most cost-effective high value care. In its absence, there will remain a lack of transparency as to the comparative benefits of innovations relative to existing treatments especially given that the bulk of research focuses on clinical domains. To this end, greater focus on quality of life studies is required, as despite the clinical predominance of most research output, few papers considered these end-points. In addition, it is unknown what impact the slowing down of basic science research outputs over the study period means in the long term with respect to identifying new pathways for improving patient outcomes. Greater emphasis on health services research would provide robust evidence on translating clinical evidence into practice. Finally, whilst citation impacts do not necessarily reflect influences on practices of care they provide some understanding of the degree of interest or quality of the paper. Given differences across countries, this may suggest that research outputs from particular countries are considered to be of higher quality and potentially have a greater impact on influencing practices of care.

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## Figure Captions

**Figure 1. Increase in radiotherapy research publication output between 2001 and 2015 (n=62,550).**

**Figure 2. Outputs of radiotherapy research papers as a function of national wealth (log-log scales).**

*Notes: Diagonal line is best power-law least-squares correlation line; dashed lines show values twice and half those of the correlation line.*

**Key:** Australia (AU), Austria (AT), Belgium (BE), Brazil (BE), Canada (CA), China (CN), Czech Republic (CZ), Denmark (DK), Finland (FI), France (FR), Germany (DE), Greece (GR), India (IN), Iran (IR), Ireland (IR), Israel (IL), Italy (IT), Japan (JP), Netherlands (NL), Norway (NO), Poland (PL), Republic of Korea (KR), Russia (RS) Singapore (SG), Spain (ES), Sweden (SE), Switzerland (CH), Taiwan (TW), Turkey (TR), the United Kingdom (UK) and the USA (US).

**Figure 3. Distribution of radiotherapy papers by research domain, 2001-15, and annual average percentage growth rates (AAPG) for the papers in the research domain.**

**Key:** BIOL ((Radio)biology); PHYS (physics); ASSU (Quality Assurance); PALL (palliative care); QUAL (quality of life); HESR (health services research); FRAC (dose fractionation studies; COMB (multimodality studies involving RT); PRED (preparation and delivery of RT).

**Figure 4. Changing proportion of closed and open access papers over time 2001-15**

**Table 1. Outputs of radiotherapy papers from the world and 25 leading countries, 2001-15.**

*Notes:% = percentage of world output; AAPG = annual average percentage growth; Ratio = output in 2011-15 / output in 2001-05; R.C. = relative commitment to radiotherapy research compared to all cancer. Cells with values > twice world average tinted bright green; those > 1.40 x world average tinted pale green; those < 0.71 x world average tinted yellow; those < 0.51 x world average tinted pink.*

| *Country* | *All yrs* | *%* | *AAPG* | *Ratio* | *R.C.* | | *Country* | *All yrs* | *%* | *AAPG* | *Ratio* | *R.C.* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Worldwide** | 62550 | | 6.2 | **1.87** | | | **Spain** | 879 | 1.4 | 9.9 | 2.64 | 0.65 |
| **United States** | 20097 | 32.2 | 3.7 | 1.47 | 1.07 | | **India** | 855 | 1.4 | 11.9 | 3.14 | 0.73 |
| **Japan** | 5019 | 8.0 | 5.4 | 1.75 | 0.92 | | **Sweden** | 834 | 1.3 | 1.7 | 1.15 | 0.96 |
| **Germany** | 4782 | 7.7 | 2.7 | 1.34 | 1.21 | | **Belgium** | 823 | 1.3 | 4.0 | 1.47 | 1.45 |
| **China** | 3122 | 5.0 | 23.3 | 10.4 | 0.53 | | **Turkey** | 796 | 1.3 | 8.8 | 2.24 | 0.85 |
| **United Kingdom** | 2986 | 4.8 | 3.1 | 1.39 | 0.92 | | **Switzerland** | 769 | 1.2 | 4.6 | 1.54 | 1.32 |
| **Canada** | 2944 | 4.7 | 6.6 | 1.91 | 1.51 | | **Denmark** | 541 | 0.9 | 11.1 | 3.01 | 1.21 |
| **France** | 2931 | 4.7 | 8.9 | 2.35 | 1.09 | | **Poland** | 497 | 0.8 | 9.6 | 2.57 | 0.78 |
| **Italy** | 2661 | 4.3 | 5.1 | 1.71 | 0.81 | | **Austria** | 486 | 0.8 | -1.2 | 0.90 | 1.14 |
| **Netherlands** | 2448 | 3.9 | 5.5 | 1.74 | 1.69 | | **Brazil** | 485 | 0.8 | 15.6 | 4.80 | 0.64 |
| **Republic of Korea** | 2140 | 3.4 | 16.0 | 4.53 | 0.99 | | **Greece** | 435 | 0.7 | 0.0 | 1.04 | 0.81 |
| **Australia** | 1464 | 2.3 | 11.5 | 3.14 | 1.13 | | **Norway** | 401 | 0.6 | 7.0 | 2.07 | 1.02 |
| **Taiwan** | 923 | 1.5 | 10.5 | 2.64 | 0.78 | | **Iran** | 299 | 0.5 | 32.1 | 19.30 | 0.88 |

**Table 2. Relative commitment of leading 25 countries to different domains of radiotherapy research, 2001-15.**

*Notes: Cells with values > twice world average tinted bright green; those > 1.40 x world average tinted pale green; those < 0.71 x world average tinted yellow; those < 0.51 x world average tinted pink.*

**Key:** BIOL ((Radio)biology); PHYS (physics); ASSU (Quality Assurance); PALL (palliative care); QUAL (quality of life); HESR (health services research); FRAC (dose fractionation studies; COMB (multimodality studies involving RT); PRED (preparation and delivery of RT).

| *R. C.* | *Total* | *PRED* | *BIOL* | *COMB* | *FRAC* | *PHYS* | *ASSU* | *PALL* | *QUAL* | *HESR* |
|---|---|---|---|---|---|---|---|---|---|---|
| **World** | 62550 | 15091 | 12149 | 10426 | 9406 | 7802 | 4444 | 3092 | 2579 | 1320 |
| **US** | 20097 | 1.11 | 0.94 | 0.90 | 0.92 | 0.99 | 0.96 | 0.89 | 0.96 | 1.08 |
| **Japan** | 5019 | 1.10 | 1.18 | 1.47 | 0.95 | 0.67 | 0.67 | 1.02 | 0.63 | 0.85 |
| **Germany** | 4782 | 1.02 | 1.23 | 0.84 | 1.03 | 0.95 | 0.72 | 1.41 | 1.22 | 0.78 |
| **China** | 3122 | 0.95 | 1.60 | 1.29 | 0.99 | 0.81 | 0.76 | 0.97 | 0.72 | 0.24 |
| **UK** | 2986 | 0.81 | 0.96 | 0.85 | 0.92 | 1.27 | 1.01 | 0.78 | 1.26 | 1.42 |
| **Canada** | 2944 | 0.97 | 0.78 | 0.62 | 0.87 | 1.47 | 1.19 | 1.73 | 1.15 | 2.05 |
| **France** | 2931 | 0.93 | 0.80 | 1.07 | 0.95 | 0.77 | 0.90 | 0.92 | 0.98 | 0.76 |
| **Italy** | 2661 | 1.02 | 0.72 | 1.35 | 1.70 | 0.88 | 1.26 | 1.09 | 0.95 | 0.85 |
| **Netherlands** | 2448 | 1.00 | 0.85 | 0.91 | 0.97 | 1.55 | 0.70 | 0.91 | 1.95 | 1.16 |
| **Republic of Korea** | 2140 | 0.94 | 1.18 | 1.54 | 1.45 | 0.65 | 0.78 | 1.12 | 0.40 | 0.20 |
| **Australia** | 1464 | 0.89 | 0.56 | 0.79 | 0.77 | 1.18 | 1.65 | 0.96 | 1.11 | 2.19 |
| **Taiwan** | 923 | 0.92 | 1.25 | 1.40 | 1.00 | 0.70 | 1.00 | 0.71 | 1.40 | 0.97 |
| **Spain** | 879 | 1.08 | 0.81 | 1.19 | 1.39 | 1.06 | 1.45 | 0.69 | 0.85 | 1.33 |
| **India** | 855 | 1.00 | 1.08 | 0.86 | 1.02 | 0.96 | 1.70 | 0.70 | 0.95 | 1.17 |
| **Sweden** | 834 | 0.59 | 1.40 | 0.45 | 0.95 | 1.24 | 1.08 | 0.44 | 1.57 | 1.45 |
| **Belgium** | 823 | 1.03 | 1.08 | 0.68 | 0.87 | 1.64 | 1.30 | 0.64 | 0.81 | 1.22 |
| **Turkey** | 796 | 0.72 | 0.64 | 1.31 | 1.17 | 0.68 | 0.70 | 1.57 | 1.22 | 0.25 |
| **Switzerland** | 769 | 1.39 | 0.79 | 0.86 | 1.01 | 1.20 | 1.11 | 0.90 | 0.59 | 1.03 |
| **Denmark** | 541 | 0.85 | 1.09 | 0.64 | 0.79 | 1.83 | 0.97 | 0.45 | 1.39 | 0.96 |
| **Poland** | 497 | 0.93 | 0.95 | 0.64 | 1.27 | 0.72 | 1.30 | 1.31 | 1.13 | 0.71 |
| **Austria** | 486 | 1.14 | 0.75 | 0.79 | 0.98 | 1.30 | 1.05 | 0.82 | 0.74 | 0.83 |
| **Brazil** | 485 | 0.85 | 0.71 | 1.15 | 1.05 | 0.67 | 2.07 | 0.51 | 0.89 | 0.86 |
| **Greece** | 435 | 0.58 | 0.95 | 1.44 | 1.14 | 1.61 | 1.62 | 1.24 | 0.79 | 0.16 |
| **Norway** | 401 | 0.52 | 1.54 | 0.82 | 0.79 | 0.77 | 0.58 | 2.52 | 2.33 | 1.16 |
| **Iran** | 299 | 0.46 | 1.11 | 0.57 | 0.34 | 2.05 | 3.28 | 0.60 | 0.77 | 0.32 |

**Table 3. Number of papers relating to Phase 1, Phase 2 and Phase 3 radiation therapy trials published by the 20 leading countries between 2001-2015.**

Notes: Number of papers expressed as fractional country counts. Ph = Phase

* Percentage contribution of each individual country to Phase 1, Phase 2 and Phase 3 research outputs.

† Ratio of papers describing phase 3 studies and phase 2 studies

| | *Phase 1* | *Phase 2* | *Phase 3* | **% of total Ph1 outputs (n=769)* | *% of total Ph2 outputs( n=1065)* | *% of total Ph3 outputs (n=1367)* | *†Ratio of Ph3:Ph2 trial outputs* |
|---|---|---|---|---|---|---|---|
| **World** | 770 | 1066 | 1367 | | | | |
| **US** | 329.5 | 349.6 | 287.6 | 42.8 | 32.8 | 21 | 0.82 |
| **Japan** | 108.1 | 98.1 | 48.9 | 14 | 9.2 | 3.6 | 0.50 |
| **Germany** | 48.2 | 47.3 | 106.9 | 6.3 | 4.4 | 7.8 | 2.26 |
| **China** | 31.6 | 61.8 | 75.6 | 4.1 | 5.8 | 5.5 | 1.22 |
| **UK** | 26.2 | 36.8 | 126.9 | 3.4 | 3.4 | 9.3 | 3.45 |
| **Canada** | 28.9 | 35.3 | 76.8 | 3.7 | 3.3 | 5.6 | 2.18 |
| **France** | 23 | 61 | 82.3 | 3 | 5.7 | 6 | 1.35 |
| **Italy** | 38.7 | 82.2 | 48 | 5 | 7.7 | 3.5 | 0.58 |
| **Netherlands** | 22.8 | 19.3 | 91.1 | 3 | 1.8 | 6.7 | 4.72 |
| **Republic of Korea** | 12.4 | 46.2 | 27.9 | 1.6 | 4.3 | 2 | 0.60 |
| **Australia** | 13.7 | 22.6 | 58 | 1.8 | 2.1 | 4.2 | 2.57 |
| **Taiwan** | 3 | 5.1 | 10.4 | 0.4 | 0.5 | 0.8 | 2.04 |
| **Spain** | 11 | 37.3 | 17 | 1.4 | 3.5 | 1.2 | 0.46 |
| **India** | 2.5 | 9.4 | 26.6 | 0.3 | 0.9 | 1.9 | 2.83 |
| **Sweden** | 3.6 | 8.8 | 36.4 | 0.5 | 0.8 | 2.7 | 4.14 |
| **Belgium** | 10 | 18.8 | 17.4 | 1.3 | 1.8 | 1.3 | 0.93 |
| **Turkey** | 0 | 6.1 | 10.1 | 0 | 0.6 | 0.7 | 1.66 |
| **Switzerland** | 12.7 | 13.4 | 16.7 | 1.7 | 1.3 | 1.2 | 1.25 |
| **Denmark** | 4.1 | 14.3 | 25 | 0.5 | 1.3 | 1.8 | 1.75 |
| **Poland** | 2.3 | 4.6 | 23.1 | 0.3 | 0.4 | 1.7 | 5.02 |

**Table 4. Five-year citation performance of 25 leading countries in radiotherapy research, 2001-11.**

*Notes: Citable = numbers of papers in these years; WS = WorldScale mean value at top 1%, 2% and 5% of citations; Arithmetic = arithmetic mean of ACI values; Geometric = geometric mean of ACI values. Countries are ranked by mean ranking on these three indicators. Cells with values > 1.40 x world mean tinted pale green; with values < 0.71 x world mean tinted yellow; with values < 0.51 x world mean tinted orange; with values < 0.2 x world mean tinted pink.*

| *Country* | *Citable* | *WS (Ranking)* | *Arithmetic (Ranking)* | *Geometric (Ranking)* |
|---|---|---|---|---|
| **Denmark** | 301 | 199 (1) | 19.8 (1) | 11.8 (1) |
| **Netherlands** | 1604 | 147 (3) | 18.7 (2) | 11.4 (2) |
| **United States** | 13,572 | 154 (2) | 17.2 (3) | 9.8(3) |
| **Switzerland** | 512 | 131 (4) | 16.7 (5) | 9.5 (5) |
| **Belgium** | 563 | 117 (5) | 16.8 (4) | 9.6 (4) |
| **Canada** | 1922 | 101 (7) | 14.7 (6) | 8.4 (6) |
| **United Kingdom** | 2045 | 100 (8=) | 14.2 (7) | 7.8 (7) |
| **Austria** | 355 | 93 (10) | 13.4 (9=) | 7.2 (10) |
| **Wld** | **39,657** | **100 (8=)** | **13.7 (8)** | **7.3 (9)** |
| **Germany** | 3307 | 79 (12) | 13.4 (9=) | 7.5 (8) |
| **Australia** | 805 | 86 (11) | 12.5 (11) | 6.8 (13) |
| **Sweden** | 571 | 74 (13) | 11.9 (13) | 7 (11) |
| **France** | 1804 | 103 (6) | 12.1 (12) | 5.6 (17) |
| **Norway** | 267 | 49 (17) | 11.1 (14) | 6.9 (12) |
| **Italy** | 1690 | 57 (14=) | 10.6 (15) | 5.3 (18) |
| **China** | 1062 | 45 (18) | 10.5 (16=) | 6.1 (15) |
| **Republic of Korea** | 1135 | 30 (21) | 10.5 (16=) | 6.3 (14) |
| **Spain** | 513 | 57 (14=) | 9.1 (19) | 4.6 (21) |
| **Greece** | 326 | 40 (19=) | 8.6 (21) | 4.8 (20) |
| **Taiwan** | 538 | 9 (24) | 9.4 (18) | 6 (16) |
| **Japan** | 3243 | 27 (22) | 8.8 (20) | 5.2 (19) |
| **Brazil** | 265 | 40 (19=) | 7.6 (22) | 4 (22) |
| **Poland** | 302 | 50 (16) | 7.1 (23) | 3.1 (24) |
| **India** | 508 | 13 (23) | 5.4 (24) | 3.3 (23) |
| **Turkey** | 473 | 3 (25) | 4.2 (25) | 2.3 (25) |
| **Iran** | 116 | 0 (26) | 3.6 (26) | 2.2 (26) |

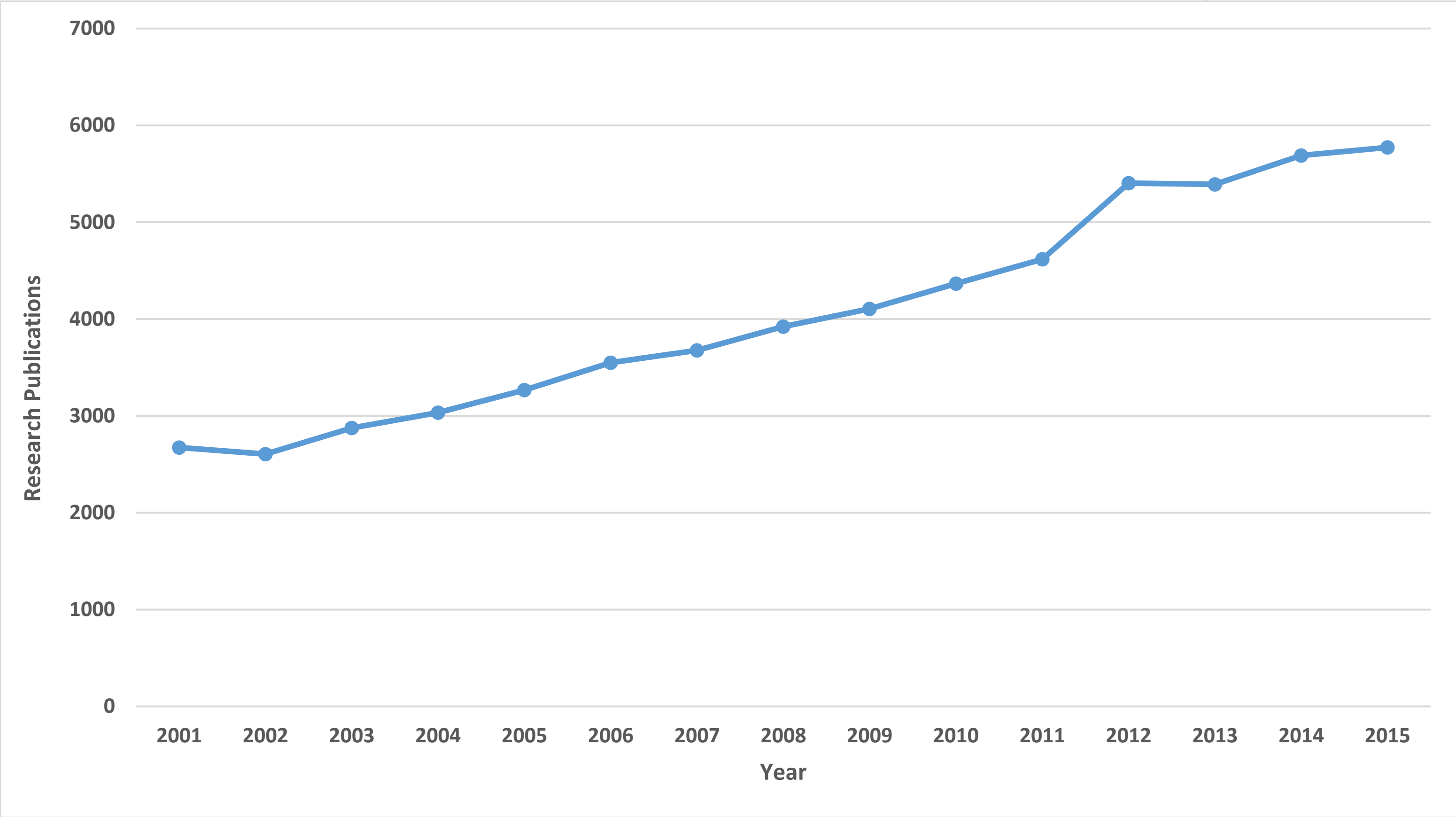
**Table 5. Presence of radiotherapy papers in the ten research domains in the top citation centiles, and overall ranking on basis of mean WorldScale values.**

*Notes: Numbers of publications with 137 citations (top 1%), 86 citations (top 2%), 50 citations (top 5%), in 5 years after publication. World, refers to citation analysis of all worldwide radiotherapy publications; WS, world scale value (ratio of percentages of a country's publications in the top x% (1%, 2%, & 5%) relative to percentages of all worldwide publications in the top x% multiplied by 100). Mean is average of WS scale values.*

**Key:** BIOL ((Radio)biology); PHYS (physics); ASSU (Quality Assurance); FRAC (dose fractionation studies; COMB (multimodality studies involving RT); PRED (preparation and delivery of RT) PALL (palliative care); QUAL (quality of life); HESR (health services research); REVS (review papers).

| *Domain* | *Citable* | *Top 5%* | *Top 2%* | *Top 1%* | *WS 5%* | *WS 2%* | *WS 1%* | *Mean* |
|---|---|---|---|---|---|---|---|---|
| **REVS** | 2733 | 256 | 104 | 59 | 189 | 191 | 216 | 199 |
| **COMB** | 6435 | 452 | 227 | 135 | 142 | 177 | 210 | 176 |
| **FRAC** | 5650 | 344 | 154 | 88 | 123 | 137 | 156 | 138 |
| **PRED** | 8944 | 601 | 207 | 94 | 135 | 116 | 105 | 119 |
| **PALL** | 1758 | 96 | 36 | 17 | 110 | 103 | 97 | 103 |
| **BIOL** | 7975 | 470 | 159 | 71 | 119 | 100 | 89 | 103 |
| **PHYS** | 4708 | 252 | 88 | 32 | 108 | 94 | 68 | 90 |
| **QUAL** | 1611 | 84 | 29 | 11 | 105 | 90 | 68 | 88 |
| **HESR** | 727 | 26 | 10 | 3 | 72 | 69 | 41 | 61 |
| **ASSU** | 2660 | 71 | 18 | 8 | 54 | 34 | 30 | 39 |

**Figure 1.**


7000
6000
5000
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3000
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1000
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Research Publications
2001
2002
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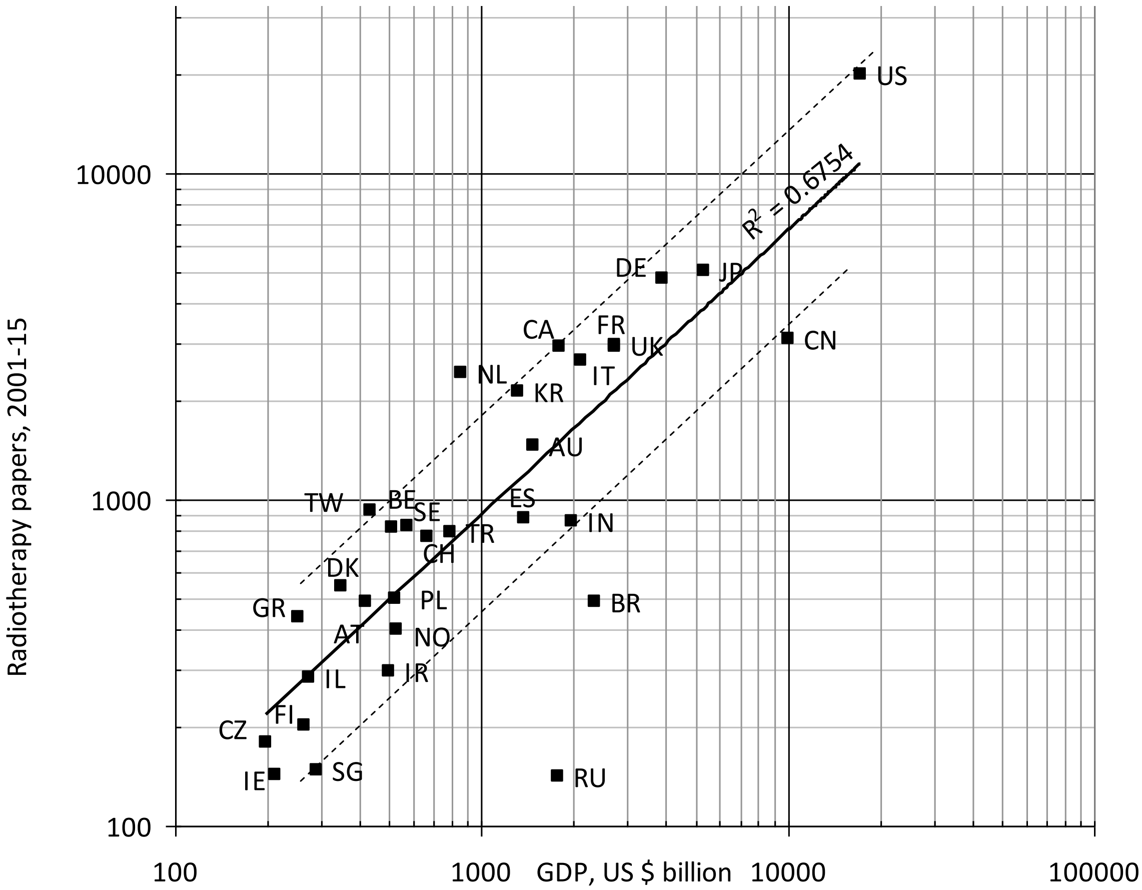
**Figure 2.**



Radiotherapy papers, 2001-15
GDP, US $ billion
100
1000
10000
100000
100
1000
10000
$R^2 = 0.6754$
US
JP
DE
CN
FR
CA
UK
IT
NL
KR
AU
ES
IN
TW
BE
SE
TR
CH
DK
PL
GR
AT
NO
BR
IR
IL
FI
CZ
SG
IE
RU

**Figure 3.**

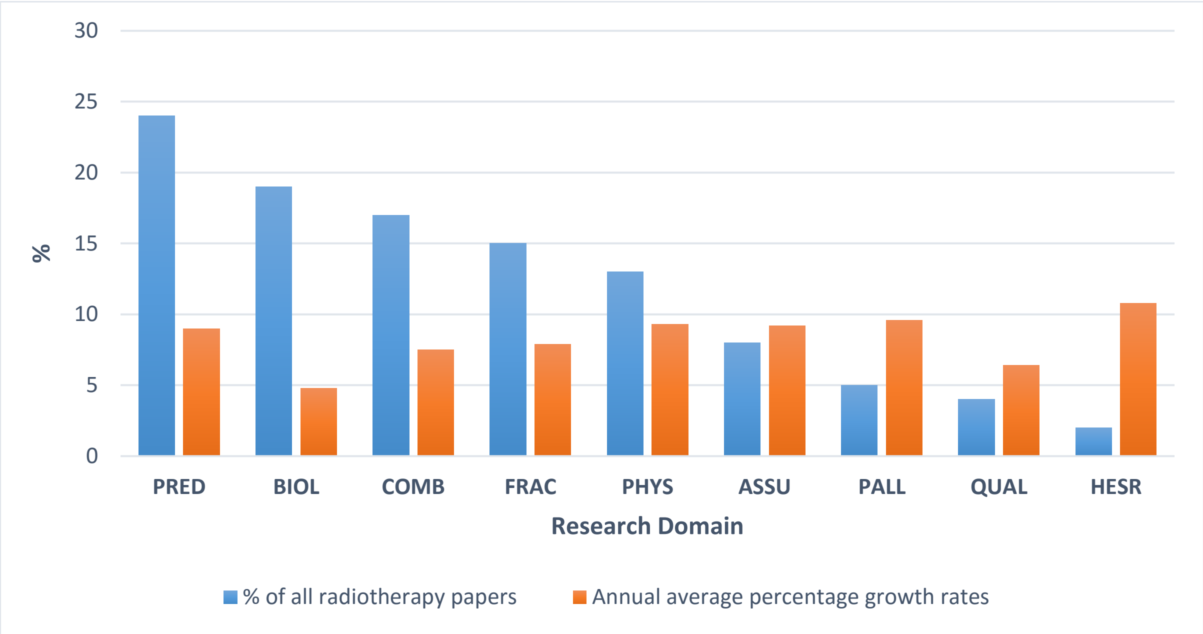
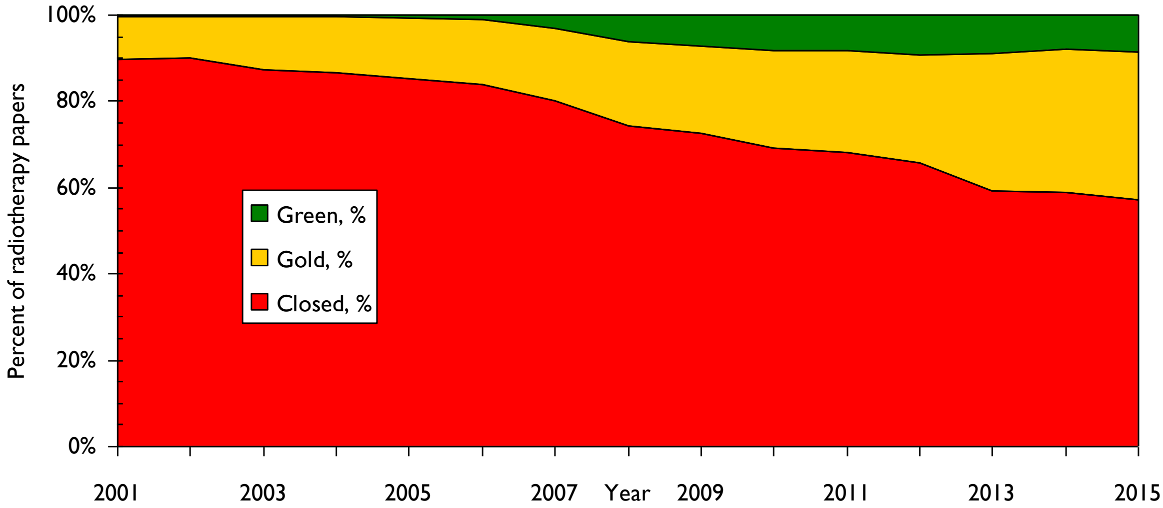

30
25
20
15
10
5
0
%
PRED
BIOL
COMB
FRAC
PHYS
ASSU
PALL
QUAL
HESR
Research Domain
% of all radiotherapy papers
Annual average percentage growth rates

Fig. 4


100%
80%
60%
40%
20%
0%
Percent of radiotherapy papers
Green, %
Gold, %
Closed, %
2001
2003
2005
2007
Year
2009
2011
2013
2015