

Original Article

Preoperative Radiotherapy for Rectal Cancer: A Bibliometric Analysis of the 100 most-cited Research Articles

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Received:

09-Jun-2021;

Revision:

18-Jul-2021;

Accepted:

28-Jan-2022;

Published:

19-Apr-2022

ABSTRACT

Background and Aims: Preoperative long-course radio-chemotherapy (LC-RCHT) or preoperative short-course radiotherapy (SC-RT) are widely used in the treatment of locally advanced rectal cancer (LARC). This study aimed to evaluate the 100 most-cited research articles focused on preoperative radiotherapy for rectal cancer to reveal existing academic trends and the direction of therapeutic research. **Materials and Methods:** This was a retrospective study based on publicly accessible data. The Web of Science database was used to identify the 100 most-cited articles. **Results:** The median values for total citation and average citation per year (CPY) were 240.50 (range, 150–3787) and 17.32 (5.03–222.76), respectively. Randomized (median: 24.88 vs 13.32, $P = 0.001$) and funded (median: 27.33 vs 14.73, $P = 0.002$) studies had more CPY than those with opposite characteristics. No significant difference was found between studies using SC-RT and LC-RCHT, in terms of average CPY (median: 15.27 for SC-RT vs 18.36 for LC-RCHT, $P = 0.303$). In terms of the primary aim of the investigation, studies investigating non-operative treatment strategies had higher CPY than those investigating other subcategories ($p = 0.029$). **Conclusion:** Randomized studies, funded studies, and studies investigating non-operative treatment were associated with more CPY. There remains equal interest in preoperative SC-RT and LC-RCHT for rectal cancer.

KEYWORDS: *Bibliometric analysis, most cited articles, non-operative treatment, preoperative radiotherapy, rectal cancer*

INTRODUCTION

Rectal cancer represents approximately one-third of all colorectal cancers and most patients have locally advanced disease at diagnosis.^[1] During the last 30 years, significant improvements have been achieved in the treatment of locally advanced rectal cancer (LARC), with the implementation of total mesorectal excision (TME) and preoperative radio (chemo) therapy regimens. For LARC, multiple studies have shown improved local control and few of these studies have also reported improved survival, with the addition of preoperative radiotherapy to surgery.^[2-4]

Both short-course radiotherapy (SC-RT) and long-course radio-chemotherapy (LC-RCHT) can be used for preoperative treatment. In the preoperative treatment

of rectal cancer, short-course radiation is generally delivered in five fractions of 5 Gy to a total dose of 25 Gy over 1 week, followed by surgery 1 week later. On the other hand, in the long-course radiation approach, a total of 45–54 Gy of radiation in 25–30 fractions over 5–6 weeks is delivered concurrently with chemotherapy, followed by surgery 6–10 weeks later. While northern European and Scandinavian countries use SC-RT, the United States and some selected European countries prefer LC-RCHT in daily practice. Currently, preoperative LC-RCHT followed by TME and adjuvant

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How to cite this article: Türkkkan G, Alkan A. Preoperative radiotherapy for rectal cancer: A bibliometric analysis of the 100 most-cited research articles. *Niger J Clin Pract* 2022;25:448-53.

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|---|---|
| Quick Response Code: | Website: www.njcponline.com |
|  | DOI: 10.4103/njcp.njcp_1592_21 |

chemotherapy is recommended as the standard treatment for patients with LARC. Recently, the total neoadjuvant therapy and non-operative treatment strategy have been also gaining increasing attention in the treatment of LARC.

On the other hand, the number of bibliometric studies in medicine is increasing. They have an impact on medical research since they can provide important indicators for the development of scientific knowledge on a particular subject. This study aimed to reveal the existing academic trends and the direction of therapeutic research by evaluating the 100 most-cited research articles on preoperative radiotherapy for rectal cancers, using both bibliometric parameters and some clinical information of these studies.

MATERIAL AND METHODS

This study did not require ethics approval since it was based on publicly accessible data. The Web of Science database was used to identify eligible studies. The terms “radi*” and “chemo*” were used in set #1, to be able to cover all the terms such as radiotherapy, radiation therapy, radiation treatment, radio-chemotherapy, chemotherapy, chemoradiotherapy, chemoradiation, etc. The search strategy is shown in the table, in detail [Table 1].

The search time ranged from 1975 to December 20, 2020 and the articles shown were sorted by the times cited in the database. The first 100 articles were evaluated. Eight of them (seven articles: meta-analysis/review, one article: case reports) were excluded, the following eight most-cited research articles were included, and in this way, the 100 most-cited research articles were obtained. The studies were ranked based on average citation per year (CPY) to reduce the excess bias of the high total citation number in older studies due to the time factor. The average CPY counts were used on analyses.

Bibliometric parameters including title, journal, year of publication, authors, department of the first author, country of correspondence, and study design were extracted. Additionally, the studies were categorized into subgroups in terms of regions where the first author was working (USA, Europe, and others), the preoperative radiotherapy course used (studies involving patients treated with SC-RT, LC-RCHT, and both SC-RT and LC-RCHT), and the primary aim of the investigation (studies investigating preoperative radio (chemo) therapy efficiency, preoperative radio (chemo) therapy side effects, non-operative treatment strategy, prognostic/predictive parameters for preoperative radio (chemo) therapy, and effects of surgical technique).

All analyses were performed by using Statistical Package for the Social Sciences (SPSS) 24.0 for Windows. The variables were tested using visual (bar charts, boxplots) and analytic methods (Kolmogorov–Smirnov/Shapiro–Wilk’s tests) to determine whether or not they are normally distributed.

Descriptive analyses were done using frequencies for each bibliometric parameter extracted. The characteristics of the articles were described by using frequencies and proportions for dichotomous and categorical variables. As the CPY was not normally distributed, the Kruskal–Wallis and Mann–Whitney U tests were conducted to analyze the impact of factors on CPY. Values of *P* of less than 0.05 were considered to be statistically significant.

RESULTS

All studies had been published between 1984 and 2017, with the peak year of 2005 (nine studies). The list of the whole cohort sorted by total citation and average CPY counts is shown in Supplementary File 1.

For the whole cohort, the median values for total citation and average CPY were 240.50 (range, 150–3787) and 17.32 (5.03–222.76), respectively. Four studies had over 100 average CPY, of which the first three were published in the “New England Journal of Medicine.” In total, 22 journals contributed to the 100 most-cited studies and the journal publishing the largest number of studies was the “Journal of Clinical Oncology” (*n* = 27), followed by the “Lancet Oncology” (*n* = 12) and the “International Journal of Radiation Oncology, Biology, Physics” (*n* = 10). The list of the journals that published the 100 most-cited research articles is shown in the table [Table 2]. The most-cited study to date was the study by Sauer *et al.*^[5] with 3787 citations and cited at 222.76 average CPY.

The median number of authors was 10 (range, 2–28). A total of 75 first authors contributed to the 100 most-cited studies, Habr-Gama A (five studies) with the highest contribution. Gérard JP and Garcia-Aguilar J had four studies, and Rödel C, Marijnen CA, Bosset JF, and Guillem FG had three studies, as a first author. Most

Table 1: Search strategy in the Web of Science database and the obtained results as of December 20, 2020

| Set | Search strategy | Results |
|-----|--|---------|
| #1 | TI = ("radi*" OR "chemo*" OR "irradiation") | 1353077 |
| #2 | TI = ("neoadjuvant" OR "preoperative" OR "nonoperative" OR "wait-and-see" OR "watchful waiting") | 73276 |
| #3 | TI = ("rectal" OR "rectum") | 46945 |
| #4 | #1 AND #2 AND #3 | 5128 |

of the first authors were surgeons (47%), followed by radiation oncologists (33%), clinical oncologists (7%), and medical oncologists (4%). Additionally, three pathologists, three radiologists, two statisticians, and one nuclear medicine physician contributed as a first author. Besides, when all authors in the studies were analyzed regardless of author order, Glimelius BLG (12 studies) had the most paper in the 100 most-cited studies, followed by Pählman L (10 studies) and van de Velde CJH (eight studies).

In total, 28 different countries contributed to the 100 most-cited articles. The United States (25 studies) was the top contributor country, followed by Sweden (17 studies), France (15 studies), and the Netherlands (13 studies). However, when articles were analyzed in terms of country of correspondence, it was seen that the 100 most-cited studies were conducted in 20 different countries. The United States (24 studies) was the leading country, followed by Sweden (12 studies), France (12 studies), and the Netherlands (11

studies). The distribution of the 100 most-cited articles based on country of correspondence is shown in the figure [Figure 1].

Nearly half of the studies (49%) were randomized studies and most of the studies (64%) had no funding sources based on the results obtained from the Web of Science database. Randomized studies had more average CPY than non-randomized studies (median values:

Table 2: The journals in which the 100 most-cited preoperative radiotherapy research articles were published

| Journal | Number of articles (n) | Impact factor |
|--|------------------------|---------------|
| Journal of clinical oncology | 27 | 28.349 |
| Lancet oncology | 12 | 35.386 |
| International journal of radiation oncology biology physics | 10 | 6.203 |
| Diseases of the colon & rectum | 9 | 4.087 |
| Cancer | 8 | 6.102 |
| Annals of surgery | 7 | 9.476 |
| British journal of surgery | 4 | 5.572 |
| New England journal of medicine | 4 | 70.670 |
| Annals of surgical oncology | 3 | 3.681 |
| Radiology | 3 | 7.608 |
| Journal of gastrointestinal surgery | 2 | 2.686 |
| American journal of clinical oncology-Cancer clinical trials | 1 | 3.015 |
| Annals of oncology | 1 | 14.196 |
| Cancer research | 1 | 8.378 |
| European journal of cancer | 1 | 6.680 |
| European journal of surgery (currently incorporated in British journal of surgery) | 1 | 5.572 |
| Histopathology | 1 | 3.294 |
| International journal of colorectal disease | 1 | 2.641 |
| Journal of nuclear medicine | 1 | 7.308 |
| Journal of the American college of surgeons | 1 | 4.450 |
| Lancet | 1 | 59.102 |
| Radiotherapy and oncology | 1 | 5.252 |

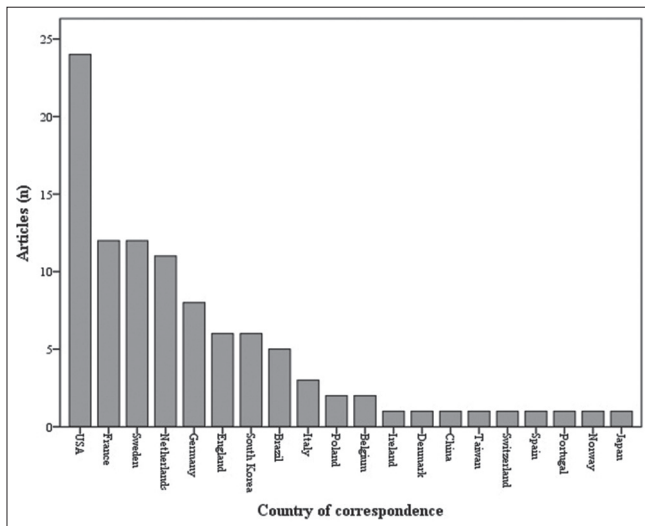


Figure 1: The distribution of the 100 most-cited articles based on country of correspondence

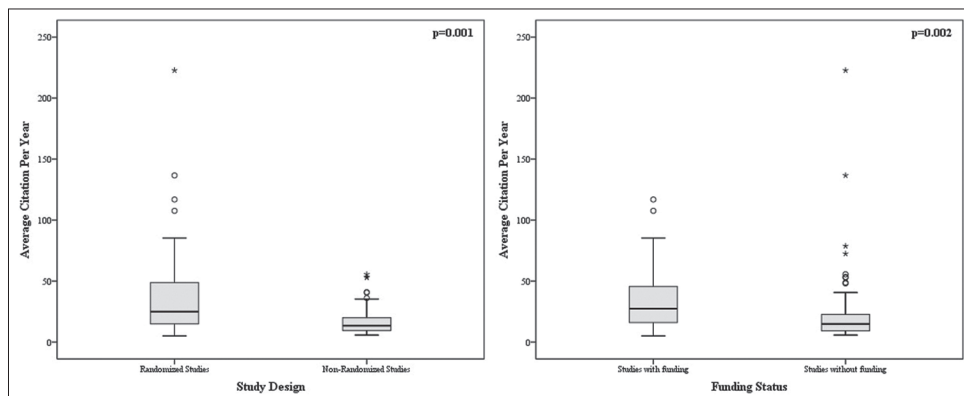


Figure 2: The boxplots of the average CPY of the articles, based on study design and funding status

24.88 vs 13.32, $P = 0.001$) and studies with funding had significantly more average CPY than studies without funding (median values: 27.33 vs 14.73, $P = 0.002$). The figure demonstrates the boxplots of the average CPY of the articles, based on study design and funding status [Figure 2].

The used preoperative radiotherapy courses among the 100 most-cited studies were as follows: LC-RCHT in 64 studies, SC-RT in 24 studies, and both LC-RCHT and SC-RT in 12 studies. Besides, when all studies were divided into two groups based on the publication date (2004) of the most-cited study, LC-RCHT was found to be much more used in studies published in 2005 and later, than the studies published in 2004 and earlier. (In 2004 or earlier: 19 SC-RT and 22 LC-RCHT studies vs in 2005 or later: five SC-RT and 42 LC-RCHT studies, $P = 0.001$). This relationship is shown in the figure which demonstrates the 100 most-cited articles categorized by the preoperative radiotherapy course used [Figure 3].

After categorizing all articles into subgroups as mentioned in the “Materials and Methods” section, studies with the first author from the United States were found to have less average CPY when compared to other groups (median values: 12.15 vs 19.20, $P = 0.003$).

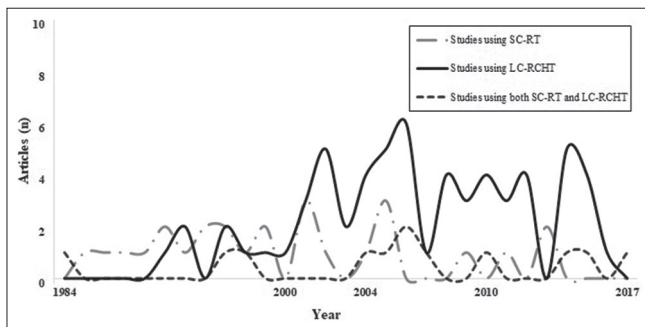


Figure 3: The 100 most-cited articles categorized by the preoperative radiotherapy course used

Additionally, after excluding studies involving patients treated with both SC-RT and LC-RCHT, there was no significant difference between studies using SC-RT and studies using LC-RCHT, in terms of average CPY (median values: 15.27 for SC-RT vs 18.36 for LC-RCHT, $P = 0.303$).

The primary aim of the investigation was to investigate the preoperative radio (chemo) therapy efficiency in 54 studies, prognostic/predictive parameters for preoperative radio (chemo) therapy in 28 studies, preoperative radio (chemo) therapy side effects in six studies, non-operative treatment strategy in six studies, and effects of surgical technique in six studies. Importantly, average CPY was significantly higher in the studies investigating non-operative treatment strategy than in the studies investigating the other four main subtopics (median values: 40.70 vs 16.42, $P = 0.023$). The figure demonstrates the boxplots of the average CPY of the articles, based on the primary aim of the investigation [Figure 4].

DISCUSSION

The primary purpose of this study was to describe the 100 potential game-changer research articles regarding preoperative radiotherapy for rectal cancers, based on citation count. All studies were also analyzed after being categorized into subgroups with regards to the regions where the first author was working, the preoperative radiotherapy course used, and the primary aim of the investigation. As far as is known, this is the first study identifying and analyzing the 100 most-cited research articles in the field of preoperative radiotherapy for rectal cancers.

Although there are some conflicting results, randomized studies and funded studies have been generally reported to receive higher citations in the literature. In a cohort

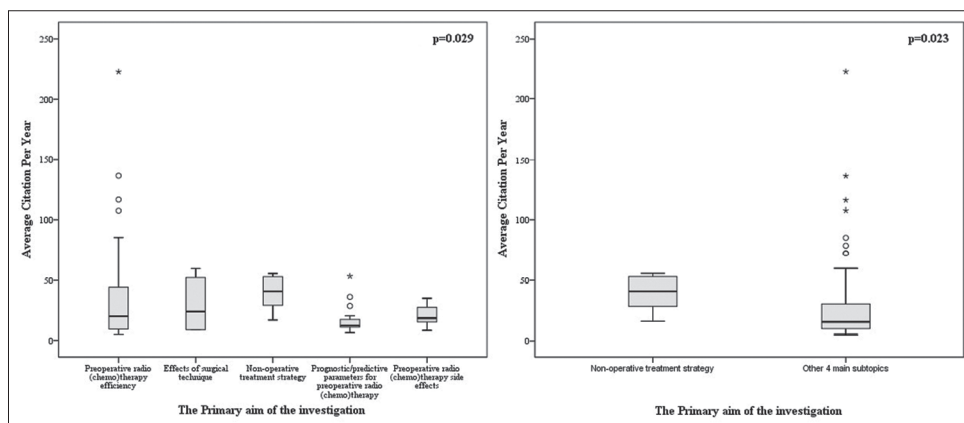


Figure 4: The boxplots of the average CPY of the articles, based on the primary aim of the investigation

study including original articles in the medical literature, regardless of study methodology, higher annual rates of citation were shown to be associated with the presence of funding and with articles dealing with oncology.^[6,7] Randomized studies were also reported to be able to lead to a higher citation rate.^[8] Consistent with these findings, our study found that funded studies and randomized studies had higher CPY than those with opposite characteristics.

The most-cited study to date was the study by Sauer *et al.*^[5] in which preoperative and postoperative RCHT were compared for the treatment of LARC. This landmark study showed improved local control and reduced toxicity with preoperative RCHT in comparison with postoperative RCHT and thus, substantially paved the way for the use of preoperative LC-RCHT instead of postoperative combination treatment. The present study's results were compatible with this historical change. It was observed that the highest number of articles among the 100 top-cited articles have been published in 2005, in other saying immediately after this top-cited landmark study. Additionally, LC-RCHT was found to be much more used in studies published in 2005 and later, when compared to those published in 2004 or earlier. It can be said that the use of LC-RCHT has gradually increased after 2004.

On the other hand, preoperative SC-RT has been used in the treatment of rectal cancer since the 1990s. Similar oncologic outcomes to preoperative LC-RCHT have been reported with the use of preoperative SC-RT in the treatment of rectal cancer.^[9] Although the number of articles using SC-RT was lower than those using LC-RCHT in this study, no significant difference was observed between studies using SC-RT and studies using LC-RCHT, in terms of CPY. These results were interpreted as that SC-RT is still an attractive and preferable preoperative radiotherapy option, although not used as much as LC-RCHT.

Ultimately, the total neoadjuvant therapy and non-operative treatment strategy have received increasing attention in the treatment of LARC. Two-phase III randomized trials investigated the role of the total neoadjuvant therapy for LARC. In experimental arms, the PRODIGE 23 trial^[10] assessed the role of neoadjuvant fluorouracil, leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX) before preoperative LC-RCHT followed by TME and adjuvant chemotherapy, while the RAPIDO trial^[11] investigated the role of preoperative SC-RT followed by capecitabine and oxaliplatin/folinic acid, fluorouracil, and oxaliplatin (CAPOX/FOLFOX) chemotherapy before TME. Both of these studies reported increased

pathological complete response rates and decreased disease-related treatment failure without overall survival advantage in experimental arms, compared to standard treatment arms. However, since these studies are very recent, they could not find a place among the 100 most-cited research articles for now, but they could be on this list in the future.

Increased complete response rates with the improvements in treatment modalities and also the better prognosis of patients with complete response led to the emergence of a non-operative treatment strategy for selected patients with LARC. The landmark study in this regard^[12] was originated in Brazil in 2004 and inspired many further studies.

In the present study, when the 100 most-cited research articles were categorized into five main subtopics based on the primary aim of the investigation, studies investigating non-operative treatment strategies seemed to have higher CPY when compared to the studies investigating the other four main subtopics. This result indicates that the non-operative treatment strategy attracts considerable attention in the treatment of LARC.

This study has some limitations. The 100 most-cited research articles were identified using only one database (the Web of Science database). Other databases may show partly different lists with different numbers of citations, due to coverage differences. Additionally, it is difficult to know if any other relevant articles were missed at screening, since the analysis was performed based on the list that the Web of Science database provided. Furthermore, missing more recent landmark studies that just have not had citations yet and the self-citation in articles are other limitations. However, it is not very possible to avoid these limitations when bibliometric parameters were used.

In conclusion, this study provides a unique historical perspective of the implementation of preoperative radiotherapy in rectal cancer, from its introduction to its current status. Besides characterizing the 100 most-cited research articles on preoperative radiotherapy for rectal cancers, this study showed that the randomized studies and funded studies were associated with more CPY. As can be understood from its high CPY number, there is a huge interest in non-operative treatment strategy. Regarding the management of LARC, there remains equal interest in both preoperative radiotherapy courses in the literature, since no significant difference was found between preoperative SC-RT and LC-RCHT studies, in terms of CPY.

Supplemental material

Supplemental material for this article is available online.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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