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**Bibliometric** **analysis** **of randomized controlled trials of colorectal cancer** **over the last decade**

Wang CY *et al*. Bibliometric analysis on RCTs of CRC

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**Abstract**

BACKGROUND

Colorectal cancer is one of the most common cancers globally. In China, its prevalence ranks fourth and fifth among females and males, respectively. Presently, treatment of rectal cancer follows a multidisciplinary comprehensive treatment approach involving surgery, radiotherapy, chemotherapy, and targeted therapy. With deepening theoretical and molecular research on colorectal cancer,randomized controlled trials (RCTs) on colorectal cancer have made significant progress. However, many RCTs have shortfalls.

AIM

To investigate the RCTs of global colorectal cancer spanning from 2008 to 2018. To provide suggestions for conducting Chinese RCTs of colorectal cancer.

METHODS

PubMed and Web of Science databases were searched to obtain RCTs of colorectal cancer carried out between January 1, 2008, and January 1, 2018. The bibliometric method was used for statistical analysis of the publication years, countries/regions, authors, institutions, source journals, quoted times, key words, and authors.

RESULTS

Colorectal cancer RCTs showed an upward trend between 2008 to 2018; the top 10 research institutions in the included literature were from the United States, the United Kingdom, and other countries with a high incidence of colorectal cancer. Most of the related research journals are sponsored by European and American countries. The 15 most cited studies involved international multicenter clinical research, having few participants from Chinese research institutions. Network visualization using key words showed that RCTs on colorectal cancer focus on screening, disease-free survival, drug treatment, surgical methods, clinical trials, quality of life, and prognosis. The result of the coauthorship network analysis showed that Chinese researchers are less involved in international exchanges compared to those from leading publication countries.

CONCLUSION

High-quality RCTs are increasingly favored by leading international journals. However, there is still a large gap in clinical research between China and leading countries. Researchers should implement standardized and accurate clinical trials, strengthen international multicenter cooperation, and emphasize quality control.

**Key words:** Colorectal cancer; Randomized controlled trial; Bibliometrics; China

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**Core tip:** Bibliometrics was used to quantitatively analyze 1555 articles from PubMed and Web of Science databases. We compared randomized controlled trials of colorectal cancer from China with those published in other countries. This is the first global analysis of this topic in which we analyzed the year of publication, countries/regions, institutions, journals, citations, key words, and authors. Suggestions on how to conduct clinical research were also given.

**INTRODUCTION**

In the past 10 years, advances in basic theoretical research on the pathogenesis and molecular mechanisms of colorectal cancer have promoted clinical research to a great extent. However, the incidence of colorectal cancer has continued to increase annually[1]. In China, colorectal cancer is the fifth most prevalent malignant tumor[2]. The current prevention, screening, diagnosis, and treatment approaches for colorectal cancer are not effective. So far, the international clinical guidelines such as the National Comprehensive Cancer Network and the European Society for Medical Oncology have not included clinical studies from China. Currently, there is increasing research interest among Chinese clinicians to conduct randomized controlled trials (RCTs), but findings from such studies have not provided clear research directions. The systematic methodological knowledge is still lacking, especially for important aspects. Several factors, such as rigorous ethical review, scientific design, research personnel, and financial and time costs, make it difficult to obtain high-quality research results. Therefore, to evaluate the research status of colorectal cancer in China and abroad, this paper used bibliometric analysis to analyze previous RCTs to provide reference data for the design, cooperation, and implementation of colorectal cancer RCTs in China.

**MATERIALS AND METHODS**

***Eligibility criteria***

Inclusion criteria: Colorectal cancer RCT study, time range from January 1, 2008 to January 1, 2018. Exclusion criteria: Repetition, excerpt, conference papers, monographs, retraction, errata, *etc*.

***Search***

The computer retrieved articles from PubMed and Web of Science databases from January 1, 2008, to January 1, 2018. The search terms were colorectal, rectal, rectum, colonic, colon, neoplasm, cancer, tumor, adenocarcinoma, randomized controlled trial, *etc*.

***Data extraction***

The publications were independently screened and extracted by two investigators. The extracted information included the publication year, country/region, authors, institutions, source journal, quoted time, and key words. Disagreements were resolved through consultation with a third researcher.

***Data analysis***

Descriptive statistical analysis was done using Microsoft Excel 2013 software; descriptive analysis included organizational distribution, journal distribution, and citation of published literature. Visual analysis was done using VOSviewer 1.6.4 software and mapped key word co-occurrences and coauthors relationship network diagram.

**RESULTS**

***Research screening process and results***

A total of 3146 articles were identified in Pubmed and 4539 articles in the Web of science, and 1029 duplicate articles among these were excluded. We read basic information such as texts and abstracts and excluded 17 informal publications and 324 articles unrelated to colorectal cancer. The types comprised of 185 articles including news, conference abstracts, monographs, excerpts, retractions, and errata, and 4575 non-RCTs. This led to the inclusion of 1555 articles. The literature screening process and results are shown in Figure 1.

***Chronological distribution***

There was a gradual increase in the number of publications on colorectal cancer RCT studies between 2008 and 2018 (Figure 2).

***Countries/regions distribution and institutional distribution***

The top 10 countries that published relevant literature and their numbers are shown in Figure 3. The top 10 research institutions that published relevant literature are listed in Table 1.

***Journal distribution and cited situation***

The journals were sorted according to the number of RCTs. Most of the journals were concentrated on the fields of cancer, immunology, gastrointestinal surgery, *etc*. The journals that contained more RCT literature usually has a higher impact factor; high-quality journals were more interested in high-level clinical research such as RCT. The top 20 journals according to the publication volume are shown in Table 2. The three most relevant publications are from the top comprehensive journal of clinical medicine: *Lancet*. Others are from authoritative journals in various clinical fields. Higher-level clinical research from authoritative journals had higher recognition. The top 15 literature by citation are shown in Table 3[3-12].

***Key word co-occurrence and coauthored network***

VOSviewer software was used to draw key word co-occurrence map. It can be observed that age, surgery, drug therapy, targeted therapy, neoadjuvant, pathology, comparative study, treatment outcome, disease-free survival, quality of life, and other key words appeared frequently (Figure 4).

The diagram was drawn according to the coauthor relationship (Figure 5). The colors in the figure indicate the authors’ research areas. Each node represents a researcher and the node size represents the number of documents. The connection between the nodes represents a cohesive relationship between the studies. A thicker line indicates a larger number of coauthors between the two studies.

**DISCUSSION**

Early diagnosis of colorectal cancer has significantly improved with better diagnosis and treatment. Innovation and development of minimally invasive technology and the reform concept of diagnosis and treatment has lowered local recurrence after surgery to 5%. Medical workers in the field of colorectal cancer in China have achieved remarkable results in the past decade[13]. However, due to the large population in China, there are nearly 400000 new patients and 200000 deaths every year; the situation is still grim[14]. China’s clinical research started late, and there was lack of experience and attention to the important research aspects. There is still a big gap between China and other countries such as Japan, South Korea, Europe, and the United States[15,16].

Current clinical RCT research hotspots include the [debate](javascript:;) between laparoscopic and open surgery, the advantages and disadvantages of the “Wait and See” strategy during pathological complete remission after neoadjuvant chemoradiotherapy, 3 or 6 mo for adjuvant chemotherapy, the feasibility of the transanal total mesorectal excision, and the best chemotherapy sequence of neoadjuvant chemotherapy for advanced rectal cancer[17-20]. These research hotspots are based abroad with Chinese researchers and institutions seldom participating. However, domestic clinicians are gradually and actively carrying out evidence-based clinical research.

Chinese clinicians have a wealth of medical information, and multicenter RCTs can utilize it to get high-quality clinical data. For example, the ‘Radical Extent of lymphadenectomy of Laparoscopic Right Colectomy for colon cancer’ study on the scope of laparoscopic right colon cancer lymphatic dissection led by Peking Union Concord Hospital was carried out in strict accordance with the implementation standards. The study conducted multiple rounds of argumentation and consideration for the surgical risks and benefits of complete mesocolic excision. Another study, ‘The randomized Neoadjuvant FOLFOX6 Chemotherapy with or without Radiation in Rectal cancer,’ led by the Sixth Affiliated Hospital of Sun Yat-sen University selected patients with stage II-III rectal cancer and discussed the necessity of receiving oxaliplatin after receiving neoadjuvant therapy. It demonstrated that FOLFOX plus radiotherapy had the best effect, but pure FOLFOX could achieve similar downregulation effects with fewer complications. Although long-term survival is still being followed, the preliminary results have already inspired researchers at home and abroad[21].

Through statistical literature analysis, the top 10 research institutions by publications were found to be in the United States, the United Kingdom, and Canada with China not on the list. Sun Yat-sen University is ranked 20th in colorectal cancer clinical research in China. *Lancet* and its subdistribution produced 7 of the 15 most cited papers. The articles focused on colonoscopy for colorectal cancer, surgical treatment of metastatic colorectal cancer, surgical procedures, open and laparoscopic surgery, first-line chemotherapy, second-line chemotherapy, targeted therapy, and the safety and efficacy of panitumumab, bevacizumab, and cetuximab. Key co-occurrence map words included age, surgery, drug therapy, targeted therapy, neoadjuvant, pathology, comparative study, treatment outcome, disease-free survival, quality of life, *etc*. Presently, research hotspots focus on colorectal cancer screening, diagnosis and treatment, surgical methods, choice of drug treatment, and evaluation of treatment outcomes and quality of life.

A co-occurrence map of coauthors showed that most researchers active in international multicenter research were from Europe, the United States, Japan, and South Korea. These coauthorships are relatively close and extensive, and researchers from Asian countries such as Japan and South Korea are less coauthored with European and United States scholars.

In the clinical research on colorectal cancer, authors such as Van Custsem, Cunningham, Rivera, Kim, and Morriya produced the largest number of publications, and there were close relationships among them. they are therefore the key leaders in this field. The Chinese rank first in the number of published literature related to colorectal cancer, but third in RCT studies with fewer multicenter RCTs. The reason may be that the cost of RCT is high, the research team is immature, the research design ideas and research endpoints are unreasonable, and data collection is irregular[22]. Key links in the implementation process are also complex, and the research team needs to address a series of questions such as medical ethics review and good clinical practice. The development of multicenter high-quality RCT research requires a sufficient amount of funding and government agency support. Researchers need to unite, forge ahead, persevere sincerely, and promote exchanges between research institutions that play an important role. Therefore, domestic researchers should pay attention to the various key aspects of RCT research, truth-seeking, pragmatism, and standardize all aspects of clinical RCT research to maintain high accuracy and credibility.

This study has some limitations. Only PubMed and Web of Science databases were searched. There were documents in other languages included in the database, and there may be publication bias. The quality of the literature was not evaluated by the methodological quality evaluation tool.

In summary, the results of bibliometric analysis of colorectal cancer-related RCTs in the past decade, in China and abroad, showed that high-quality RCTs were increasingly favored by top international journals. Although China’s clinical research has achieved positive initial results, there are still large gaps when compared to Europe and the United States. Domestic researchers should implement standardized and accurate clinical trials, strengthen multicenter cooperation at home and abroad, and implement high quality colorectal cancer-related RCT clinical research to promote the field in China.

**ARTICLE HIGHLIGHTS**

***Research background***

In the past decade, clinical research on colorectal cancer has made significant progress with deepening theoretical and molecular research on its pathogenesis. However, many randomized controlled trials (RCTs) have shortfalls, such as lacking systematic methodological knowledge, insufficient sample size, *etc*.

***Research motivation***

Clinical colorectal cancer research in China has progressed, but the quality of RCTs is still low. Therefore, we compared the RCTs in China with those of other countries to identify deficiencies and improve Chinese research.

***Research objectives***

We used bibliometric analysis to evaluate the research status of colorectal cancer RCTs in China and abroad and provide references for the design, cooperation, and implementation of colorectal cancer RCTs in China.

***Research methods***

We retrieved the RCTs studies related to colorectal cancer published between 2008 and 2018 in PubMed and the Web of Science. The literature was independently screened and extracted by two investigators. The bibliometric methods were used for statistical analysis of the publication years, countries/regions, authors, institutions, source journal, quoted times, key words, and authors. We used Microsoft Excel 2013 and VOSviewer 1.6.4 software to analyze the data.

***Research results***

Colorectal cancer RCTs have shown an upward trend from 2008 to 2018. Most of the top 10 research institutions were from the United States and the United Kingdom, and most of the related research journals were sponsored by European and American countries. The 15 most cited studies were comprised of international multicenter clinical research, with few participants from Chinese institutions. Network visualization using key words showed that RCTs on colorectal cancer focused on screening, disease-free survival, drug treatment, surgical methods, clinical trials, quality of life, and prognosis. The results of the coauthorship network analysis showed that Chinese researchers are less involved in international exchanges.

***Research conclusions***

High-quality RCTs are increasingly favored by top international journals. There is a large gap between Chinese and international clinical research; researchers should gradually standardize clinical trials, ensure accuracy, strengthen international multicenter cooperation, and emphasize quality control.

***Research perspectives***

There is a large gap between Chinese and international clinical research according to our bibliometric analysis. Chinese researchers should gradually standardize clinical trials, ensure accuracy, strengthen international multicenter cooperation, and emphasize quality control.

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**Footnotes**

**Conflict-of-interest statement:** The authors declare no conflict of interest.

**PRISMA 2009 Checklist statement:** The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised in accordance with this checklist.

**Data sharing statement:** No additional data are available.

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**Peer-review report’s scientific quality classification**

Grade A (Excellent): 0

Grade B (Very good): 0

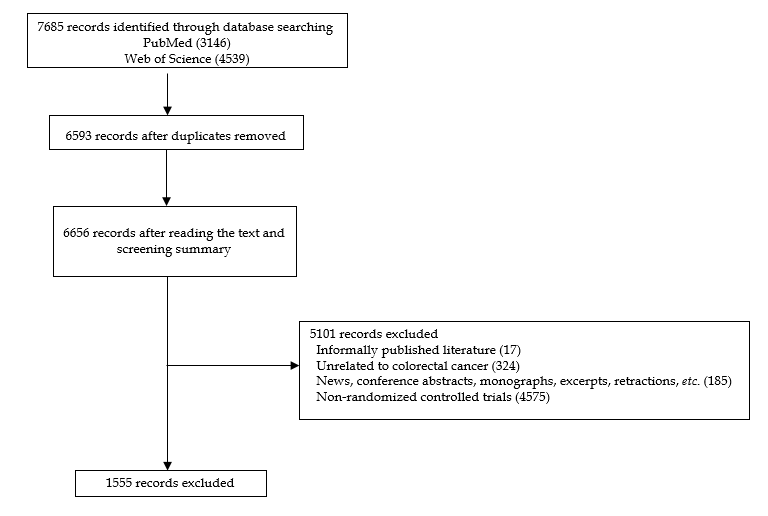
Grade C (Good): C, C

Grade D (Fair): 0

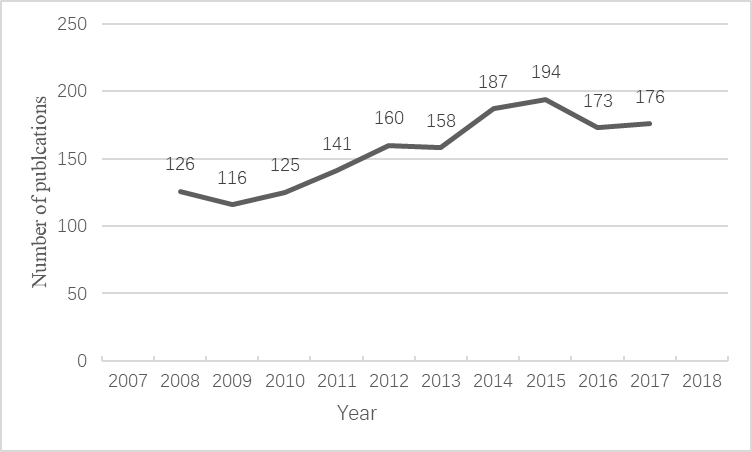
Grade E (Poor): 0

**P-Reviewer:** Mohamed SY, Vynios D **S-Editor:** Gong ZM **L-Editor:** Filipodia **E-Editor:** Liu JH

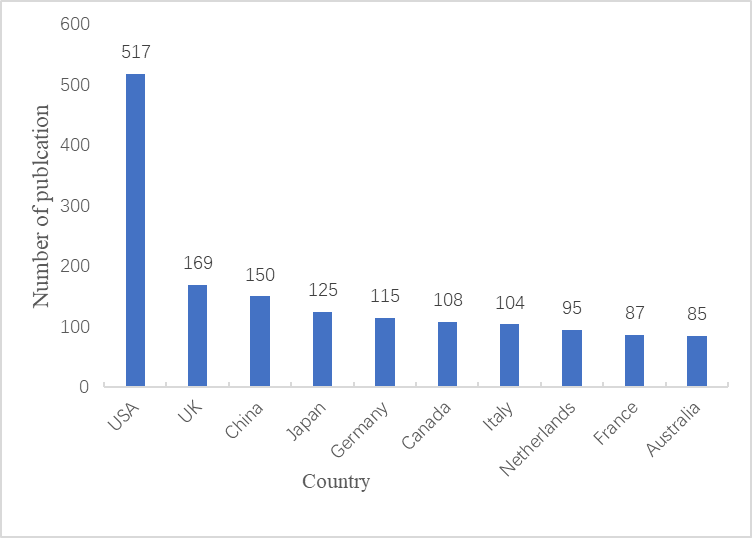
**Figure Legends**



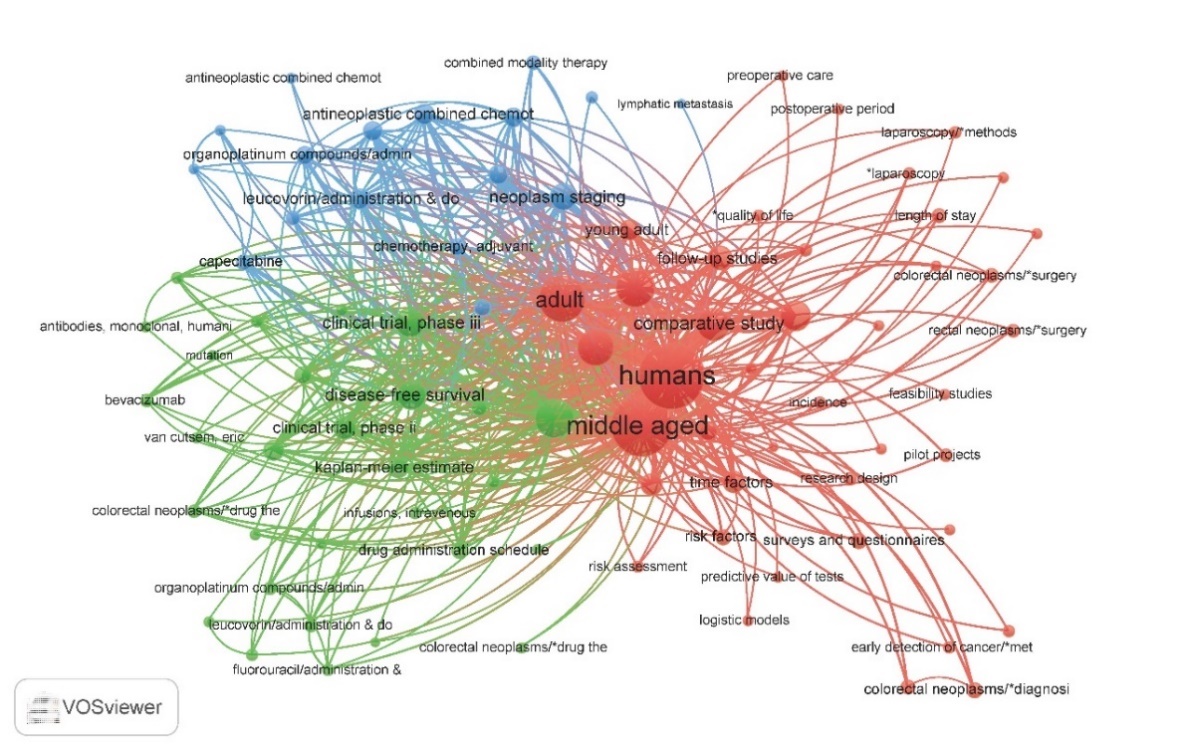
**Figure 1 Results of the literature search.**



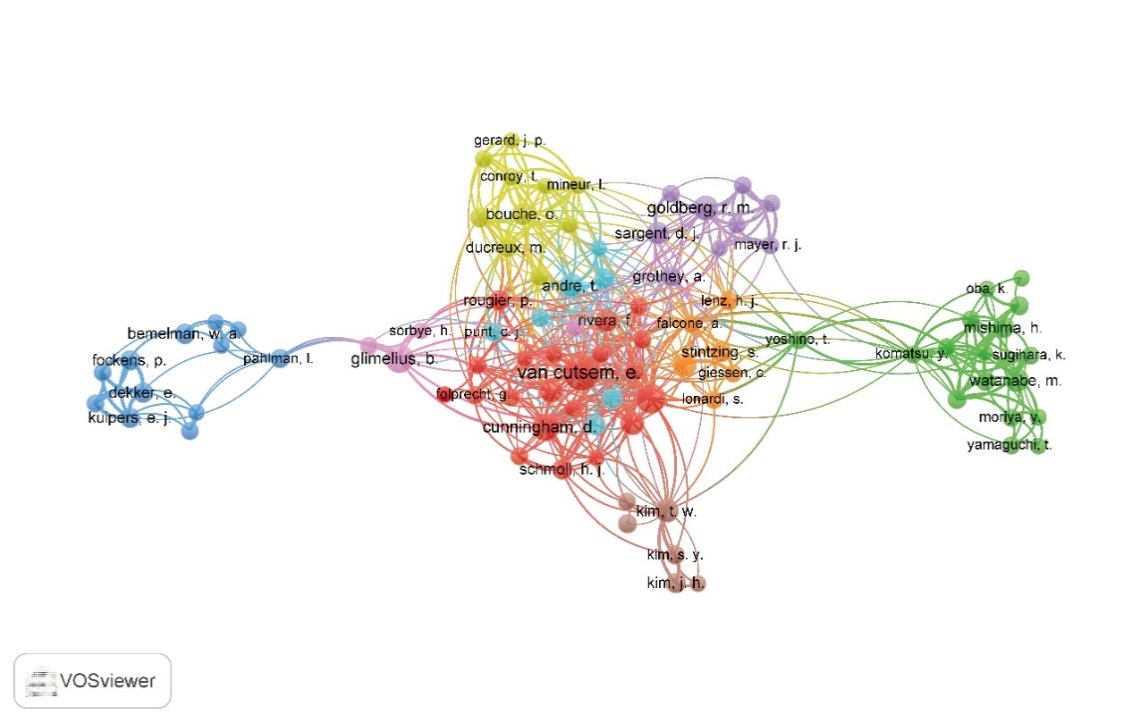
**Figure 2 Chronological distribution**.



**Figure 3 Countries/regions distribution.**



**Figure 4 Network visualization using key words.**



**Figure 5 Network visualization using researcher and coauthor.**

**Table 1 The top 10 research institutions by publication**

|  |  |  |
| --- | --- | --- |
| **Institution** | **Country** | **Number** |
| Harvard University | United States | 52 |
| University of California | United States | 51 |
| University of Texas | United States | 41 |
| University of London | United Kingdom | 40 |
| University of Toronto | Canada | 33 |
| Boston Healthcare system | United States | 30 |
| NIH National Institute of Health | United States | 29 |
| University College London | United Kingdom | 25 |
| National Cancer Institute NCI | United States | 24 |
| Mayo Clinic | United States | 24 |

**Table 2 Top 20 journals by publication**

|  |  |  |  |
| --- | --- | --- | --- |
| **Journal** | **Number** | **IF 2017** | **Country** |
| *Journal of clinical oncology* | 84 | 26.3 | United States |
| *Annals of oncology* | 69 | 13.93 | United Kingdom |
| *BMC Cancer* | 55 | 3.29 | United Kingdom |
| *The Lancet Oncology* | 49 | 36.42 | United States |
| *Trials* | 42 | 2.07 | United Kingdom |
| *European Journal of cancer* | 38 | 7.19 | United Kingdom |
| *British Journal of Surgery* | 36 | 5.43 | United Kingdom |
| *International Journal of colorectal disease* | 32 | 2.53 | Germany |
| *British journal of cancer* | 32 | 5.92 | United Kingdom |
| *Annals of surgery* | 32 | 9.2 | United States |
| *Diseases of the colon and rectum* | 28 | 3.62 | United States |
| *Colorectal Disease* | 28 | 2.78 | United Kingdom |
| *Cancer* | 26 | 6.54 | United States |
| *Chinese Journal of Gastrointestinal Surgery* | 23 |  | China |
| *Surgical endoscopy* | 23 | 3.12 | United States |
| *Clin Colorectal Cancer* | 21 | 3.86 | United States |
| *Lancet* | 17 | 53.25 | United Kingdom |
| *Cancer epidemiology* | 17 | 2.89 | United Kingdom |
| *Gut* | 15 | 17.02 | United Kingdom |
| *BMJ Open* | 15 | 2.41 | United Kingdom |

IF: Impact factor.

**Table 3 Top 10 cited colorectal cancer randomized controlled trial-related literature in the domestic and international publications in 2008-2018**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Ref.** | **Title** | **Journal** | **Cited** | **Year** |
| Nordlinger *et al*[3] | Perioperative chemotherapy with FOLFOX4 and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC Intergroup trial 40983): a randomized controlled trial | *Lancet* | 1104 | 2008 |
| Atkin *et al*[4] | Once-only flexible sigmoidoscopy screening in prevention of colorectal cancer: a multicentre randomised controlled trial | *Lancet* | 961 | 2010 |
| Grothey *et al*[5] | Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial | *Lancet* | 935 | 2013 |
| Tol *et al*[6] | Chemotherapy, Bevacizumab, and Cetuximab in Metastatic Colorectal Cancer | *New England Journal of Medicine* | 904 | 2009 |
| Baxter *et al*[7] | Association of Colonoscopy and Death From Colorectal Cancer | *Annals of Internal Medicine* | 835 | 2009 |
| Hecht *et al*[8] | A Randomized Phase IIIB Trial of Chemotherapy, Bevacizumab, and Panitumumab Compared With Chemotherapy and Bevacizumab Alone for Metastatic Colorectal Cancer | *Journal of Clinical Oncology* | 596 | 2009 |
| Maughan *et al*[9] | Addition of cetuximab to oxaliplatin-based first-line combination chemotherapy for treatment of advanced colorectal cancer: results of the randomised phase 3 MRC COIN trial | *Lancet* | 574 | 2011 |
| Peeters *et al*[10] | Randomized Phase III Study of Panitumumab With Fluorouracil, Leucovorin, and Irinotecan (FOLFIRI) Compared With FOLFIRI Alone As Second-Line Treatment in Patients With Metastatic Colorectal Cancer | *Journal of Clinical Oncology* | 549 | 2010 |
| Folprecht *et al*[11] | Tumour response and secondary resectability of colorectal liver metastases following neoadjuvant chemotherapy with cetuximab: the CELIM randomised phase 2 trial | *Lancet Oncology* | 523 | 2010 |
| Verwaal *et al*[12] | 8-year follow-up of randomized trial: Cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy in patients with peritoneal carcinomatosis of colorectal cancer | *Annals of Surgical Oncology* | 448 | 2008 |