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Treatment in locally advanced rectal cancer: a machine learning bibliometric analysis

Francesca De Felice, Daniele Crocetti, Niccolò Petrucciani, Liliana Belgioia, Paolo Sapienza, Nadia Bulzonetti, Francesco Marampon, Daniela Musio and Vincenzo Tombolini

Abstract: A bibliometric analysis was performed using a machine learning bibliometric methodology in order to evaluate the research trends in locally advanced rectal cancer treatment between 2000 and 2020. Information regarding publication outputs, countries, institutions, journals, keywords, funding, and citation counts was retrieved from Scopus database. During the search process, a total of 2370 publications were identified. The vast majority of papers originated from the United States of America, reflecting also its research drive in the collaboration network. Neoadjuvant treatment was the topic most studied in the highly cited studies. New keywords, including neoadjuvant chemotherapy, multiparametric magnetic resonance imaging, circulating tumor DNA, and genetic heterogeneity, appeared in the last 2 years. The quantity of publications on locally advanced rectal cancer treatment since 2000 showed an evolving research field. The 'new' keywords explain where research is presently heading.

Keywords: bibliometric analysis, chemotherapy, machine learning, radiotherapy, rectal cancer, surgery

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Correspondence to:
Francesca De Felice
Department of Radiotherapy, Policlinico Umberto I, Sapienza University of Rome, Viale Regina Elena 326, 00161 Rome, Italy.
fradefelice@hotmail.it

Daniele Crocetti
Paolo Sapienza
Department of Surgery 'Pietro Valdoni', Policlinico Umberto I, Sapienza University of Rome, Rome, Italy

Niccolò Petrucciani
General Surgery Unit, Department of Medical and Surgical Sciences and Translational Medicine, St. Andrea University Hospital, Sapienza University of Rome, Rome, Italy

Liliana Belgioia
Radiation Oncology Department, IRCCS Ospedale Policlinico San Martino, University of Genoa, Genova, Italy

Nadia Bulzonetti
Francesco Marampon
Daniela Musio
Vincenzo Tombolini
Department of Radiotherapy, Policlinico Umberto I, Sapienza University of Rome, Rome, Italy

Introduction

Rectal cancer is one of the most frequently diagnosed cancers in both sexes worldwide.[1]

Depending on the stage of disease at diagnosis, a variable percentage of patients experience treatment failure within 5 years.[2] Although locally advanced rectal cancer (LARC) patients currently benefit from trimodality approach, the prognosis of these patients remains quite unfavorable, with a high risk (approximately 40%) of developing distant metastasis.[3]

At present, total neoadjuvant therapy or chemotherapy block after surgery represents effective therapeutic strategies for LARC treatment, but actually the optimal temporal sequencing of treatment modalities, as well as the optimal drug schemes, remains a hot topic in the field of gastrointestinal oncology.[2] In this scenario, a bibliometric analysis of the current LARC landscape can be helpful to clarify clinicians' understanding of the large and growing body of evidence on the topic. Bibliometric analysis is a statistical evaluation of scientific publications and represents an effective method to measure and quantitatively describe their influence in clinical practice over time.[4]

Here, we presented a bibliometric analysis of the publications on LARC in the past 20 years. The aim is to identify the trends of present studies and provide some directions for future research.

Methods and materials

The search was conducted on the Scopus database. To retrieve studies on LARC, the following search terms were used: 'locally' AND 'advanced'

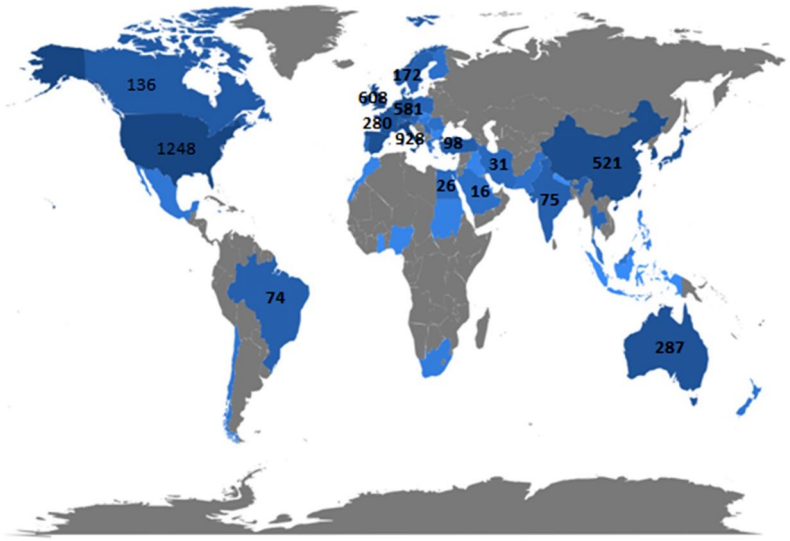

Figure 1. Country-specific production.

AND 'rectal cancer or rectal neoplasms' AND 'treatment or therapy or therapeutics'. A dataset to include English language manuscripts published between 1 January 2000 and 31 March 2020 was generated. The dataset included a comma-separate values (CSV) file with metadata of all the articles, such as author(s), document title, year, source title, volume, issue, pages, citation count, document type, affiliations, editor(s), keywords, and sponsor.

Statistical analysis was carried out using RStudio Version 1.0.143 – © 2009-2016 RStudio, Inc. A machine learning bibliometric methodology was applied to evaluate the distribution of each factor. The bibliometrix R package was used (https://www.bibliometrix.org/). Global collaboration maps were performed using 'Biblioshiny ()' function.

Results

In total, 2370 documents matched the choice criteria across 6 document types. The 6 document types were article ($n=1980$), review ($n=297$), conference paper ($n=34$), letter ($n=30$), editorial ($n=17$), and short survey ($n=12$). The annual publication numbers grew slowly in the first 10 years analyzed, from 28 (in the 2000s) to 75 (in the 2009s). In the last 9 years (2010–2019), the annual publication number has increased rapidly, rising from 88 documents in 2010 to 230 documents in 2019.

Country-specific production and collaboration

Publications on LARC treatment between 2000 and 2020 came from 59 countries worldwide (Figure 1). The most productive country in the LARC research field was the United States of America, with a publication share of 52.7% ($n=1248$). Italy ranked second ($n=928$, 39.2%), followed by South Korea ($n=700$, 29.5%), the United Kingdom ($n=608$, 25.7), Germany ($n=581$, 24.5%), and China ($n=521$, 22%). The remaining top 20 most productive countries were mostly in Europe. Figure 2 displayed country collaborations. The network diagram – each node represented a country, node size corresponded to publications number, connecting lines represented countries cooperation, and line thickness indicated collaboration frequencies – showed that the United States of America was the leader of LARC research in cooperation with the other countries. Asian territories such as Japan, India, and Taiwan had slighter collaboration networks than European and North American countries.

Documents by affiliation

The distribution of institute contributions to publications reiterated the predominance of the United States of America in the LARC research field. The most productive institution was the Memorial Sloan Kettering Cancer Center, accounting for 3.5% ($n=82$) of the entire documents on this topic. The University of Texas MD Anderson Cancer Center was second in productivity with a total of 59 publications. Whereas the National Cancer Center (Gyeonggi) and the Catholic University of the Sacred Heart (Rome) ranked third and fourth, with 48 and 43 documents, respectively.

Journals

The 2370 articles were published in 401 journals, with 189 journals publishing only one article. The 'International Journal of Radiation Oncology Biology Physics' is at the top of the list with a total number of 119 publications, followed by the 'Diseases of the Colon and Rectum' journal ($n=81$) and the 'Colorectal Disease' journal ($n=65$). A graph was also used to show the trend in the publications of these top three productive journals (see Figure 3). Starting the year 2000, there were quite a few articles published in these journals and they progressively increased since 2010. Interestingly, the annual number of articles

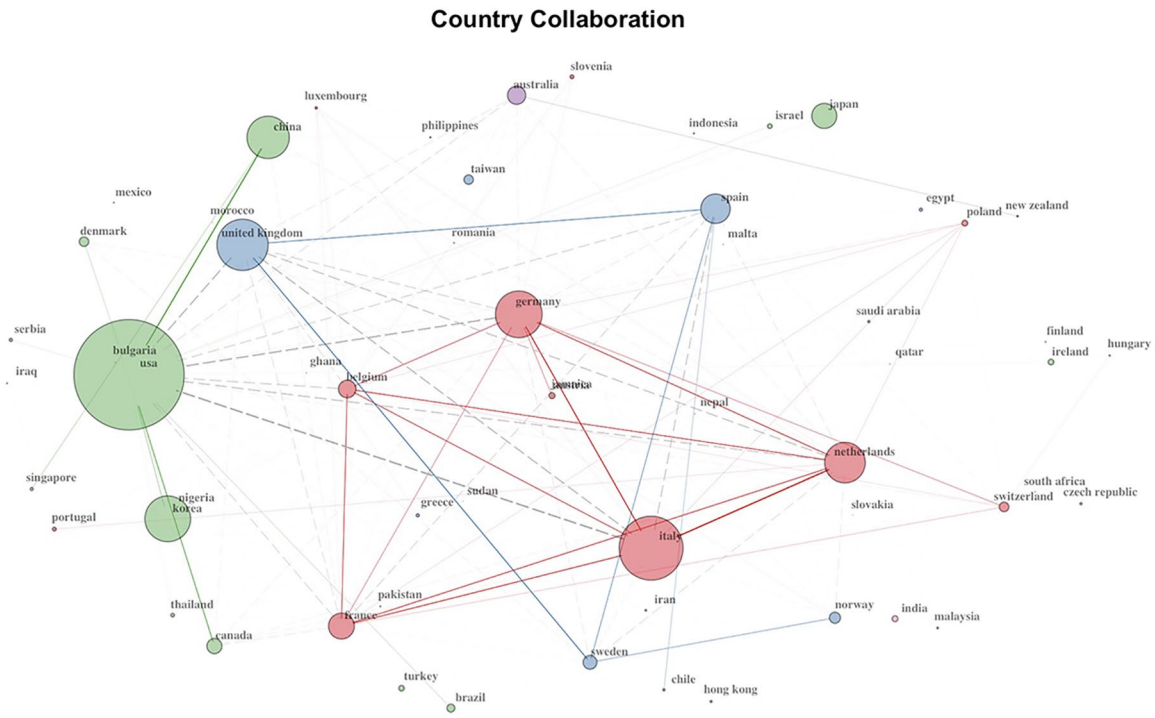

Figure 2. Country collaboration.

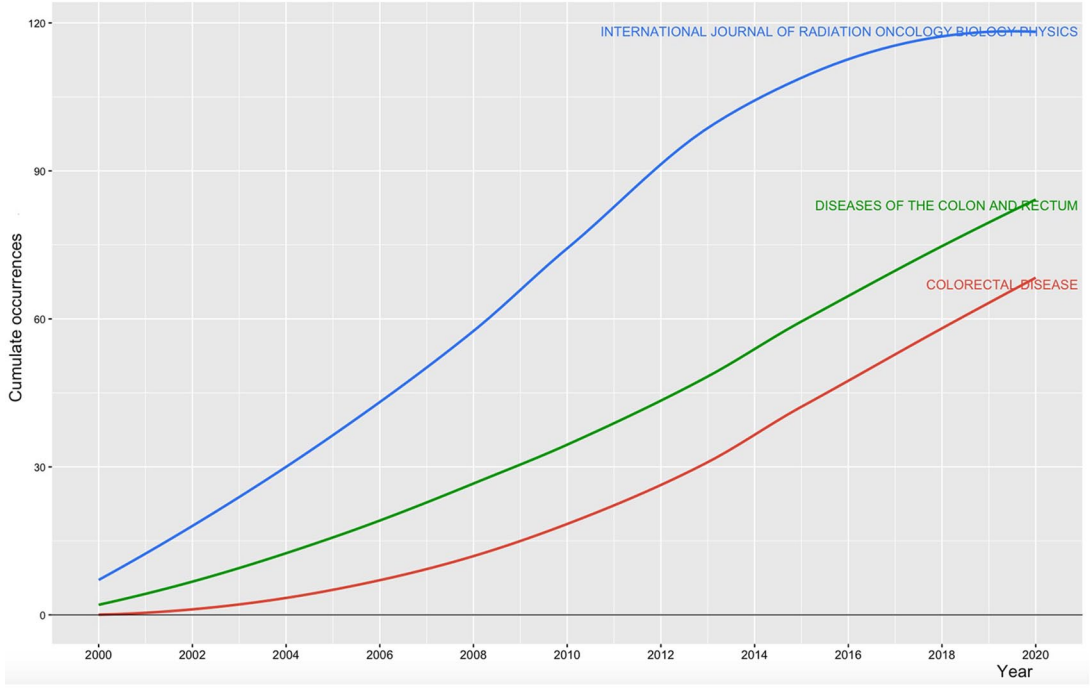

Figure 3. Publications by year of the top three productive journals.

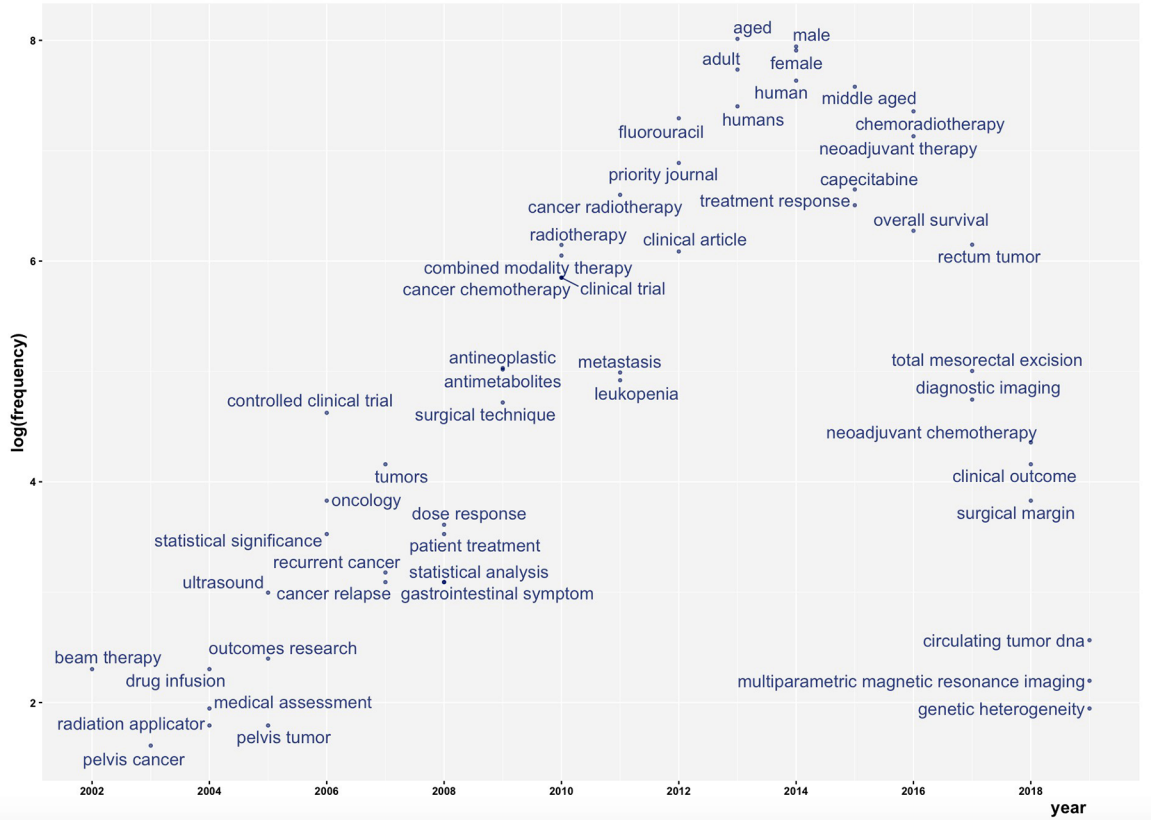

Figure 4. Keywords trend topic.

in *International Journal of Radiation Oncology Biology Physics* has increased rapidly over a 20-year period.

Keywords

Apart from the most used searching keywords 'rectal cancer/neoplasm' (3292 occurrences), 'aged' (3021 occurrences), adult (2287 occurrences), and 'treatment outcomes' (1598 occurrences), the other keywords that frequently appeared at the same time are illustrated in Figure 4. New keywords, such as neoadjuvant chemotherapy, multiparametric magnetic resonance imaging, circulating tumor DNA, and genetic heterogeneity, appear to become areas of research interest in the last 2 years.

Citation counts

Table 1 lists the 20 most cited papers. The number of citations ranged from 3885 for Sauer and colleagues[5] – 'Preoperative versus postoperative chemoradiotherapy for rectal cancer' – to 270 for Ghadimi and colleagues[24] – 'Effectiveness of gene expression profiling for response prediction of rectal adenocarcinomas to preoperative chemoradiotherapy' –. The most recent manuscript was published by the German Rectal Cancer Study Group in 2015 and looked at the addition of oxaliplatin to fluorouracil-based neoadjuvant chemoradiotherapy and adjuvant chemotherapy in the treatment of LARC.[22] The *Journal of Clinical Oncology* had the most citations ($n=8$ and 3808 citations). Overall, the neoadjuvant treatment of LARC was the topic most widely studied ($n=11$).[5–12,18,20,22] Two manuscripts looked at the surgical approach.[14,15] Four papers studied the prognostic basis of clinicopathological factor and three studies analyzed the predictive features on magnetic resonance images.[13,16,17,19,21,23,24] Seven papers were consensus statements of guidelines.[6,8–11,14,15]

Funding sponsor

The top 10 most productive funding agencies for LARC research are depicted in Figure 5. The National Natural Science Foundation of China

Table 1. Most cited papers.

Title	Authors	Year	Journal	Citations (n)
Preoperative versus postoperative chemoradiotherapy for rectal cancer[5]	Sauer and colleagues	2004	*New England Journal of Medicine*	3885
Preoperative versus postoperative chemoradiotherapy for locally advanced rectal cancer: Results of the German CAO/ARO/AIO-94 randomized phase III trial after a median follow-up of 11 years[6]	Sauer and colleagues	2012	*Journal of Clinical Oncology*	932
Long-term outcome in patients with a pathological complete response after chemoradiation for rectal cancer: A pooled analysis of individual patient data[7]	Maas and colleagues	2010	*The Lancet Oncology*	862
Preoperative multimodality therapy improves disease-free survival in patients with carcinoma of the rectum: NSABP R-03[8]	Roh and colleagues	2009	*Journal of Clinical Oncology*	582
Comparison of two neoadjuvant chemoradiotherapy regimens for locally advanced rectal cancer: Results of the phase III trial accord 12/0405-Prodige 2[9]	Gérard and colleagues	2010	*Journal of Clinical Oncology*	544
Primary tumor response to preoperative chemoradiation with or without oxaliplatin in locally advanced rectal cancer: Pathologic results of the STAR-01 randomized phase III trial[10]	Aschele and colleagues	2011	*Journal of Clinical Oncology*	484
Preoperative chemoradiotherapy and postoperative chemotherapy with fluorouracil and oxaliplatin versus fluorouracil alone in locally advanced rectal cancer: Initial results of the German CAO/ARO/AIO-04 randomised phase 3 trial[11]	Rödel and colleagues	2012	*The Lancet Oncology*	406
Efficacy, safety, and biomarkers of neoadjuvant bevacizumab, radiation therapy, and fluorouracil in rectal cancer: A multidisciplinary phase II study[12]	Willet and colleagues	2009	*Journal of Clinical Oncology*	396
Diffusion MRI for prediction of response of rectal cancer to chemoradiation[13]	Dzik-Jurasz and colleagues	2002	*Lancet*	367
Open versus laparoscopic surgery for mid-rectal or low-rectal cancer after neoadjuvant chemoradiotherapy (COREAN trial): Survival outcomes of an open-label, non-inferiority, randomised controlled trial[14]	Jeong and colleagues	2014	*The Lancet Oncology*	336
Laparoscopic total mesorectal excision (TME) for rectal cancer surgery: Long-term outcomes[15]	Leroy and colleagues	2004	*Surgical Endoscopy and Other Interventional Techniques*	322
Magnetic resonance imaging-detected tumor response for locally advanced rectal cancer predicts survival outcomes: MERCURY experience[16]	Patel and colleagues	2011	*Journal of Clinical Oncology*	317

(continued)

Table 1. (continued)

Title	Authors	Year	Journal	Citations (n)
Prognostic value of pathologic complete response after neoadjuvant therapy in locally advanced rectal cancer: Long-term analysis of 566 ypCR patients[17]	Capirci and colleagues	2008	*International Journal of Radiation Oncology Biology Physics*	307
Long-term oncologic outcome following preoperative combined modality therapy and total mesorectal excision of locally advanced rectal cancer[18]	Guillem and colleagues	2005	*Annals of Surgery*	305
Rectal cancer: Review with emphasis on MR imaging[19]	Beets-Tan and colleagues	2004	*Radiology*	284
Randomized phase III study comparing preoperative radiotherapy with chemoradiotherapy in nonresectable rectal cancer[20]	Brændengen and colleagues	2008	*Journal of Clinical Oncology*	283
Does downstaging predict improved outcome after preoperative chemoradiation for extraperitoneal locally advanced rectal cancer? A long-term analysis of 165 patients[21]	Valentini and colleagues	2002	*International Journal of Radiation Oncology Biology Physics*	282
Oxaliplatin added to fluorouracil-based preoperative chemoradiotherapy and postoperative chemotherapy of locally advanced rectal cancer (the German CAO/ARO/AIO-04 study): Final results of the multicentre, open-label, randomised, phase 3 trial[22]	Rödel and colleagues	2015	*The Lancet Oncology*	278
T-level downstaging and complete pathologic response after preoperative chemoradiation for advanced rectal cancer result in decreased recurrence and improved disease-free survival[23]	Theodoropoulos and colleagues	2002	*Diseases of the Colon and Rectum*	271
Effectiveness of gene expression profiling for response prediction of rectal adenocarcinomas to preoperative chemoradiotherapy[24]	Ghadimi and colleagues	2005	*Journal of Clinical Oncology*	270

topped the list with 43 funded articles, followed by The National Institutes of Health (US) and the National Cancer Institute (US), with 30 funded articles and 24 funded articles, respectively.

Discussion

This bibliometric analysis confirmed that LARC treatment was highly represented in medical literature over the last 20 years. A relative increase in the number of published articles indicated that LARC treatment has gained an increasing scientific attention, especially since the 2010s. Nearly all of the most productive countries were economically prosperous, assuming that socioeconomic development is directly linked to scientific investments. The United States of America detected the most productive institutions of publications and was the center of collaboration network. Notably, the United States of America was highly connected to European countries. The vast majority of the highly cited studies looked at chemotherapy regimens in the neoadjuvant setting. Nearly half of these related papers examined the clinical benefit of adding oxaliplatin to standard neoadjuvant fluoropyrimidine (5FU)-based chemoradiotherapy and reported the results of clinical trials. The intrinsic bias involved with citation rate should be considered. Surely, their inclusion in international guidelines should be interpreted as a sign of prestige and importance.

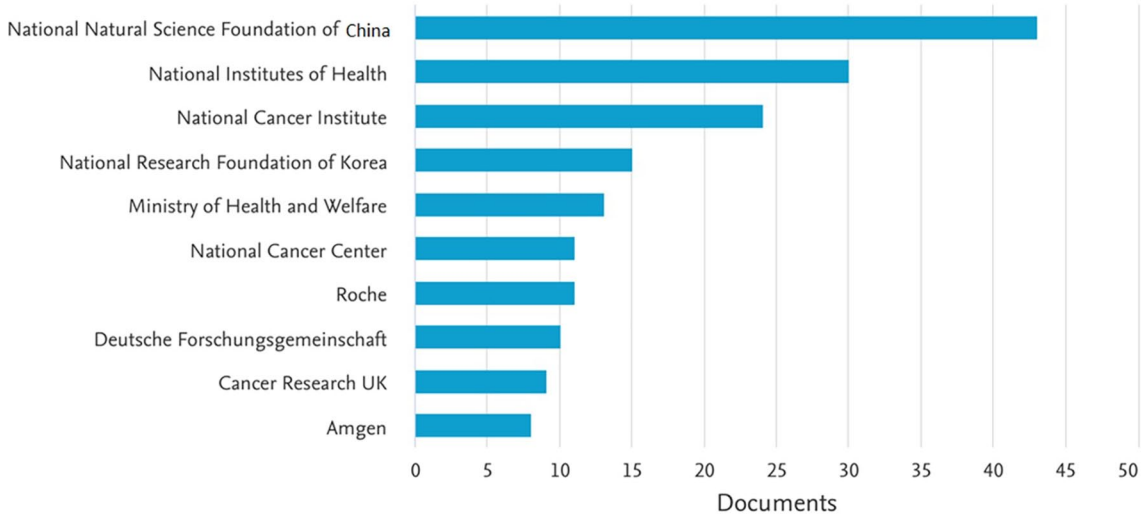

Figure 5. Funding sponsor.

On the contrary, there was a lack of papers focusing on new surgical approaches. This was likely due to the lack of controversy regarding this topic: if feasible, anterior resection using total mesorectal excision continues to be the gold standard in LARC. The funding countries analysis showed the massive investment of China in LARC research. Overall, the research picture was not static. More recently used keywords – neoadjuvant chemotherapy, multiparametric magnetic resonance imaging, circulating tumor DNA, and genetic heterogeneity – had a higher frequency rate, which suggests a significant influence within the next 5–10 years. This assumption also corresponds with the research results of Wang and colleagues.[25] They published a bibliometric study on rectal cancer in the past 25 years (1994–2018), identifying 23,492 publications. They searched the public version of PubMed indexed and included all rectal cancer records, from an early stage disease to the metastatic setting. The prognostic role of multiparametric magnetic resonance imaging and new treatment strategies was empathized in the patients with advanced rectal cancer. It is clear that both timing and effectiveness of multiagent chemotherapy remain a hot topic as shifting systemic chemotherapy in a neoadjuvant phase or adding monoclonal antibody agents can result in a significant outcomes improvement. There is a growing body of research on these topics, but it is likely too new to feature at this time.[26–30] Surely total neoadjuvant therapy seems to be a potential treatment opportunity to ameliorate survival outcomes in LARC patients, as recently reported in the Rectal cancer And Preoperative Induction therapy followed by Dedicated Operation (RAPIDO) trial and the Unicancer Gastrointestinal Group and Partenariat de Recherche en Oncologie Digestive (UNICANCER-PRODIGE) 23 trial.[29,30] But, at present a clear standard treatment in this clinical situation is still lacking and further investigations are necessary.

The main limitation of this article is the potential for several biases which may affect results. The aim was not to perform an analysis of the quality of papers, but a descriptive quantitative analysis. Moreover, this bibliometric analysis was only based on Scopus database. We recognized that the final results may differ according to the inclusion of other search terms, databases, or languages. All conclusions should be interpreted within the context of these limitations. Despite these limitations, however, our study offered potential insights into the use of bibliometric data as a source for research input. Moreover, it offered further understanding of the potential use of big data in the oncologic field. A next step should be to dig deeper into the concept of sharing large databases.

Conclusion

We analyzed the evolution of the scientific production in terms of number and main trends in

LARC. Neoadjuvant chemotherapy, genetics, and biomarkers represent the highest research potential.

Conflict of interest statement

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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ORCID iD

Francesca De Felice https://orcid.org/0000-0002-5119-8358

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