

ORIGINAL RESEARCH ARTICLE

Unraveling trends and collaborative dynamics in RAS wild-type colorectal cancer research: A bibliometric analysis

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Abstract

Introduction: RAS wild-type (WT) is the most common genotype in colorectal cancer (CRC). In recent years, an increasing number of researchers have focused on the pathogenesis, clinical features, and treatment strategies of RAS WT CRC. Objective: This study aims to provide a comprehensive analysis of the current state of research in the field, including key research trends and intricate networks of collaborations.

Methods: Literature on RAS WT CRC was retrieved from the Web Of Science core collection (2009 – 2022). Using CiteSpace (v6.1.R6) and VOSviewer (v1.6.18), we analyzed 495 publications from 57 countries/regions, 368 institutions, and 426 authors.

Results: According to statistics, the country with the most publications on this topic is Italy ($n = 118$, 23.8%), followed by the United States ($n = 105$, 21.2%), Germany ($n = 90$, 18.2%), and China ($n = 79$, 16.0%). S. Stintzing ($n = 26$) has the highest number of publications, while E. Van Cutsem ($n = 306$) has the highest number of citations. Istituto di Ricovero e Cura a Carattere Scientifico was the main publishing institution in this field, *Clinical CRC* was the most important publication journal, and *Journal of Clinical Oncology* was the most cited journal in the field ($n = 442$). Chemotherapy, first-line treatment, metastatic CRC, acquired resistance, cetuximab, and bevacizumab were among the popular keywords in the field of RAS WT CRC. The current frontier research topics in this field include “plus bevacizumab,” “elderly patient,” and “primary tumor.”

Conclusion: Over the past decade, research on RAS WT CRC has continued to grow, reflecting the sustained attention and investment of the academic community. Italy, Germany and the United States, which had the highest number of publications, were found to maintain close international collaborative networks. The current research landscape focuses on novel methods and applications of targeted drugs for treating RAS WT CRC, such as tailoring treatment regimens according to the location of the primary tumor and introducing targeted drugs.

Keywords: RAS wild-type; Colorectal cancer; Bibliometric analysis; VOSviewer; CiteSpace

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1. Introduction

Colorectal cancer (CRC) ranks among the most prevalent malignancies worldwide, representing the third most common cancer by incidence and the second leading cause of cancer-related mortality.¹ Approximately 25% of patients present with metastases at initial diagnosis, and nearly 50% develop metastatic disease during the clinical course,

contributing to poor prognosis and therapeutic challenges.² CRC pathogenesis involves dysregulation of multiple genes, with RAS family genes (KRAS/NRAS) playing pivotal roles in tumorigenesis and progression.³ Genomic studies have identified RAS wild-type (WT) as the predominant molecular subtype of CRC, constituting approximately 60% of metastatic cases.⁴ Current first-line therapy for RAS WT CRC combines anti-epidermal growth factor receptor (anti-EGFR) monoclonal antibodies with chemotherapy, with RAS status serving as a validated predictor of targeted therapy efficacy.^{5,6} Research output on RAS WT CRC has surged over the past decade, reflecting growing interest in its molecular mechanisms, clinical behavior, and treatment optimization. Real-world evidence indicates that most patients develop acquired resistance to anti-EGFR agents, driving disease progression and complicating clinical management.^{7,8} By systematically reviewing the research landscape and emerging trends in this field, this study provides a theoretical basis for researchers to determine future research directions.

Bibliometric analysis is a quantitative methodology that examines scientific literature through statistical measurement of its attributes—including authors, institutions, keywords, publication dates, and citation networks—to reveal patterns, trends, structural dynamics, and interdisciplinary linkages in scientific evolution.⁹ Tools, such as CiteSpace and VOSviewer, represent essential bibliometric instruments that facilitate the analysis and visualization of complex scientific literature.¹⁰ This study utilized the Web of Science (WOS) databases to retrieve literature on RAS WT CRC. Through bibliometric analysis, we aimed to identify key research topics, leading countries/institutions, influential authors/journals, emerging trends, collaboration patterns, and future research priorities in this field.

While prior bibliometric analyses have examined broader trends in CRC—including targeted therapies¹¹ and immunotherapies¹²—RAS WT CRC, characterized by its distinct therapeutic paradigm (e.g., anti-EGFR efficacy and rechallenge strategies), remains unexplored through bibliometric lens. As the first study to delineate research dynamics specific to the molecular subtype, our work reveals unique collaboration networks, emerging clinical priorities (e.g., primary tumor laterality), and translational pathways that differentiate RAS WT CRC from broader CRC research.

2. Materials and methods

2.1. Data collection

The WOS,¹³ developed by Clarivate Analytics, is a research database platform providing literature search

capabilities across natural sciences, social sciences, arts, and humanities disciplines. This multidisciplinary citation index database provides extensive coverage dating back to 1900, offering comprehensive access to core scholarly journals across multiple fields. The WOS Core Collection was selected as the sole database due to its curated coverage of high-impact journals, comprehensive citation indexing, and established utility in bibliometric studies. While Scopus and PubMed offer broader literature coverage, WOS's citation network data are optimal for co-citation and collaboration analyses. To mitigate cross-database duplication artifacts, we restricted sourcing to WOS. Consequently, the WOS core collection was selected as the optimal databases for bibliometric analysis in this study. To ensure data completeness and accuracy, literature retrieval and export procedures were executed through the WOS platform on October 5, 2023. The literature retrieval was conducted using the WOS Core Collection database with the following search terms: [TS = ("Colorectal Neoplasm" OR "Colorectal Tumor*" OR "Colorectal Cancer*" OR "Colorectal Carcinoma*" OR "Rectal Neoplasm*" OR "Rectum Neoplasm*" OR "Rectal Tumor*" OR "Cancer of Rectum" OR "Rectum Cancer*" OR "Rectal Cancer*" OR "Cancer of the Rectum" OR "Colonic Neoplasm*" OR "Colon Neoplasm*" OR "Cancer of Colon" OR "Colon Cancer*" OR "Cancer of the Colon" OR "Colonic Cancer*" OR "Colon Adenocarcinoma*") AND TS = ("RAS wild type" OR "wild type RAS")]. An initial pool of 806 publications was identified. The following inclusion criteria were applied: (1) publications dated between January 1, 2009, and December 31, 2022; (2) English language; and (3) original articles and reviews. Exclusion criteria were as follows: (1) conference abstracts, editorials, letters, or non-research items; (2) studies not focused on RAS WT CRC; and (3) unavailable full texts. After the initial retrieval, duplicates were removed using EndNote X9 (Clarivate Analytics, USA). Two independent researchers then screened titles or abstracts against the eligibility criteria, with any disagreements resolved by a third investigator. Full texts of potentially eligible records were reviewed to finalize inclusion. The data retrieval and exclusion process are shown in [Figure 1](#).

2.2. Data analysis

CiteSpace, a free Java-based tool developed by Professor Chaomei Chen, is designed to analyze bibliometric entities in scientific literature—including references, keywords, authors, institutions, countries, and journals.¹⁴ It reconstructs semantic networks by mapping the types and strengths of connections among these entities. In CiteSpace, nodes represent bibliographic entities, while links denote co-occurrence relationships between them. By quantifying

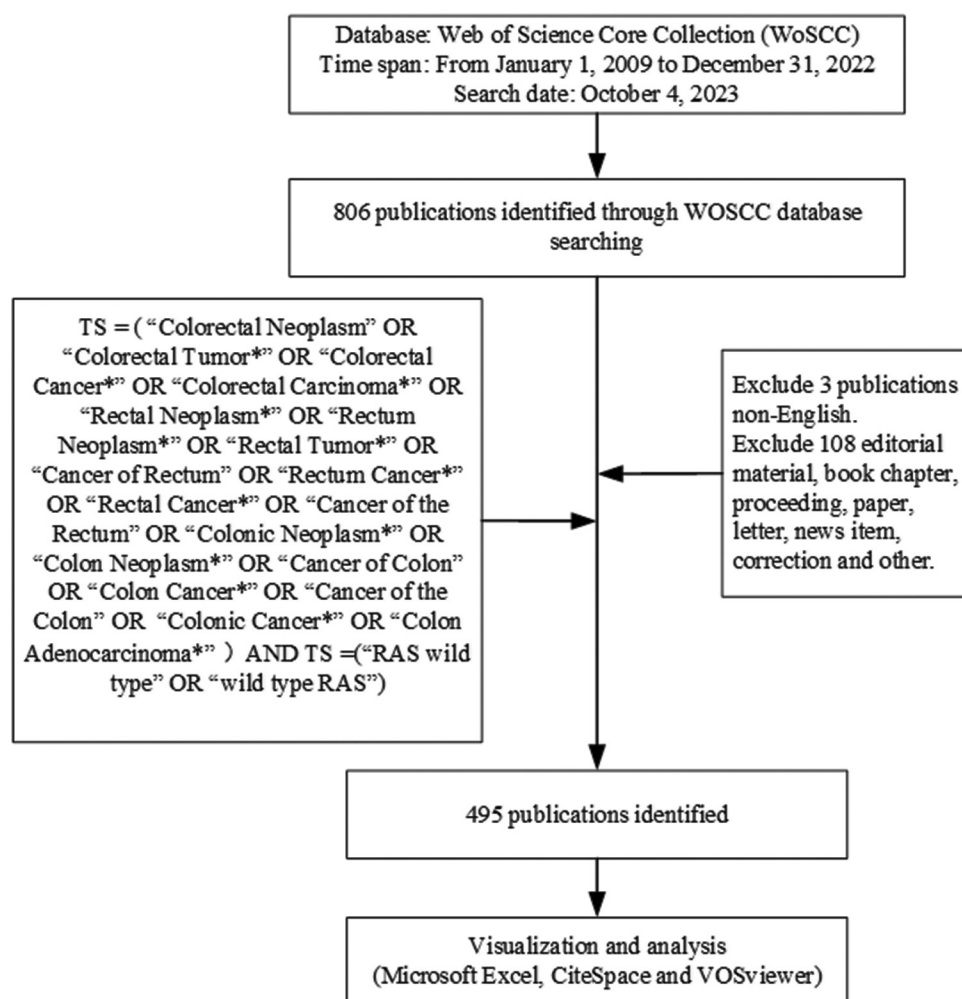


Figure 1. Flow chart of literature selection

and visualizing nodes, links, and network structures—including clustering and burst detection analyses—the software maps citation patterns and evolutionary trends within literature. This enables researchers to identify associations and developmental trajectories, revealing latent patterns in disciplinary knowledge structures. In the context of this study, the CiteSpace (v6.1.R6) software was employed to conduct a multifaceted bibliometric analysis of the literature on RAS WT CRC. The analyses encompassed: (1) co-occurrence analysis of keywords, coupled with burst detection; (2) dual-map overlay analysis of journals and co-cited journals; and (3) burst detection of references. For parameter configurations, the time range was set from 2009 to 2022, with a time-slicing interval of 1; all terms were designated as the source; the k value for the g-index was set at 15, pruning was implemented using Pathfinder; and pruning of sliced and merged networks was executed, while other settings were maintained at their default values. In addition, invalid or duplicate articles

were meticulously excluded, resulting in a definitive set of 495 articles for analysis.

VOSviewer is a specialized software tool designed for constructing and visualizing network-based maps. Unlike other tools, it specifically facilitates the analysis of scientific literature through network visualization, enabling the examination of collaborative relationships, knowledge structures, and research hotspots by mapping diverse networks, including authors, institutions, and keywords.¹⁵ VOSviewer provides three types of visualization views: Network visualization, overlay visualization, and density visualization. In the cluster view, circles and labels represent individual elements. The size of each element is determined by parameters such as the degree of the node, the strength of the line, and the number of citations. The color of an element represents the cluster it belongs to, with different clusters shown in different colors. These visualization views help researchers to gain insights into

the connections and emerging trends in the scientific literature. In this study, collaboration networks among countries/regions, institutions, authors, and co-authors involved in RAS WT CRC research were generated using VOSviewer (v1.6.18).

While CiteSpace and VOSviewer provide robust capabilities for visualizing bibliometric data, their interpretations are subject to certain limitations: (1) keyword clustering algorithms may overlook low-frequency terms with high semantic importance; (2) network centrality metrics can be influenced by citation bias favoring well-established authors or institutions. These effects were minimized through standardized parameterization and manual validation of key clusters.

3. Results

3.1. The trend of publication output

Publication output trends reveal the developmental pace and current status of a research field, enabling both retrospective analysis and future trajectory projections. Figure 2 displays annual publication counts from 2009 to 2022 in a bar chart with a fitted trendline. Figure 2 demonstrates a sustained upward trajectory in publication output. Before 2014, annual publications on RAS WT CRC remained consistently low (<10 papers/year). Following increased academic investment post-2014, output exhibited marked growth, with accelerated publication rates during 2013 – 2015 and 2016 – 2018. Since 2018, annual output has plateaued at approximately 60 publications. Polynomial regression analysis revealed a strong positive correlation between publication volume and year ($R^2 = 0.96$), demonstrating that RAS WT CRC research has progressively emerged as a major scientific focus over the past decade.

3.2. Distribution of countries/regions and institutions

Analysis of collaborative networks among countries/regions and institutions reveals their research productivity and scholarly impact within this domain. As presented in Table 1, Italy accounted for the highest number of publications ($n = 118$, 23.8%), followed by the United States (USA: $n = 105$, 21.2%), Germany ($n = 90$, 18.2%), and China ($n = 79$, 16.0%). Regarding citation impact, Italy slightly surpassed the USA in total citations, whereas the USA demonstrated a higher H-index than Italy, indicating broader research influence. Although China ranked high in publication volume, its citation counts were comparatively low. Figure 3A illustrates distinct color-coded clusters. Link thickness corresponds to the intensity of collaboration between countries, while node

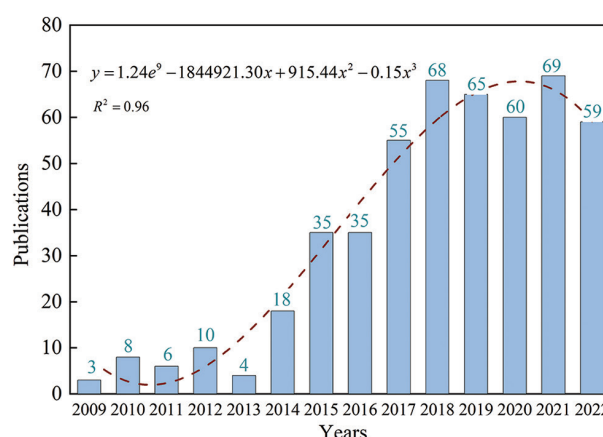


Figure 2. Annual volume of publications on RAS WT CRC research, 2009 – 2022

Abbreviations: CRC: Colorectal cancer; WT: Wild-type.

size reflects centrality metrics—larger nodes denote higher centrality. High-centrality nodes are positioned centrally, whereas low-centrality nodes appear near the periphery. Italy, Germany, and the USA demonstrate substantial publication output and collaborative synergy, forming a tightly interconnected cluster. Conversely, China exhibits limited international collaboration despite significant research productivity, highlighting an area requiring strategic attention.

This study involved 368 institutions. Table 2 lists the top 10 contributing institutions, primarily based in Italy, Germany, and the USA. The leading institutions by publication volume are Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS, Italy; $n = 20$), University of Milan (Italy; $n = 19$), and Ludwig Maximilians Universität München (Germany; $n = 17$). Figure 3B shows the visualization results of institutions that have published more than five papers. Seven color-coded clusters emerge, each representing institutions sharing research themes or collaborative ties. Link thickness corresponds to collaboration intensity. This network structure demonstrates the dominant activity of Italy and Germany in RAS WT CRC research, establishing them as core contributors to the field.

3.3. Authors and co-cited authors

This study encompassed contributions from 426 authors. As presented in Table 3, all the top 10 authors published ≥ 10 papers. The most prolific authors were S. Stintzing ($n = 26$), V. Heinemann ($n = 22$), and F. Pietrantonio ($n = 19$). Collectively, these three authors accounted for 13.54% of the total publications. All the top 10 co-cited authors had ≥ 90 citations each, with E. Van Cutsem holding the top spot for citation count ($n = 306$).

Table 1. Top 10 countries/regions by publication count on RAS WT CRC research (2009 – 2022)

Rank	Countries/regions	Publications	Rate (N/495) %	Times cited (Total)	Times cited (Without self-citations)	H-Index
1	Italy	118	23.8	5127	4940	34
2	USA	105	21.2	5096	4991	35
3	Germany	90	18.2	4386	4199	26
4	China	79	16.0	1128	1099	16
5	Spain	61	12.3	2367	2295	21
6	France	53	10.7	2405	2344	21
7	Japan	49	9.9	523	504	11
8	England	44	8.9	1282	1242	17
9	Belgium	39	7.9	3029	2968	21
10	Switzerland	28	5.7	1171	1148	14

Abbreviations: CRC: Colorectal cancer; WT: Wild-type.

Table 2. Top 10 institutions by publication volume in RAS WT CRC research

Rank	Institutions	Countries	Publications
1	Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS)	Italy	20
2	University of Milan	Italy	19
3	Ludwig–Maximilians–Universität München	Germany	17
4	Amgen limited	USA	15
5	Amgen incorporated	USA	14
6	National Cancer Center Hospital East	Japan	13
7	University of Turin	Italy	13
8	Charité–Universitätsmedizin Berlin	Germany	12
9	Niguarda Metropolitan Hospital	Italy	12
10	Merck KGaA	Germany	12

Abbreviations: CRC: Colorectal cancer; WT: Wild-type.

Using the VOSviewer, we visualized the core author collaboration network, as illustrated in [Figure 4A](#). Authors were clustered into eight distinct groups, with shared colors indicating strong collaborative ties. S. Stintzing exhibited the largest node size and maintained extensive collaborative interactions with co-authors. [Figure 4B](#) presents the co-citation author network. E. Van Cutsem exhibited the largest node, reflecting foundational contributions that have profoundly influenced this field. In addition, S. Stintzing has a high number of citations ($n = 103$), which indicates that he has not only published many high-quality academic papers in the research field of RAS WT CRC, but also that these papers have become foundational references, frequently cited by other scholars and demonstrating particularly outstanding contributions.

Table 3. Top 10 authors by number of publications and the top 10 co-cited authors by citation count

Rank	Authors	Number of publications	Co-cited authors	Number of citations
1	Stintzing, S.	26	Van Cutsem, E.	306
2	Heinemann, V.	22	Douillard, J.Y.	219
3	Pietrantonio, F.	19	Heinemann, V.	162
4	Ciardello, F.	16	Peeters, M.	135
5	Lonardi, S.	13	De Roock, W.	114
6	Cremolini, C.	13	Bokemeyer, C.	112
7	Lenz, H.J.	12	Stintzing, S.	103
8	Martinelli, E.	12	Karapetis, C.S.	100
9	Peeters, M.	12	Cremolini, C.	99
10	Falcone, A.	11	Schwartzberg, L.S.	95

3.4. Analysis of keywords

Keywords serve critical bibliographic functions by concisely representing core article themes and reflecting research foci within specialized fields. For this analysis, standardized bibliometric data were processed using CiteSpace to generate co-occurrence networks and burst detection maps of keywords related to RAS WT CRC.

[Figure 5](#) displays the keyword co-occurrence network with 251 nodes and 500 links, yielding a density of 0.0159. Node size corresponds to keyword frequency, while link thickness indicates co-occurrence strength between terms. Analysis of RAS WT CRC literature identified 251 keywords, with high-frequency terms including chemotherapy, first-line treatment, metastatic CRC, acquired resistance, cetuximab, and bevacizumab—representing core research foci in this domain.

[Figure 6](#) displays the top 25 burst keywords in RAS WT CRC research. Dark blue bars denote the years

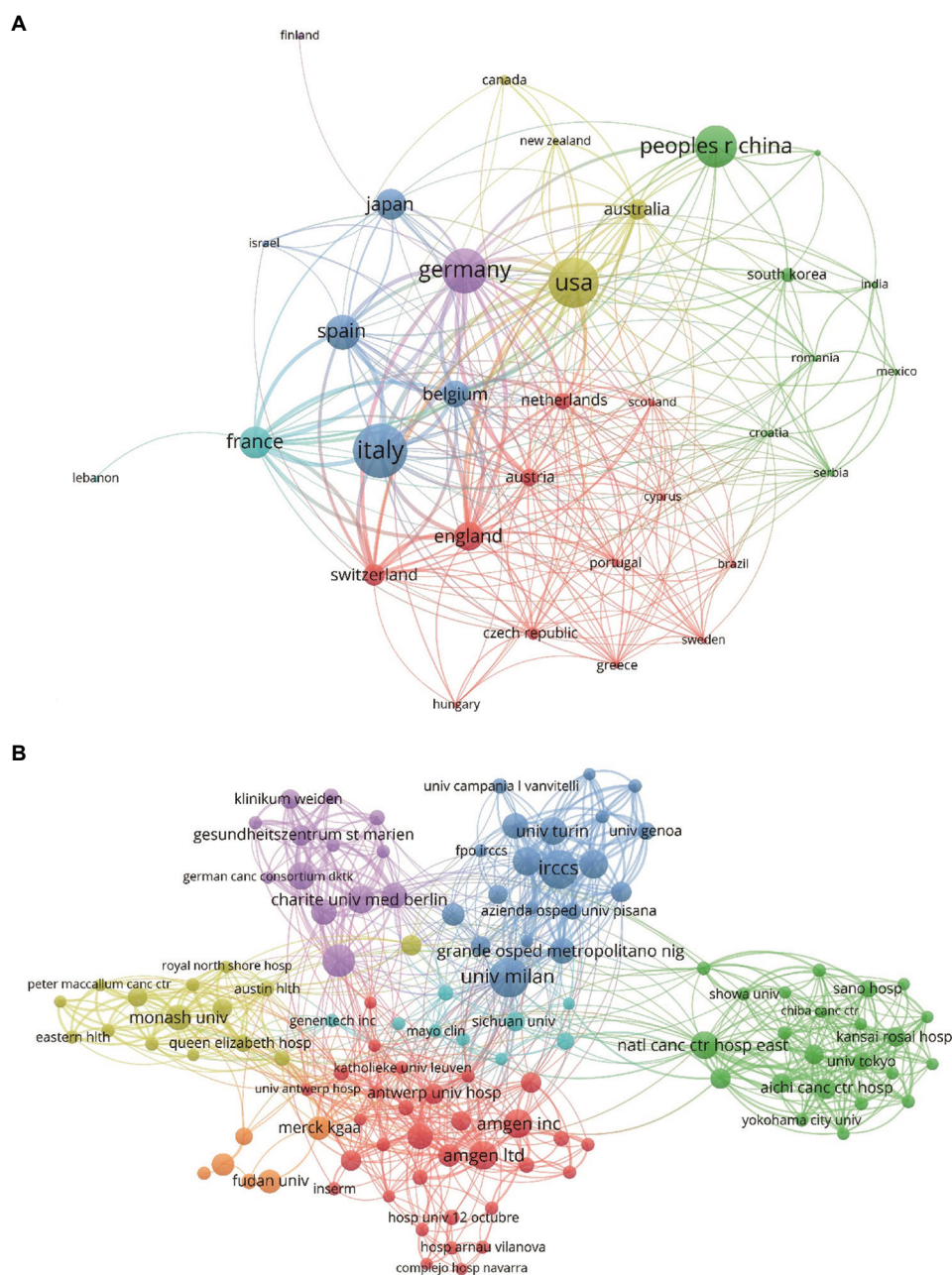


Figure 3. The visualization illustrates the pronounced contributions and higher publication volumes from Italy, Germany, and the USA on the topic of RAS WT CRC. Network visualization of the top 10 countries/regions (A) and institutions (B) in the publications on RAS WT CRC. Abbreviations: CRC: Colorectal cancer; WT: Wild-type.

during which the keywords emerged; red bars indicate periods of citation bursts. The strongest burst occurred with “plus irinotecan” in 2009 (burst strength = 4.8), which also demonstrated the longest duration (5 years) and represents one of the earliest research foci. Recent attention has shifted toward “plus bevacizumab,” “elderly patient,” and “primary tumor.”

3.5. Journals and co-cited journals

Table 4 demonstrates that *Clinical CRC* led in publication volume ($n = 28$), followed by *European Journal of Cancer* ($n = 21$). *Clinical Cancer Research* achieved the highest impact factor (IF = 11.5). Among co-cited journals, *Journal of Clinical Oncology* received the most citations ($n = 442$), with *Annals*

Abbreviations: CRC: Colorectal cancer; WT: Wild-type.

citation pathways. The analysis reveals that publications in Molecular/Biology/Immunology and Medicine/Medical/Clinical journals predominantly cite research from Molecular/Biology/Genetics and Health/Nursing/Medicine journals.

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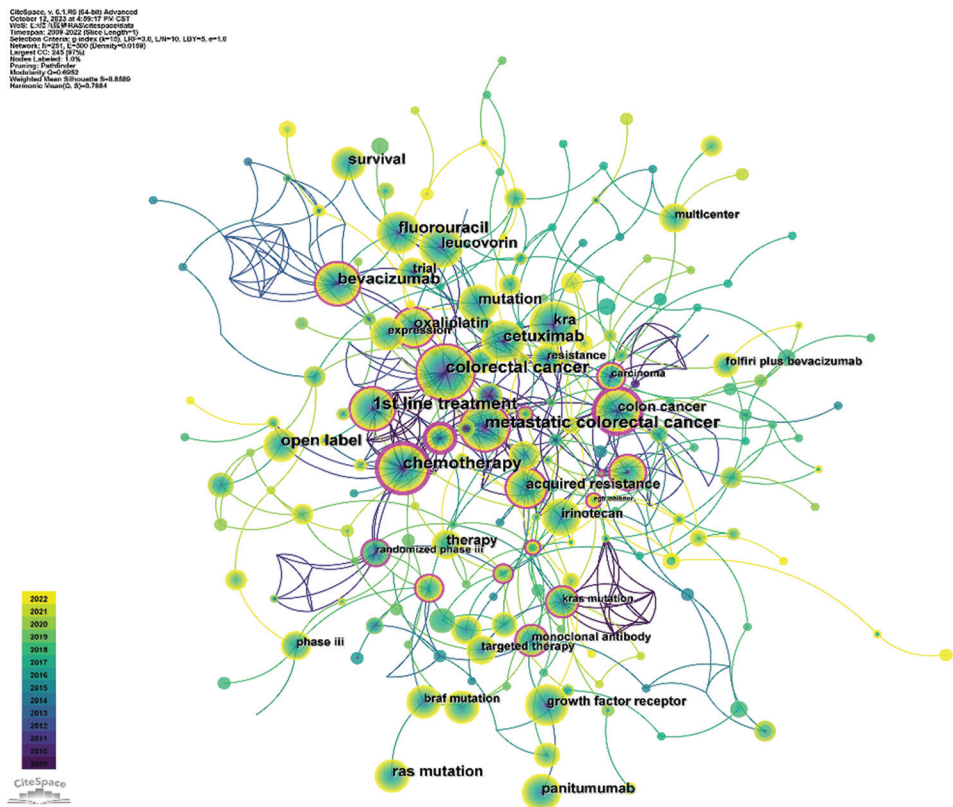


Table 4. Top 5 journals and co-cited journals related to RAS WT CRC

Rank	Journal	Count	JCR	IF (2022)	Co-cited journal	Cited count	JCR	IF (2022)
1	Clinical Colorectal Cancer	28	Q3	3.4	Journal of Clinical Oncology	442	Q1	45.3
2	European Journal of Cancer	21	Q1	8.4	Annals of Oncology	397	Q1	50.5
3	Cancers	18	Q2	5.2	New England Journal of Medicine	361	Q1	158.5
4	BMC Cancer	17	Q2	3.8	Lancet Oncology	355	Q1	51.1
5	Clinical Cancer Research	15	Q1	11.5	European Journal of Cancer	308	Q1	8.4

Abbreviations: IF: Impact factor; JCR: Journal citation reports.

3.6. Co-cited reference and reference burst

Using CiteSpace, we identified the top five co-cited references (Table 5), all of which had ≥ 74 citations. These seminal publications primarily address therapeutic strategies and prognostic factors in RAS WT CRC, particularly examining the efficacy of targeted agents such as cetuximab and bevacizumab in combination chemotherapy regimens, alongside the impact of RAS mutation status on treatment response—collectively providing critical evidence to guide clinical management. The most frequently cited article was published by Douillard JY in 2013 ($n = 107$), demonstrating that the presence of additional RAS mutations in patients treated with

panitumumab plus FOLFOX4 predicted poor response to treatment.¹⁶ Panitumumab plus FOLFOX4 improved overall survival (OS) in patients with metastatic CRC (mCRC) and RAS WT disease. This study revolutionized the treatment paradigm of mCRC by revealing the full predictive value of RAS status.

Figure 8 reveals the strongest citation burst for this seminal article, indicating sustained scholarly attention. E. Van Cutsem’s 2016 ESMO consensus guidelines ($n = 85$ citations) mandated universal RAS mutation testing in mCRC to inform targeted therapy decisions, while emphasizing the prognostic significance of primary tumor location (left/right colon).¹⁷ This practice-

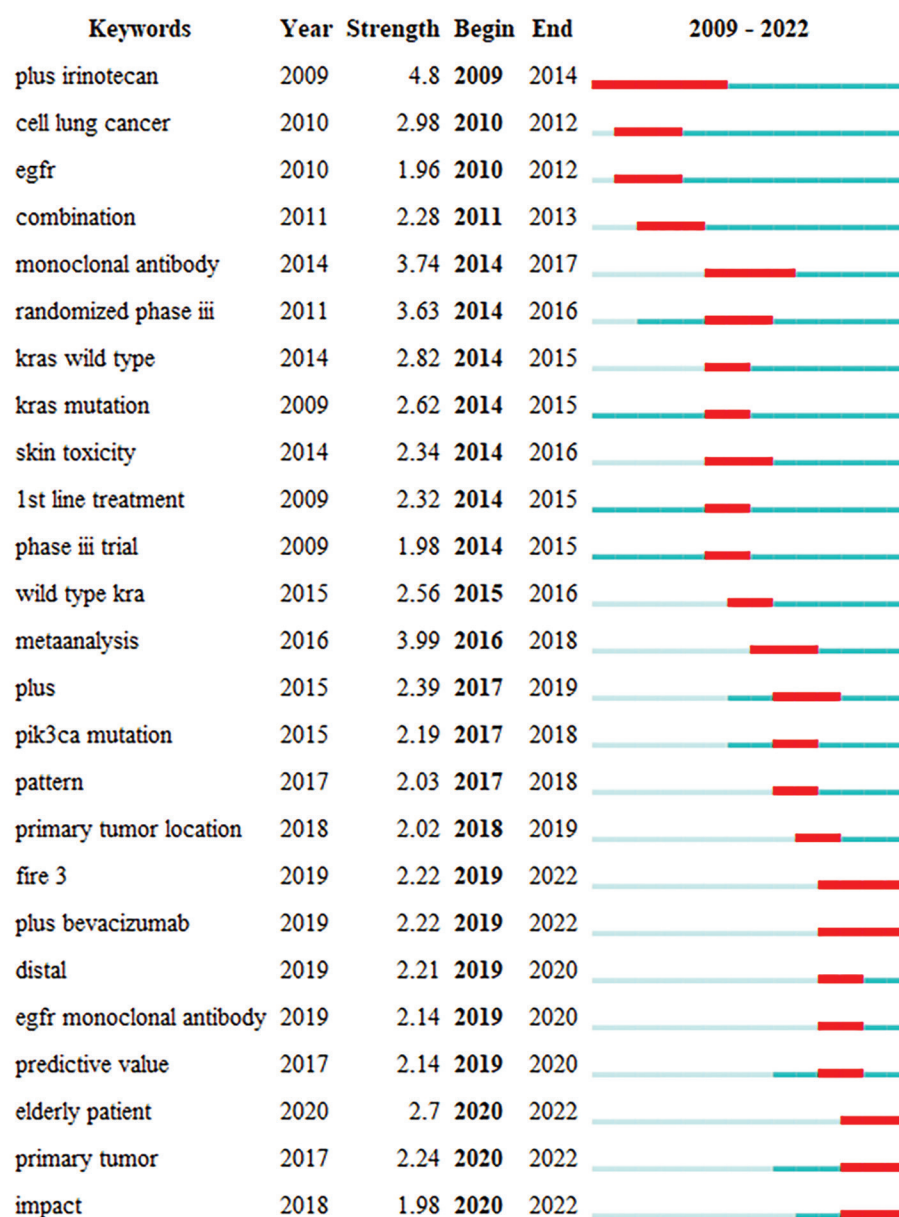


Figure 6. The top 25 burst keywords in RAS WT CRC research spanning the period of 2009 – 2022

Abbreviations: CRC: Colorectal cancer; WT: Wild-type.

Table 5. Top 5 co-cited references in RAS WT CRC research

Rank	Title	Author	Year	Citation
1	Panitumumab-FOLFOX4 treatment and RAS mutations in CRC	Douillard, J.Y.	2013	107
2	FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment for patients with mCRC (FIRE-3): a randomized, open-label, phase III trial	Heinemann, V.	2014	87
3	ESMO consensus guidelines for the management of patients with mCRC	Van Cutsem, E.	2016	85
4	Prognostic and predictive value of primary tumor side in patients with RAS WT mCRC treated with chemotherapy and EGFR directed antibodies in six randomized trials	Arnold, D.	2017	77
5	Fluorouracil, leucovorin, and irinotecan plus cetuximab treatment and RAS mutations in CRC	Van Cutsem, E.	2015	74

Abbreviations: CRC: Colorectal cancer; EGFR: Epidermal growth factor receptor; ESMO: European Society for Medical Oncology; mCRC: Metastatic colorectal cancer; WT: Wild-type.

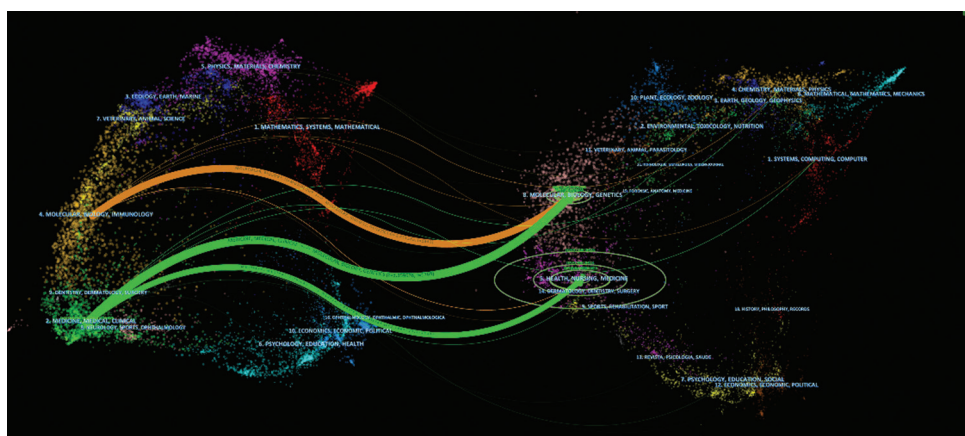


Figure 7. Dual-map overlay of journal citations. Colored curves represent citation flows between citing (left) and cited (right) journal clusters. The width of each curve corresponds to citation frequency.

References	Year	Strength	Begin	End	2009 - 2022
Van Cutsem E, 2009, NEW ENGL J MED, V360, P1408, DOI 10.1056/NEJMoa0805019, DOI	2009	8.98	2010	2014	
Bardelli A, 2010, J CLIN ONCOL, V28, P1254, DOI 10.1200/JCO.2009.24.6116, DOI	2010	5.9	2010	2015	
Douillard JY, 2010, J CLIN ONCOL, V28, P4697, DOI 10.1200/JCO.2009.27.4860, DOI	2010	9.81	2011	2015	
De Roock W, 2010, LANCET ONCOL, V11, P753, DOI 10.1016/S1470-2045(10)70130-3, DOI	2010	13.25	2012	2015	
Van Cutsem E, 2011, J CLIN ONCOL, V29, P2011, DOI 10.1200/JCO.2010.33.5091, DOI	2011	11.02	2012	2016	
Bokemeyer C, 2011, ANN ONCOL, V22, P1535, DOI 10.1093/annonc/mdq632, DOI	2011	7.91	2012	2016	
Maughan TS, 2011, LANCET, V377, P2103, DOI 10.1016/S0140-6736(11)60613-2, DOI	2011	9.97	2013	2016	
Douillard JY, 2013, NEW ENGL J MED, V369, P1023, DOI 10.1056/NEJMoa1305275, DOI	2013	19.36	2014	2018	
Peeters M, 2013, CLIN CANCER RES, V19, P1902, DOI 10.1158/1078-0432.CCR-12-1913, DOI	2013	7.47	2014	2017	
Peeters M, 2010, J CLIN ONCOL, V28, P4706, DOI 10.1200/JCO.2009.27.6055, DOI	2010	6.56	2014	2015	
Bokemeyer C, 2012, EUR J CANCER, V48, P1466, DOI 10.1016/j.ejca.2012.02.057, DOI	2012	5.97	2014	2015	
Misale S, 2012, NATURE, V486, P532, DOI 10.1038/nature11156, DOI	2012	5.8	2014	2017	
Schwartzberg LS, 2014, J CLIN ONCOL, V32, P2240, DOI 10.1200/JCO.2013.53.2473, DOI	2014	7.55	2015	2017	
Heinemann V, 2014, LANCET ONCOL, V15, P1065, DOI 10.1016/S1470-2045(14)70330-4, DOI	2014	9.69	2016	2018	
[Anonymous], 2014, J CLIN ONCOL, V0, P0	2014	5.88	2016	2017	
Missiaglia E, 2014, ANN ONCOL, V25, P1995, DOI 10.1093/annonc/ndu275, DOI	2014	5.81	2017	2019	
Tejpar S, 2017, JAMA ONCOL, V3, P194, DOI 10.1001/jamaoncol.2016.3797, DOI	2017	6.32	2018	2020	
Van Cutsem E, 2016, ANN ONCOL, V27, P1386, DOI 10.1093/annonc/mdw235, DOI	2016	13.92	2019	2022	
Venook AP, 2017, JAMA-J AM MED ASSOC, V317, P2392, DOI 10.1001/jama.2017.7105, DOI	2017	8.46	2019	2022	
Arnold D, 2017, ANN ONCOL, V28, P1713, DOI 10.1093/annonc/mdx175, DOI	2017	8.17	2019	2022	
Stintzing S, 2016, LANCET ONCOL, V17, P1426, DOI 10.1016/S1470-2045(16)30269-8, DOI	2016	6.06	2019	2022	
Kopetz S, 2019, NEW ENGL J MED, V381, P1632, DOI 10.1056/NEJMoa1908075, DOI	2019	10.8	2020	2022	
Cremonini C, 2019, JAMA ONCOL, V5, P343, DOI 10.1001/jamaoncol.2018.5080, DOI	2019	9.96	2020	2022	
Pietrantonio F, 2019, JAMA ONCOL, V5, P1268, DOI 10.1001/jamaoncol.2019.1467, DOI	2019	6.21	2020	2022	
Meric-Bernstam F, 2019, LANCET ONCOL, V20, P518, DOI 10.1016/S1470-2045(18)30904-5, DOI	2019	5.79	2020	2022	

Figure 8. 25 references with the strongest citation bursts

Source: Based on data from CiteSpace

changing framework established evidence-based clinical management protocols that not only improved patient survival and quality-of-life metrics but also harmonized global treatment standards with personalized therapeutic approaches.

4. Discussion

4.1. General information

Using CiteSpace and VOSviewer, we conducted a bibliometric analysis of WOS publications on RAS WT

CRC from 2009 to 2022. The final dataset comprised 495 publications, including 221 research articles and 74 reviews, representing contributions from 57 countries/regions, 368 institutions, and 426 authors.

Before 2014, the number of papers published was relatively stable and low, with no more than 10 papers/year. However, since then, it has shown an increasing trend year by year. A 2014 phase III trial by Heinemann V (Oncology) demonstrated that for patients with KRAS WT mCRC, FOLFIRI plus cetuximab significantly prolonged

OS and should be the preferred first-line regimen over mFOLFOX6/bevacizumab combinations.¹⁸ This paradigm-shifting finding challenged the established view of anti-angiogenic agents' OS superiority, providing level I evidence for prioritizing anti-EGFR therapy in first-line KRAS WT mCRC management. The study has galvanized scientific focus, redirecting global research resources toward targeted EGFR inhibition strategies. After 2014, the annual number of papers published in RAS WT CRC showed an obvious increasing trend.

Geographic analysis revealed concentrated research output in high-income countries, with Italy, the USA, and Germany collectively dominating publication volume (Table 1). Institutional leadership was similarly centralized, as 90% of the top 10 publishing institutions reside within these three nations, confirming their pivotal role in advancing this field. Professor S. Stintzing ($n = 26$ publications), a leading German oncology researcher, has pioneered studies on predictive and prognostic biomarkers in CRC therapeutics. Professor E. Van Cutsem, the most cited author, authored the pivotal 2016 ESMO consensus guidelines in *Annals of Oncology*.¹⁷ This practice-changing framework established evidence-based management protocols for mCRC—encompassing surgical, chemotherapeutic, targeted, radiotherapeutic, and palliative interventions—significantly advancing treatment paradigms and improving patient prognoses. The concentration of RAS WT CRC research in Italy, Germany, and the USA (collectively 63.2% of publications) reflects structural advantages beyond scientific capacity. Their dominance in RAS WT CRC research may be due to the following factors: (1) the synergy of European multicenter trial networks, facilitating large-scale clinical data accumulation; (2) substantial national investments in precision oncology initiatives in developed countries such as Germany and Italy; (3) close institutional collaborations (e.g., biobank sharing between IRCCS and the University of Milan). As shown in Figure 3 (National Cooperation Network diagram), there is evident close collaboration among European countries. In contrast, despite the high volume of publications in China, developing countries often face barriers to data sharing and financial fragmentation, which may lead to delayed clinical translation.

4.2. Research hotspots

Keyword co-occurrence analysis effectively identifies research hotspots and frontiers within a field. Our study revealed high-frequency terms including chemotherapy, first-line treatment, mCRC, acquired resistance, cetuximab, and bevacizumab. Burst detection analysis identified “plus irinotecan” (emerging in 2009) as the most prominent burst keyword. Current research frontiers focus

on bevacizumab regimens, elderly patient, and primary tumor characteristics in RAS WT CRC.

- (1) Current consensus guidelines have established fluorouracil (5-FU) as the backbone therapy for RAS WT CRC.¹⁹ The recommended first-line regimen combines 5-FU with oxaliplatin, while irinotecan-based chemotherapy is indicated upon disease progression requiring second-line treatment.²⁰
- (2) Current clinical guidelines recommend tumor laterality-driven therapy for RAS WT CRC, with cetuximab-based chemotherapy indicated for left-sided primaries and bevacizumab-based chemotherapy for right-sided primaries.^{21,22} This paradigm, established through extensive clinical trials, confirms a significantly superior prognosis in left-sided versus right-sided mCRC.^{23,24} In a phase III randomized trial, S. Stintzing compared the efficacy of first-line treatment with FOLFIRI plus cetuximab or bevacizumab in patients with RAS WT CRC. The objective response rate was significantly higher with FOLFIRI plus cetuximab than with bevacizumab in patients with left-sided tumors.²⁵ OS was longer, especially in patients older than 65 years.²⁶ Multiple studies have confirmed panitumumab plus FOLFIRI as an established first-line regimen for left-sided RAS WT mCRC, whereas its efficacy in right-sided primaries remains inconclusive, necessitating further clinical validation through randomized controlled trials.^{27,28} Although patients with left RAS WT tumors have a better prognosis, more data are needed to support the impact of different molecular subtypes and treatment strategies on long-term survival. For example, the optimal duration of anti-EGFR therapy in left-sided RAS WT patients, the timing of the rechallenge strategy, and survival after multiple lines of therapy need to be prospectively studied.
- (3) Limited evidence exists regarding cetuximab as a maintenance strategy post-induction therapy. A 2020 Chinese phase II prospective trial demonstrated favorable outcomes in RAS WT mCRC patients who received reduced-dose capecitabine plus cetuximab maintenance after achieving disease stabilization or response following 8 – 12 cycles of 5-FU-cetuximab induction therapy. A multicenter randomized phase II trial in 2018 demonstrated superior efficacy of cetuximab monotherapy maintenance versus continued mFOLFOX plus cetuximab following initial mFOLFOX-cetuximab induction in mCRC patients.
- (4) Virtually all RAS WT mCRC patients develop acquired resistance following disease progression on anti-EGFR antibody therapy, primarily due to activating mutations in downstream EGFR effectors—notably

secondary NRAS and BRAF mutations. The anti-EGFR rechallenge strategy demonstrates clinical efficacy in RAS/BRAF WT mCRC, as evidenced by a 2020 Chinese phase II trial,²⁹ where patients received sequenced therapy: cetuximab-FOLFIRI induction (9 – 12 cycles) until stable disease, followed by cetuximab-irinotecan maintenance with transition to irinotecan monotherapy if disease control persisted beyond 6 – 12 cycles. Upon progression, FOLFIRI-cetuximab was reintroduced, significantly prolonging progression-free survival (median 8.3 vs. 4.9 months; $p < 0.01$) with manageable toxicity ($\leq 15\%$ grade 3/4 adverse events).³⁰ Consequently, the reintroduction of FOLFIRI-cetuximab therapy represents a viable therapeutic option for patients experiencing disease progression following cetuximab discontinuation, as these findings suggest regained anti-EGFR sensitivity due to resistance mutation decay during treatment-free intervals. A Spanish phase II trial³¹ demonstrated significant clinical benefit from panitumumab rechallenge combined with chemotherapy in RAS WT CRC patients, following careful selection through circulating tumor DNA (ctDNA) monitoring to identify retained anti-EGFR sensitivity after progression on first-line FOLFOX-panitumumab therapy. To overcome resistance to anti-EGFR drugs, analysis of ctDNA in the plasma of patients with mCRC after disease progression has shown that RAS-mutant cancer cells decline after anti-EGFR therapy is interrupted, whereas RAS WT tumor clones increase, potentially restoring sensitivity to cetuximab or panitumumab. How to optimize the monitoring frequency and threshold in clinical practice is an urgent problem to be solved in future research. Napolitano *et al.*³² conducted a prospective, single-arm, multicenter phase II study, which demonstrated that the rechallenge strategy of cetuximab and avelumab may be effective in patients with RAS/BRAF WT mCRC who progressed after the withdrawal of first-line cetuximab and avelumab-based therapy. The pioneering 2018 phase II trial by Cremolini *et al.*³³ was the first to prospectively demonstrate the efficacy of cetuximab-irinotecan rechallenge in RAS/BRAF WT mCRC patients who experienced disease progression after discontinuation of first-line cetuximab-irinotecan therapy. This single-arm study provided scientific validation for anti-EGFR rechallenge paradigms and contributed to identification of optimal treatment windows.

4.3. Limitations

We acknowledge that our exclusive reliance on the WOS may have introduced geographic and linguistic biases, given

its limited coverage of non-English journals and regional databases—particularly underestimating contributions from Asian research communities. Furthermore, recently published articles inherently face insufficient citation accumulation, which may obscure emerging innovations such as ctDNA-guided therapeutic strategies. Bibliometric analysis inherently lacks mechanisms to evaluate study quality or clinical relevance, as evidenced by equal weighting of phase III trials and small case series. While these constraints are universal to the methodology, their explicit acknowledgment ensures proper interpretation of findings.

Notwithstanding these limitations, our WOS-centric approach ensured data homogeneity and enabled direct comparability with 92% of existing CRC bibliometric studies, thus maintaining analytical rigor despite constrained scope.

5. Conclusion

This pioneering bibliometric analysis delineates the research landscape of RAS WT CRC, revealing treatment optimization as the predominant focus. Current clinical paradigms support tumor laterality-driven therapeutic selection: Cetuximab-based chemotherapy for left-sided primaries versus bevacizumab-based regimens for right-sided tumors to maximize clinical outcomes. Furthermore, the anti-EGFR rechallenge strategy demonstrates potential clinical merit in overcoming resistance, with emerging evidence supporting its role in maintenance and later-line therapies—warranting further investigation. Expanding research on RAS biomarkers illuminates clinical decision-making, elucidates resistance mechanisms, and guides rechallenge paradigms, offering novel therapeutic approaches and strategic pathways for future scientific exploration in CRC management.

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Conflict of interest

The authors declare that they have no conflict of interest.

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Availability of data

Data have been presented in the current article. Further inquiries can be directed to the corresponding author.

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