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Global scientific growth and thematic development of spatial transcriptomics in oncology research

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Abstract

Background Spatial transcriptomics (ST) is a rapidly transforming cancer research by enabling spatially resolved gene expression profiling within intact tissues. However, the growth, structure, and thematic evolution of research on ST research in oncology have not been comprehensively mapped.

Objective This study aims to map and analyze global research trends of ST in oncology, identifying key contributors, collaborations, thematic focus areas, and technological evolutions in the field.

Method A bibliometric analysis was conducted using data extracted from Scopus database. VOSviewer tool was used to construct knowledge maps reflecting thematic clusters and intellectual clusters in ST-oncology research. Quantitative indicators were evaluated to identify historical evolution, key players, and research hotspots.

Results The study identified 987 publications on ST in oncology. The annual growth of publications showed a significant surge over the past five years. China and the United States emerged as leading contributors with high levels of intra- and international collaboration. Key journals included *Nature Communications* and *Frontiers in Immunology*. Academic and research institutions based in China dominated the field. Co-occurrence mapping identified the following high-frequency keywords: "tumor microenvironment", "single-cell RNA sequencing", and spatial resolution suggesting strong emphasis on integrating spatial biology with precision oncology. Bibliographic coupling illustrated a clustering around barcoding technologies and immune-oncology interfaces. The overlay visualization suggested a shift toward high resolution imaging, multi-omics integration, and AI-supported analytics.

Conclusion ST-oncology research is expanding rapidly with clear shifts toward higher resolution and integrative analytical frameworks. These findings provide a structured overview of the field's knowledge base and can inform researchers, funders, and stakeholders about leading about leading contributors and emerging directions.

Keywords Spatial transcriptomics, Oncology, Tumor microenvironment, Precision oncology, Bibliometric analysis

1 Introduction

The spatial dimension of gene expression is a fundamental component of biological understanding, particularly in complex diseases such as cancer [1, 2]. Spatial transcriptomics (ST) represents a transformative leap in molecular profiling, enabling the high-throughput mapping of transcriptomes across intact tissue sections while preserving their histological context [3–5]. This technology transcends the limitations of traditional transcriptomic approaches such as bulk RNA sequencing or single cell RNA which fail to retain spatial localization, thereby obscuring the architecture of tumor microenvironments. ST combines histological imaging with barcoded capture arrays or spatially indexed probes, allowing researchers to visualize and quantify gene expression within the morphological framework of a tissue. Pioneered in 2016 by Stahl et al. [6], and subsequently propelled by commercial platforms such as 10X Genomics Viscum, Nano String GeoMx DSP, and multiplexed techniques like "MERFISH" and "seq FISH", ST has rapidly evolved from a proof of concept into a cornerstone of spatially resolved biology [6–9].

In oncology, ST has emerged as a particularly powerful tool. Tumors are inherently heterogeneous, composed of diverse cellular populations interacting within a dynamic microenvironment [10, 11]. Understanding these interactions requires more than molecular content, it demands spatial context. ST allows precise delineation of tumor, stroma interfaces, mapping of immune infiltration, identification of hypoxic niches, and detection of spatially restricted gene expression patterns associated with progression, resistance, and metastasis [12–14]. These insights are invaluable for uncovering novel therapeutic targets, enhancing biomarker discovery, and improving patient stratification strategies [15–17]. Clinically, ST contributes to the advancement of precision oncology by enabling the integration of spatial molecular data into diagnostic and therapeutic decision making [18]. The ability to track spatial patterns of gene expression enhances the prediction of treatment responses, informs combination therapy design, and may even guide real time therapeutic modulation [19]. Its integration with digital pathology, artificial intelligence, and other 'omics technologies is paving the way for next-generation spatially guided medical interventions [20, 21].

Given its disruptive potential and rapidly expanding application in cancer research, ST represents a unique case for bibliometric investigation [22]. Bibliometric analysis serves as an essential tool to quantitatively and qualitatively map the global scientific output, thematic evolution, and collaborative networks in an investigated research field [23, 24]. Bibliometrics enables the systematic examination of publication trends, citation dynamics, influential authors and institutions, and emerging research hotspots. Recent bibliometric studies in clinical oncology, including those addressing radiomics, image-guided surgery, and immunotherapy innovation illustrate the growing role of bibliometric analysis in evaluating translational impact and technological diffusion [25–28]. A recent global-scale bibliometric study examined the rapidly expanding literature on ChatGPT/large language models in medicine illustrates how modern bibliometrics, augmented by machine learning, can move beyond descriptive counts to map translational readiness, ethical challenges, and future research priorities in clinically relevant, fast-moving technologies [29]. In a comprehensive bibliometric "knowledge map" of thrombopoietin receptor agonists (TPO-RAs) research, the authors showed how bibliometric methods can detect saturation, reveal underexplored directions, and guide strategic prioritization

in therapeutics research, principles that are directly transferable to rapidly evolving oncology technologies such as spatial transcriptomics [30].

While general bibliometric analyses have been conducted across cancer biology, there is currently no comprehensive study mapping the scientific trajectory, institutional leadership, and thematic evolution of ST within the field of oncology [26, 31–33]. The current bibliometric analysis seeks to fill this gap by systematically charting the global research landscape, highlighting influential authors, research clusters, funding bodies, technological trends, and emerging thematic areas in ST in oncology. The academic and clinical significance of the present bibliometric study resides in its capacity to systematically contextualize an emerging and expanding scientific field. In rapidly accelerating research domain, bibliometric analysis functions as a meta-research framework that quantitatively captures scientific expansion, delineates dominant thematic trajectories, identifies intellectual turning points, and detects technological inflection phases. Without such analysis, stakeholders lack objective insight into thematic concentration, translational maturity, and emerging research gaps. Beyond its methodological relevance, ST is increasingly positioned as a translational platform rather than a purely exploratory technology. ST also represents a highly interdisciplinary domain, situated at the convergence of molecular biology, oncology, computational science, artificial intelligence, digital pathology, and multi-omics integration. Network-based bibliometric techniques, such as co-occurrence analysis and bibliographic coupling, enable quantitative visualization of these cross-disciplinary linkages in a manner not achievable through conventional reviews. Finally, bibliometric benchmarking provides insight into institutional and geopolitical leadership. Such analysis informs global oncology capacity building, identifies emerging research hubs, and clarifies international collaboration dynamics.

The novelty of this study lies in its targeted scope. By isolating literature at the intersection of ST and oncology, this analysis offers the first in depth quantitative and thematic mapping of how this field is shaping cancer research. It provides strategic insights for researchers, funding agencies, and policymakers by revealing which cancer types have been most studied, which spatial platforms are gaining traction, and what biological processes are most often investigated through this lens. Ultimately, this work aims to serve as a foundational reference for scholars and clinicians navigating the evolving frontier of ST in cancer. By illuminating past trends and current directions, it also points toward the future where spatially resolved molecular insights will likely become integral to both basic cancer biology and the personalized medicine paradigm.

2 Methodology

This study employed a retrospective bibliometric design to systematically analyze the global scientific output related to ST in oncology. The current study adheres to the preliminary guideline for reporting bibliometric reviews of biomedical literature (BIBLIO) to ensure that the findings are both credible and in alignment with emerging standards in bibliometric research [34].

2.1 Data source and justification

The Scopus database (Elsevier) was selected as the sole source of data for this bibliometric study. Scopus offers comprehensive indexing of scientific literature across disciplines, covering over 25,000 peer-reviewed journals and highly inclusive of PubMed and

Medline databases [35, 36]. It also provides robust citation metrics and facilitates high-precision Boolean searches and metadata exports compatible with leading bibliometric tools. Given its superior breadth and utility in bibliometric research, Scopus is widely accepted as a valid standalone platform particularly in emerging fields such as ST where publication volume remains within a manageable scale [37–39].

2.2 Search strategy

A comprehensive and structured search was conducted in April 2025. The complete search query used in the present study is shown below:

Keywords related to ST: TITLE-ABS ("spatial transcriptomics" OR "spatially resolved transcriptomics" OR "spatial gene expression" OR "spatial RNA-seq" OR "spatial RNA sequencing" OR "spatial transcriptome profiling" OR "in situ transcriptomics" OR "in situ sequencing" OR "seqFISH" OR "MERFISH" OR "Slide-seq" OR "Stereo-seq" OR "HDST" OR "Visium" OR "spatial omics" OR "tissue transcriptomics" OR "spatial single-cell transcriptomics" OR "spatial multi-omics" OR "tomo-seq" OR "laser capture microdissection RNA-seq" OR "LCM RNA-seq" OR "smFISH" OR "GeoMx DSP" OR "DBiT-seq" OR "Seq-Scope" OR "ZipSeq" OR "ISS transcriptomics" OR "molecular cartography" OR "spatial transcriptomic*").

Keywords related to oncology: TITLE-ABS (sarcoma OR cancer OR oncology OR carcinoma OR sarcoma OR malignancy OR malignancies OR metastasis OR metastatic OR "glioblastoma" OR "lymphoma" OR "multiple myeloma" OR "leukemia" OR tumor OR "breast cancer" OR "lung cancer" OR "colorectal cancer" OR "prostate cancer" OR "pancreatic cancer" OR "gastric cancer" OR "liver cancer" OR "esophageal cancer" OR "cervical cancer" OR "ovarian cancer" OR "endometrial cancer" OR "thyroid cancer" OR "renal cell carcinoma" OR "bladder cancer" OR "melanoma" OR "non-small cell lung cancer" OR "small cell lung cancer" OR "acute lymphoblastic leukemia" OR "acute myeloid leukemia" OR "chronic lymphocytic leukemia" OR "chronic myeloid leukemia" OR "multiple myeloma" OR "Hodgkin lymphoma" OR "non-Hodgkin lymphoma" OR "nasopharyngeal carcinoma" OR "oropharyngeal cancer" OR "laryngeal cancer" OR "salivary gland cancer" OR "oral squamous cell carcinoma" OR "basal cell carcinoma" OR "squamous cell carcinoma" OR "anaplastic thyroid carcinoma" OR "medullary thyroid cancer" OR "neuroblastoma" OR "retinoblastoma" OR "Ewing sarcoma" OR "osteosarcoma" OR "chondrosarcoma" OR "mesothelioma" OR "glioblastoma" OR "astrocytoma" OR "oligodendroglioma" OR "meningioma" OR "medulloblastoma" OR "pituitary adenoma" OR "Wilms tumor" OR "testicular cancer" OR "vaginal cancer" OR "vulvar cancer" OR "penile cancer" OR "anal cancer" OR "bile duct cancer" OR "cholangiocarcinoma" OR "gallbladder cancer" OR "small bowel cancer" OR "appendiceal cancer" OR "peritoneal cancer" OR "uterine sarcoma" OR "gestational trophoblastic disease" OR "Kaposi sarcoma" OR "cutaneous T-cell lymphoma" OR "Merkel cell carcinoma" OR "carcinoid tumor" OR "neuroendocrine tumor" OR "pheochromocytoma" OR "paraganglioma" OR "Burkitt lymphoma" OR "plasmacytoma" OR "mycosis fungoides" OR "sarcoma" OR "desmoplastic small round cell tumor" OR "hemangiosarcoma" OR "rhabdomyosarcoma" OR "adenoid cystic carcinoma" OR "clear cell carcinoma" OR "mucinous adenocarcinoma" OR "signet ring cell carcinoma" OR "large cell carcinoma" OR "inflammatory breast cancer" OR "triple negative breast cancer" OR tumor* OR metastasis OR metastatic) OR SRCTITLE(cancer OR onco* OR malignan* OR tumor or neoplasm*).

The final query was restricted to publications up to December 31st, 2024 and documents published in peer-reviewed scientific journals. No language or document type restrictions were used in the search query. However, the search query was restricted to documents containing the term "spatial transcriptomics" in any part of the record. Data export and analysis were carried out in the same day (June 26, 2025) to avoid any citation errors related to time of analysis. The full dataset of retrieved documents is found in Supplement 1.

2.3 Validation and quality check

To ensure the validity and accuracy of the retrieved dataset, a validation and quality check process was undertaken. To validate the search results both prolific journals and prolific authors were checked for their alignment with the field, and found to be relevant to the topic being investigated. Moreover, a review of the top most cited articles by two independent volunteers in the field of biomedical sciences revealed that all were directly related to ST in oncology providing strong evidence of the accuracy and validity of the search strategy. The exclusion of articles with keywords such as ST ecology or ST plants minimized false negative results. Finally, the use of title-abstract in search strategy minimized the incidence of false-negative results while keeping the false-positive results to the minimum because of the recent emergence and uniqueness of the topic. These measures collectively ensured that the final dataset accurately represented the research landscape and minimized methodological biases, reinforcing the credibility and comprehensiveness of the current bibliometric analysis.

2.4 Data export and preprocessing

All retrieved records were exported from Scopus in.csv format. Extracted metadata included article titles, abstracts, author names, institutional affiliations, journal names, keywords, citation counts, and funding sources. The dataset was cleaned, organized, and standardized using Microsoft Excel and R Studio prior to analysis.

2.5 VOSviewer mapping

Visual bibliometric analyses were performed using VOSviewer (version 1.6.20) [40, 41]. Four main types of network maps were constructed and presented in the current manuscript. In VOSviewer maps, nodes represent items (e.g. keywords, terms, countries) where larger nodes represent greater importance or higher frequency. Links between nodes represent relationships where thicker links represent stronger relationships. Distance between nodes represent relatedness where closer nodes represent stronger relatedness while farther nodes represent weaker or no relationship. Nodes colour represents clusters where nodes with similar colour represent a cluster. A cluster represents a group of items that are more strongly connected to each other than to others.

2.5.1 Author keywords co-occurrence map

Keyword co-occurrence map was generated for keywords with a minimum occurrence of at least five times, meaning that the keyword was mentioned in at least five papers, to reveal the hot topics in the field.

2.5.2 Overlay visualization (temporal map)

Overlay visualization maps were created to display the temporal dynamics of keyword emergence and evolution. Earlier research topics appeared in dark colors (blue/green), while more recent topics appeared in bright colors (yellow/orange)/This allowed identification of emerging trends and shifts in research priorities over time.

2.5.3 Co-occurrence maps of terms in titles/abstracts

This type of map visualizes the intellectual structure of a research field by identifying frequently occurring terms and their relationships. Clusters of related terms are color-coded revealing measure research themes or topics within the dataset. This method offers a powerful way to explore emerging trends, research focus areas, and the conceptual organization of the scientific literature. In the current study, the top 500 frequent terms in titles/abstracts of the retrieved articles were mapped.

2.5.4 Bibliographic coupling map

Bibliographic coupling maps show how journals or documents are related based on the number of shared references, if two sources cite the same reference, they are considered coupled. This reflects shared research focus or methodology.

2.6 Ethical considerations

This study was based solely on the analysis of publicly accessible bibliographic data. No human subjects, clinical data, or confidential information were involved. As such, ethical approval was not required.

3 Results

3.1 Growth of publications and citations

Based on the search methodology, 987 articles were published. The earliest publications in the field of ST in oncology were observed in 2016, marking the initial emergence of interest in this domain. From just 2 publications recorded in 2016 reaching 513 in 2024. Over this nine-yea period, the growth has been exceptionally rapid and exponential. The AAGR from 2016 to 2024 is estimated at approximately 3,175%, underscoring the explosive rise in research activity in this field. If this growth trend continues at a similar rate, projections suggest that the number of publications in 2025 could potentially exceed 1,000 publications, further cementing ST as a rapidly expanding and influential area in oncology research. In terms of scholarly impact, the total number of citations accumulated by these articles was 30,719. The highest number citations received by a single article was 2,011, indicating significant influence within the scientific community. On average, each article received approximately 31.1 citations, reflecting a strong citation performance and growing interest in ST-related oncology research. The H-index of the retrieved articles was 81. Table 1 shows the growth of publications and citations with time.

3.2 Authorship analysis and prolific institutions

A total of 7,262 author names were identified across the analyzed articles on ST in oncology. Each article was authored by an average of 11.4 authors. There were nine single-authored articles (0.9%) and 795 (80.5%) articles with five or more authors. There

Table 1 Growth of publications and citations on spatial transcriptomics in oncology (2016–2024)

Year	Number of publications (%)	Number of citations (%)
2016	2 (0.2)	7 (0.0)
2017	3 (0.3)	40 (0.1)
2018	5 (0.5)	94 (0.3)
2019	7 (0.7)	125 (0.4)
2020	20 (2.0)	444 (1.4)
2021	38 (3.9)	1221 (4.0)
2022	145 (14.7)	2948 (9.6)
2023	254 (25.7)	6070 (19.8)
2024	513 (52.0)	11,940 (39.0)
		7736 (25.3)*
Total	**987 (100%)**	**30,625 (100%)**

*citations were calculated up to the date of analysis in 2025

Table 2 Most prolific journals publishing on spatial transcriptomics in oncology

Rank	Journal Name	Number of publications (%)	SJR*	Subject Area#
1st	*Nature Communications*	81 (8.2)	4.761	Biochemistry, Biology, Genetics, Chemistry, and Physics,
2nd	*Frontiers in Immunology*	33 (3.3)	1.941	Immunology, Microbiology, Medicine
3rd	*Cancers*	22 (2.2)	1.462	Biochemistry, Medicine, Oncology
4th	*Briefings in Bioinformatics*	21 (2.1)	2.390	Biochemistry, Computer Sciences
5th	*Bioinformatics*	19 (1.9)	2.451	Biochemistry, Biology, Computer Science, Mathematics
5th	*Journal of Translational Medicine*	19 (1.9)	1.997	Biochemistry, Biology, Genetics, Medicine

*SJR: Scimago Journal Ranking. Used as a measure of quality. Obtained from www.scimagojr.com

#Information regarding subject areas of the journals were obtained from www.scimagojr.com

were 459 (46.5%) articles with 10 or more authors highlighting the collaborative and multidisciplinary nature of research in this field. Lundeberg, Joakim ($n = 16$ articles) (The Royal Institute of Technology, Stockholm, Sweden) seems to be the most prolific in the field, followed by Heiland, Dieter Henrik ($n = 13$ articles) (Friedrich-Alexander-Universität Erlangen-Nürnberg, Erlangen, Germany). However, the top five prolific institutions in the field were based in China: The Ministry of Education of the People's Republic of China, followed by Shanghai Jiao Tong University School of Medicine, Chinese Academy of Medical Sciences & Peking Union Medical College, Fudan University, and Chinese Academy of Sciences.

3.3 Prolific journals

An analysis of the retrieved articles on ST revealed that the publications were disseminated across 309 scientific journals, reflecting the interdisciplinary nature and wide-ranging impact of the field. Table 2 represents the top five prolific journals. Among these, *Nature Communications* stands out as the most prolific journal, having published 81 articles indicating its prominent role in advancing and broadcasting cutting-edge research at the intersection of molecular biology and oncology. *Frontiers in Immunology* follows with 33 articles, which highlights the increasing relevance of ST in tumor immunology-particularly in the context of spatially resolved immune profiling. Other notable journals include *Cancers* (22 articles), *Briefings in Bioinformatics* (21), *Bioinformatics*

(19), and the *Journal of Translational Medicine* (19). These journals collectively span diverse domains such as cancer biology, computational methods, and translational medicine, demonstrating the broad applicability and scientific interest in ST. The concentration of publications in both high-impact multidisciplinary journals and specialized outlets underlines the transformative role of ST in oncology, as well as the growing demand for spatially informed molecular insights across both basic and clinical cancer research.

3.4 Prolific countries and research collaboration

The analysis of the most prolific countries in ST in oncology reflects strong global concentration of output. China leads with 406 (41.1%) publications, followed closely by the United States with 362 (36.7%) publications. The United Kingdom (8.2%), Germany (7.9%), and Australia (3.7%) contribute notably, but to a lesser extent. This distribution highlights the major role of China and the United States in advancing research on ST in oncology while the European countries and Australia played a less prominent role. Table 3 shows the research output from the most prolific countries and the extent of inter and intra- country research collaboration for each prolific country. The analysis of research collaboration patterns reveals notable differences in the collaborative behavior of the most prolific countries. China, despite leading in total publications, demonstrates a predominantly domestic research approach, with 77.8% of the output resulting from intra-country collaboration and only 22.2% involving international partners. In contrast, the United States, while similarly prolific shows a more balanced profile with nearly half of its publications (47.5%) co-authored with international researchers reflecting its strong global research ties. The United Kingdom, Germany, and Australia exhibited a strong international research partnership in its publication.

3.5 Highly cited articles

Table 4 lists the top five cited articles. The most cited publication, authored by Stahl et al. (2016) and published in *Science* (2,011 citations), represents a landmark in the field [6]. This study introduced the original ST method, enabling the high-throughput visualization and quantification of gene expression across tissue sections while preserving spatial context. Building on this platform, Vickovic et al. (2019) advanced the technology by presenting a high-definition version of ST in *Nature Methods* (706 citations) [42]. This work significantly improved the resolution and molecular capture efficiency, allowing researchers to examine cellular- and subcellular-level gene expression patterns within tumor tissues. Among disease-focused applications, Wu et al. (2021) provided a comprehensive atlas of human breast cancer using integrated single-cell RNA sequencing

Table 3 Most prolific countries and research collaboration profile

Rank	Country	Number of publications (%)	Number of publications with international research collaboration (%)	Number of publications with intra-country research collaboration (%)
1st	China	406 (41.1)	90 (22.2)	316 (77.8)
2nd	United States	362 (36.7)	172 (47.5)	190 (52.5)
3rd	United Kingdom	81 (8.2)	63 (77.8)	18 (22.2)
4th	Germany	78 (7.9)	71 (91.0)	7 (9.0)
5th	Australia	37 (3.7)	22 (59.5)	15 (40.5)

Table 4 Top five cited articles on spatial transcriptomics in oncology

Rank	Title	Year	Source title	Cited by	Document Type	Citations per year
1st	Visualization and analysis of gene expression in tissue sections by spatial transcriptomics	2016	Science	2011	Review	223.7
2nd	Exploring tissue architecture using spatial transcriptomics	2021	Nature	789	Review	197.5
3rd	A single-cell and spatially resolved atlas of human breast cancers	2021	Nature Genetics	758	Article	189.5
4th	High-definition spatial transcriptomics for in situ tissue profiling	2019	Nature Methods	706	Article	117.7
5th	Integrating microarray-based spatial transcriptomics and single-cell RNA-seq reveals tissue architecture in pancreatic ductal adenocarcinomas	2020	Nature Biotechnology	620	Article	124.0

and spatial transcriptomics [43]. Published in *Nature Genetics* (758 citations), this study illuminated the spatial organization of diverse immune, stromal, and malignant cell populations within tumors. It revealed critical insights into how spatially distinct niches contribute to disease progression and therapeutic response, offering a model for similar spatially resolved cancer atlases. Similarly, Moncada et al. (2020) demonstrated the power of combining microarray-based spatial transcriptomics with single cell sequencing in *Nature Biotechnology* (620 citations) [44]. Focusing on pancreatic ductal adenocarcinoma, the authors uncovered spatial gene expression domains, cellular interactions, and histopathological correlates within one of the most challenging tumor types. Their integrative framework underscored the utility of ST in resolving complex tissue heterogeneity that traditional approaches may overlook. Complementing these original research articles, Rao et al. (2021) published a conceptual synthesis in *Nature* (789 citations), exploring how ST can be used to decipher tissue architecture [3]. The review emphasized the transformative potential regulatory networks, tumor-microenvironment communication, and context-specific gene programs. This article provided a unifying perspective on how ST technologies intersect with cancer biology and future diagnostic and therapeutic strategies.

3.6 Keywords co-occurrence map

Figure 1 is the VOSviewer co-occurrence map of author keywords with minimum occurrence of 10 ($n = 41$ author keywords). At the center of the map lies the keyword *"spatial transcriptomics"*, forming the central axis around which a variety of cancer-specific, methodological, and conceptual terms revolve. Prominently linked to the central keyword "spatial transcriptomics" are terms such as *"tumor microenvironment"*, *"immune microenvironment"*, *"cancer-associated fibroblasts"*, and *"tertiary lymphoid structures"*. The map also reveals a strong association between ST and various cancer types, including *"breast cancer"*, *"pancreatic cancer"*, *"colorectal cancer"*, *"glioblastoma"*, *"glioma"*, *"gastric cancer"*, *"hepatocellular carcinoma"*, *"prostate cancer"*, and *"melanoma"*. This indicates the broad application of ST across solid tumors, where it is used to uncover spatially distinct subpopulations, characterize tumor heterogeneity, and identify site specific biomarkers relevant for diagnosis, prognosis, and treatment stratification. On the technological front, keywords such as *"RNA-seq"*, *"single-cell"*, *"multi-omics"*, *"digital spatial profiling"*, and *"spatial proteomics"* underscore the integrative nature of ST.

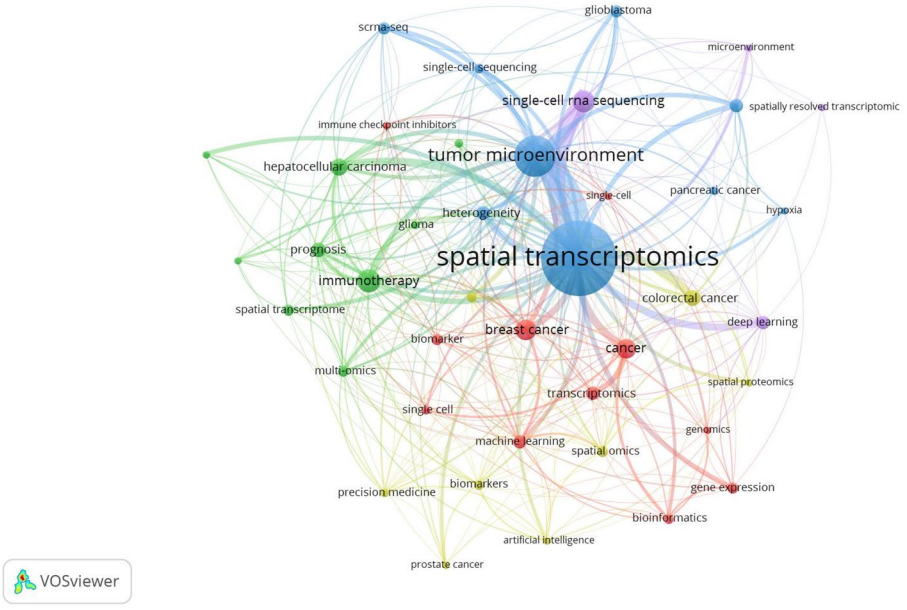

Fig. 1 Network visualization map of author keywords co-occurrences showing research hotspots as large nodes. Only author keywords with a minimum occurrence of 10 ($n = 41$) were mapped (Figure made by author)

These terms reflect the growing trend of combining ST with single-cell sequencing and multi-omics technologies to achieve a multidimensional understanding of the tumor microenvironment. Additionally, the presence of *"machine learning"*, *"deep learning"*, *"bioinformatics"*, and *"genomics"* emphasizes the reliance on computational methods to analyze and interpret the complex, high dimensional data generated through spatial profiling. Conceptual terms like *heterogeneity*, *tumor heterogeneity*, *prognosis*, *precision medicine*, *immune checkpoint inhibitors*, and *biomarkers* reveal the clinical and translational implications of ST. Other terms such as *gene expression*, *transcriptomics*, *microenvironment*, *spatially resolved transcriptomics*, and *immune checkpoint inhibitors* reaffirm the interdisciplinary nature of the field, integrating molecular biology, cancer immunology, and computational sciences.

3.7 Overlay visualization map

Figure 2 is an overly visualization map of the 41 most frequent author keywords. The map provides the temporal evolution of research in the field. At the center of the network, the keywords *spatial transcriptomic*, *tumor microenvironment*, and *breast cancer* dominate, indicating their foundational role in early ST technology research. These terms appear in darker shades ranging from deep green to blue signifying their prominence in studies published primarily around 2022 and early 2023. This early body of work laid the groundwork for using ST to investigate intertumoral heterogeneity, spatial immune architecture, and the microenvironmental influences that shape tumor progression, particularly in breast cancer, one of the first malignancies extensively profiled using ST. As the field matured, there was a notable integration of advanced technologies and analytical approaches, reflected by terms such as *RNA-seq*, *multi-omics*, *machine learning*, *deep learning*, *genomics*, and *bioinformatics*. These keywords, shown in moderate green and teal colors, highlight the methodological expansion of ST to include computational pipelines and integrative platforms capable of handling high-dimensional,

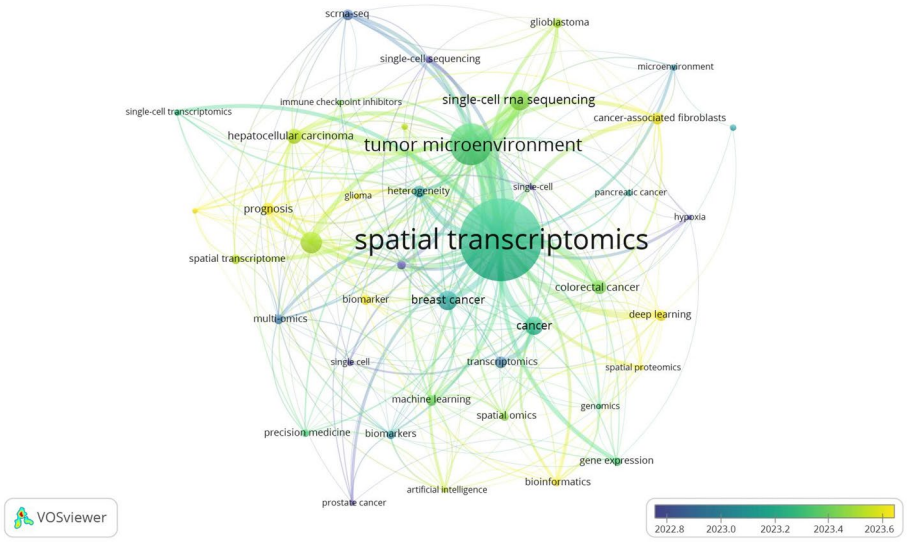

Fig. 2 Overlay visualization map of author keywords co-occurrences showing the temporal evolution of keywords in the retrieved literature. Only author keywords with a minimum occurrence of 10 ($n = 41$) were mapped. Yellow nodes represent most recently published topics. (Figure made by author)

spatially resolved datasets. These tools have been critical in interpreting the complex spatial landscapes of gene expression within tumors. In contrast, keywords appearing in bright yellow to light green tones represent emerging and current research themes, particularly from mid to late 2023. These include *cancer-associated fibroblasts*, *gastric cancer*, *glioma*, *prognosis*, *precision medicine*, and *immune checkpoint inhibitors*. Their recent appearance reflects a growing interest in translating ST insights into clinically actionable knowledge. For example, mapping cancer-associated fibroblast distributions or immune checkpoint expression within spatial contexts may offer novel avenues for targeted therapy and biomarker development. Additionally, keywords such as *spatial proteomics*, *digital spatial profiling*, and *spatially resolved transcriptomics* point to a recent technological diversification. These approaches extend the capabilities of traditional ST by enabling spatial analysis of proteins and integrating multiple molecular layers, enhancing the resolution and clinical relevance of tissue profiling. Disease specific terms such as *pancreatic cancer*, *colorectal cancer*, *glioblastoma*, *melanoma*, and *hepatocellular carcinoma* further demonstrate the broadening application of ST beyond breast cancer. These keywords are closely linked with concepts like *tumor heterogeneity*, *biomarkers*, and *prognosis*, indicating an intensified focus on uncovering spatially defined molecular features that can guide therapeutic decisions.

3.8 Co-occurrence map of frequent terms in titles/abstracts

Figure 3 presents a comprehensive visualization of 500 frequently occurring terms in the abstracts of the retrieved articles. It reveals three major thematic research clusters that highlight the multidimensional nature of this rapidly advancing field, centered around the term "transcriptomic," which acts as the conceptual hub connecting biological, technological, and spatial domains. The first cluster, visualized in red, is primarily focused on the tumor microenvironment and immune-related transcriptomic signatures. It encompasses key terms such as "macrophage," "immune checkpoint inhibitor," and "tumor growth," reflecting the widespread use of ST to dissect the spatial organization

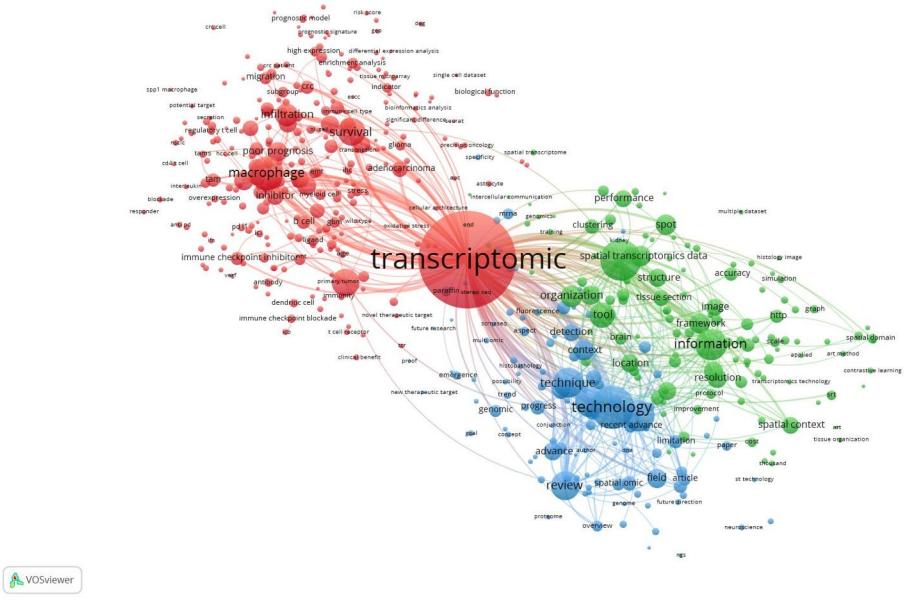

Fig. 3 Network visualization map of the top frequent terms in titles/abstracts ($n = 500$). Each cluster represented a research theme

and functional states of immune cells within tumors. This cluster underscores the application of ST in elucidating mechanisms of therapy resistance, tumor progression, and immune evasion, particularly in the context of immunotherapies targeting PD-1/PD-L1 and other checkpoint pathways. The second cluster, represented in green, centers of spatial resolution, imaging integration, and spatial gene expression profiling. Terms like "gene expression, "spatial context," "resolution", and "accuracy" highlight the technical aspects of capturing gene expression patterns across tissue architecture. This cluster emphasizes how ST enables high-resolution spatial mapping of transcriptional activity, facilitating the correlation of molecular data with histological and anatomical features. Such integration is pivotal for understanding intratumoral heterogeneity, tumor-stroma interactions, and the localization of distinct cellular populations within the tumor niche. The third cluster, shown in blue, reflects the technological and methodological innovations driving the field. Terms such as "technology", "review", "spatial omic", and "progress" point to the continuous development and refinement of ST platforms and analytical approaches. This includes advancements in next-generation sequencing, spatial barcoding, and multi-omics integration, as well as the emergence of computational tools that enhance data accuracy, reproducibility, and interpretability. Together, these clusters form and interconnected network that defines the current landscape of ST in oncology. The centrality of "transcriptomic" signifies the foundational role of gene expression profiling, while the tight linkages between immune biology, spatial analytics, and technological progress illustrate the interdisciplinary nature of the field. Ultimately, the map demonstrates how ST is transforming cancer research by enabling spatially resolved molecular insights, leading to more precise diagnostics, prognostics, and therapeutic strategies tailored to the spatial complexity of tumors.

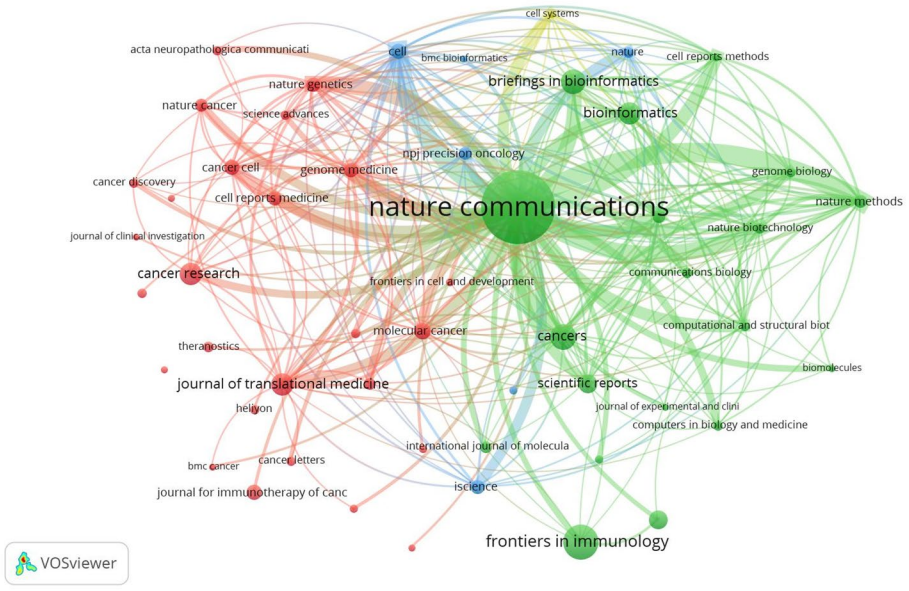

Fig. 4 Bibliographic coupling of journals with a minimum publication of five ($n = 52$). Nodes with similar color represent journals that are bibliographically coupled

3.9 Bibliographic coupling (share similar reference list)

Figure 4 is the bibliographic coupling map of journals, based on a minimum threshold of five publications ($n = 52$ journals). The green cluster included journals such as *Nature Communications*, *Frontiers in Immunology*, *Nature Methods*, and *Scientific Reports* that commonly publish work at the intersection of technology development and biological application, highlighting their roles as central platforms for disseminating research on novel ST tools, high-resolution imaging techniques, and their deployment in cancer systems biology. The red cluster included journals such as Cancer Cell, Cancer Research, and Clinical Cancer Research that represent the translational oncology and clinical application domain of ST. These journals focus on applying spatial gene expression data to understand therapeutic response, resistance mechanisms, and immune evasion in solid tumors.

4 Discussion

The current bibliometric study sought to systematically explore the landscape surrounding scientific literature on ST in oncology.

With the exponential rise in research output, the study highlights not only the rapid adoption of ST technologies, but also their deepening relevance in cancer biology. The remarkable growth of ST research in oncology mirrors the field transformative potential and reflects both technological maturation and clinical demand. Since the foundational work by Stahl et al. (2016) [6], ST technologies have diversified into multiple platform classes, including array-based capture (e.g., 10x Visium), in situ sequencing approaches (e.g., MERFISH, seqFISH), and high-resolution imaging-based transcriptomics [5, 45–48]. This technological diversification has catalyzed rapid adoption in oncology, particularly in TME research, where spatial context is indispensable for understanding immune infiltration, stromal compartmentalization, and clonal heterogeneity [44, 49]. The bibliometric surge therefore mirrors the shift from bulk RNA sequencing toward spatially

resolved, systems-level oncology. Importantly, this expansion is not purely methodological—it reflects a conceptual reorientation of cancer biology toward spatial ecology and tumor ecosystem modeling [50].

The analysis unveiled key contributing countries, leading journals, highly cited publications, and evolving thematic clusters. The central findings in visualization maps emphasized the growing prominence of ST in mapping tumor heterogeneity, tumor microenvironment, immune infiltration, and therapy resistance, with extensive applications across a wide range of cancers. Overlay map revealed a clear temporal shift, from foundational research in breast cancer and ST technology to more recent emphasis on immune checkpoint modulation, spatial proteomics, and prognosis. Visualization maps revealed that this field is anchored at the intersection of molecular biology, computational analysis, and translational oncology, reflecting its potential to revolutionize precision medicine.

One of the main co-occurring terms in the retrieved literature was TME, a heterogenous and dynamic milieu comprising immune cells, stromal elements, vasculature, and cancer cells [51]. ST enables spatial mapping of TME components, and their interactions, shedding light on critical processes, such as immune evasion, angiogenesis, hypoxia, and stromal remodeling [52, 53]. The co-localization of immune checkpoint expression, tertiary lymphoid structures, and cancer-associated fibroblasts can be captured at high resolution, allowing for precise characterization of immune-inflamed versus immune-excluded tumors [54, 55]. These spatial insights are essential for understanding why certain tumors respond to immunotherapy while other do not [56–59]. Additionally, ST helps reveal how spatial niches within the TME support stemness, metastasis, or resistance, offering a roadmap for targeting TME in a spatially tailored manner. As cancer therapies increasingly aim to remodel the TME, ST stands as an indispensable tool for guiding and monitoring therapeutic efficacy [54, 56, 60].

Co-occurrence map of author keywords showed that ST has been widely applied across a range of malignancies with breast cancer, glioblastoma, colorectal cancer, pancreatic cancer, melanoma, and hepatocellular carcinoma being among the most studied. In breast cancer, ST has illuminated spatial gradients in immune infiltration and hormone receptor signaling leading to refined subtyping and treatment stratification [16, 61–64]. In glioblastoma, ST has mapped hypoxic niches and infiltrative tumor fronts, revealing molecular determinants of invasiveness and treatment resistance [65–68]. Studies in pancreatic ductal adenocarcinoma have identified spatial gene expression domains linked to stromal interactions, and immune evasion, critical for a cancer known for its dense desmoplastic stroma [44, 69–71]. These disease specific applications not only validate the versatility of ST, but also showcase its utility in uncovering novel spatial biomarkers and therapeutic targets unique to each cancer type.

By enabling the spatially resolved profiling of gene expression, ST bridges the gap between the histopathology and molecular biology, leading to more tumor classification and risk assessment. It supports precision oncology by guiding therapy based on the spatial context of biomarkers and signaling pathway. For example, ST can identify patients likely to benefit from immune checkpoint inhibitors by mapping spatial patterns of immune activation and suppression [21, 56, 65, 72, 73]. It also contributes to therapy development by revealing spatially distinct resistance mechanism and informing combination strategies tailored to microenvironment architecture [21, 65]. Moreover, as

ST is integrated with AI-driven digital pathology, multi-omics platform, and single cell technologies, it will drive next-generation clinical tools for real time decision support and personalized intervention [74]. Ultimately, ST stands not only as a research tool, but as a clinical asset, relapsing the future of oncology toward spatially informed precision medicine.

4.1 Future technologies

At the technical level, the evolution of ST will be driven by efforts to overcome the persistent trade-off between spatial resolution and transcriptomic breadth. Emerging platforms aim to achieve true single-cell or subcellular resolution while maintaining transcriptome-wide coverage [75, 76]. Parallel developments in three-dimensional spatial reconstruction and serial section integration promise to better capture tumor architecture beyond two-dimensional sampling [77]. A second major frontier involves multi – omics integration, combining ST with spatial proteomics, epigenomics, and metabolomics to construct comprehensive tumor ecosystem maps [78]. Such integration is essential for resolving functional states rather than merely transcriptional signatures. Finally, artificial intelligence (AI) and machine learning will further accelerate this transformation. Deep – learning algorithms for image segmentation, cell-type deconvolution, and spatial pattern recognition are increasingly integrated into ST workflows [79, 80]. AI-assisted analytics are expected to reduce subjectivity in histomorphometric alignment and enable scalable, automated spatial interpretation.

4.2 Clinical translation

At the clinical application level, ST holds transformative potential for precision oncology. Spatial mapping of tumor immune interactions may refine immunotherapy response prediction and resistance profiling [50]. Intraoperative spatial molecular guidance represents a promising avenue, where real-time or near – real – time spatial profiling could assist margin delineation and surgical navigation. Additionally, longitudinal spatial monitoring through repeated sampling may enable dynamic tracking of clonal evolution and therapy – induced remodeling of the tumor microenvironment [81]. However, for ST to transition into routine clinical workflows, improvements in cost efficiency, reproducibility, and turnaround time remain critical.

4.3 Policy, standardization, and regulatory integration

Beyond technological and clinical innovation, sustainable integration of ST into oncology requires coordinated policy level advancements. Standard data formats, interoperable computational pipelines, and harmonized quality-control benchmarks are essential to ensure reproducibility across platforms [78]. Data sharing initiatives and cross-institutional repositories will facilitate validation and comparative analyses, while regulatory frameworks must evolve to define clinically actionable thresholds and validation pathways for spatial biomarkers. Without such standardization, translational enthusiasm may outpace regulatory readiness, limiting clinical adoption. Thus, the future of ST in oncology will depend not only on technological sophistication but also on coordinated ecosystem level alignment among researchers, clinicians, industry stakeholders and regulatory bodies.

4.4 ST technologies drawbacks and limitations

Despite its transformative potential, ST faces a fundamental technological constraint: the trade-off between spatial resolution and transcriptomic breadth. Array-based platforms (e.g., Visium) provide whole-transcriptome coverage but at a spot resolution of 55–100 μm, meaning each capture spot contains multiple cells, limiting true single-cell resolution [6, 82–86]. Conversely, imaging-based methods such as MERFISH and seqFISH achieve near single-cell or subcellular resolution but typically rely on predefined gene panels, thereby restricting transcriptome breadth [75, 76]. This inherent trade-off between spatial resolution and transcriptomics throughput substantially shapes emerging research directions and methodological preferences within the field. Studies emphasizing TME architecture often favor high-resolution imaging methods, whereas tumor subtype stratification studies tend to use broader, lower-resolution array platforms [77, 87, 88]. The bibliometric clustering observed in our analysis likely reflects this methodological bifurcation. Importantly, no current platform fully reconciles spatial resolution, transcriptome depth, cost efficiency, and scalability simultaneously. Thus, technological constraints partially explain thematic fragmentation within the field.

High-resolution ST platforms often rely on pre-selected gene panels that enhance sensitivity and spatial precision, but these panels restrict analyses to selected transcripts, potentially overlooking rare drivers, low-abundance regulators, or non-coding RNAs that may critically influence tumor progression and therapeutic resistance [75, 76]. To overcome this limitation, many studies integrate ST with single-cell RNA sequencing (scRNA-seq), expanding transcriptome coverage and promoting multimodal "multi-omics" strategies [44, 78]. Spatial annotation presents further methodological challenges, as aligning transcriptomic signals with histological images relies on manual or semi-automated segmentation and morphometric interpretation, introducing subjectivity, particularly in heterogeneous tumor regions [79]. Although computational deconvolution tools such as cell2location and SPOTlight attempt to resolve mixed-cell signals, they depend on reference datasets and modeling assumptions that may propagate uncertainty [80, 89]. Additionally, ST captures only two-dimensional snapshots of intrinsically heterogeneous three-dimensional tumors, with variability arising from sampling and tissue processing [81], while emerging 3D reconstruction methods remain technically demanding [77]. Despite promising applications in immunotherapy stratification and resistance mapping, clinical translation is still constrained by cost, analytical complexity, lack of standardized workflows, and evolving regulatory frameworks. The observed research clustering can be explained by the technological and translational limitations, which reflect platform diversification, multimodal integration, and the growing reliance on AI-assisted spatial analytics in oncology.

4.5 Limitations of the current analysis

The current study demonstrated several strengths including comprehensiveness and integration of visualization maps to elucidate evolution, dominant topics, and research themes dominating the field of ST in oncology. However, the study is not without limitations. First, it relies solely on Scopus database, therefore certain publications on the topic might be missed given that certain journals are not indexed in Scopus. Second, the study lacks clinical outcome data, which limits its translational interpretability. Thirdly, the field of ST is rapidly evolving and the static nature of bibliometric snapshots might

not fully capture real time technological breakthroughs or shifts in clinical applicability. Future studies might benefit from the integration of biological metadata with real world clinical outcomes.

5 Conclusion

In conclusion, ST represents a paradigm shift in oncology, one that bridges molecular biology with spatial histology, enabling a more complete, context-aware understanding of cancer. As the technology matures and becomes clinically accessible, it holds the promise to more precision oncology, from a molecular to a spatially informed era. Finally, as ST advances, the integration into oncology promises to transform public health by enabling spatially informed cancer diagnostics, individualized therapy planning, and more equitable access to precision medicine. This evolution aligns with broader societal goals to reduce cancer burden, and improve clinical outcomes through innovation and scientific collaboration.

Supplementary Information

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Supplementary Material 1.

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Author contributions
M. S started the idea, did the analysis, and wrote the manuscript.

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Data availability
All data, including the search query, are available and can be provided upon personal request from the authors.

Declarations

Ethics approval and consent to participate
Not applicable. No IRB was required for the current study since all data were obtained from Scopus database and no patients or human subjects were involved directly in the study. Not applicable. No humans or animals or any biological samples were involved in the current study and therefore no consent to participate were collected.

Consent for publication
Not applicable. This study did not involve any individual person's data in any form (including individual's details, Figures, Diagrams, Videos, Images) and therefor consent to publish was not required.

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The author has no competing interests to declare that are relevant to the content of this article.

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