Top-100 Most-cited Articles on Esophageal Cancer: A Bibliometric Analysis

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Research

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Abstract

Background A citation classic is a highly cited work in a field and regarded as an influential contribution to the field's advancements and literature. Analyzing citation classics and top articles promotes the recognition of research trends within a field. We present the results of the first analysis to identify the 100 most frequently cited research studies on esophageal cancer or esophagogastric junction cancer using the bibliometric analysis method.

Method We searched the Web of Science on September 24, 2020. Articles were listed in descending order by the total number of citations, and the top-100 most-cited original articles on esophageal cancer or esophagogastric junction cancer were extracted and evaluated.

Results The top-100 citation classics in esophageal cancer were published from 1981 to 2018. A significant increase was found in the number of citation classics from the early 1990s to the late 2000s, which was paralleled by an increase in randomized controlled trials focusing on the clinical treatment of tumors. The medians of the total and annual citations in our analysis were 444.50 (interquartile range [IQR] 346.25-684.50) and 30.08 (IQR 19.10-56.60), respectively. The majority of articles were published in the *Journal of Clinical Oncology* (n=26), originated in the United States (n=38) and focused on clinical therapies (n=59). The median impact factor of the journals was 27.603 (IQR 9.727-32.956).

Conclusion Our analysis provides a historical perspective on the scientific progress of esophageal cancer and contributes to the recognition of important advances in this specialty.

Background

Esophageal cancer is the eighth most common cancer and the sixth cause of death by cancer worldwide according to the Global Cancer Observatory 2018^[1]. The incidence of esophageal cancer is calculated by geographical distribution. Southeast Asia, especially China, is a high incidence area, with an estimated 477,900 new cases and 375,000 deaths in 2015 alone^[2]. Due to the anatomic location of the esophagus, its lymphatic drainage ranges from the lower neck to the abdominal trunk, and laterally along the esophageal wall to the surrounding trachea, heart, large vessels and vertebral body. Therefore, its recurrence and metastasis rates are very high and the overall survival is poor. A large number of research studies have been conducted in recent years with the intent to improve the overall survival rate of esophageal cancer. With the development of radiation technology and new drugs, the multidisciplinary comprehensive treatment of this cancer has gradually matured.

Retrospective analyses of historical trends in research on esophageal cancer and the examination of the literature that has had a significant impact on the field can provide insight into scientific progress over time and identify areas of greatest interest along with understudied areas. Frequently cited works often represent landmarks in the literature that have gained recognition by researchers in the field and laid the groundwork for important clinical research findings^[3]. Bibliometric analyses of a discipline's most-cited articles, also called citation classics^[4], provide insight into research areas that have influenced the discipline. The number of citations and citation density (i.e., annual number of citations since the date of publication) can be used as an indicator of the influence of a certain publication on a respective field^[5]. Examining citation classics in a field facilitates the identification of important literature and provides insight into research trends over time. Although articles on citation classics in the areas of critical care medicine^[6], pituitary adenoma^[7], neuroimaging^[8], neuro-oncology^[9], ischemic stroke^[10], obstetrics and gynecology^[11] and urogynecology^[12] have recently been conducted using bibliometric analysis, no studies have examined the research literature on esophageal cancer. Therefore, this study aimed to analyze the 100 most-cited original articles in the field of esophageal cancer using the bibliometric analysis method and to provide guidance to investigators in this field.

Materials And Methods

Search Strategies and Inclusion Criteria

Web of Science Core Collection includes the Science Citation Index Expanded as well as other citation indexes. We searched the Web of Science Core Collection (Clarivate Analytics) on September 24, 2020 using the following terms: [(esophageal cancer) OR (esophagogastric junction cancer) OR (esophageal carcinoma) OR (esophagogastric junction carcinoma) OR (esophagus tumor)]. Incites Journal Citation Reports (JCR) was used to identify the journal impact factors.

Search results were sorted by the total number of citations in descending order. Articles were first screened by title for their relevance to the esophagus, and the remaining articles underwent a review of the abstract or the full text. Only original articles were included. Systematic reviews, secondary analyses (e.g., meta-analyses), case reports or case series, meeting reports and guidelines and consensus statements were excluded from the study because they did not reflect trends in esophageal cancer research. After two independent authors screened the studies, the top-100 most-cited articles were included in the final analysis.

Approval from an ethics committee to conduct this research was not required because this study did not involve the collection of original data from humans or animals or interventions.

Data Collection

The following parameters were extracted from each article: article title, country of origin, year of publication, journal name, journal impact factor (IF; Data were collected from Incites Journal Citation Reports for the year 2019), total number of citations, number of annual citations, tumor type, study design, topic theme and type of treatment. Country of origin was based on the affiliation of the corresponding author. If there were multi-corresponding authors in an article, the first corresponding author's country was collected. The number of annual citations was calculated by dividing the total number of citations by the number of years, which was from the date of publication to 2018. Study designs included the randomized controlled trial (RCT), prospective study, retrospective study, laboratory investigation and observational study (i.e., cross-sectional study, case-control study or cohort study). In order to assess trends in the literature, articles were classified by their primary themes, which included therapies, pathogenesis or clinical presentation and imaging. Therapy-related articles were subdivided into surgery, chemotherapy, radiation therapy, chemotherapy combined with radiotherapy (i.e., chemoradiotherapy), new agents (i.e., immunotherapy) and metal stents.

Statistics

Data are presented using descriptive statistics. Spearman's correlations between continuous variables that were not normally distributed were analyzed using the Statistical Package for Social Sciences software version 23.0 (SPSS Inc., Chicago, IL). A p-value < 0.05 was considered statistically significant.

Results

The 100 most-cited articles in the field of esophageal cancer or esophagogastric junction (EGJ) cancer and the number of citations are presented in Table 1. The total number of citations of the 100 articles ranged from 3,641 to 314, with a median of 444.50 total citations (interquartile range [IQR] 346.25-684.50) and a median of 30.08 annual citations (IQR 19.10-56.60). The top-3 ranked articles were clinical studies, whose themes were related to perioperative chemotherapy^[13], postoperative chemoradiotherapy for gastric or EGJ adenocarcinoma^[14] and preoperative chemoradiotherapy for esophageal squamous cell carcinoma (ESCC) or adenocarcinoma^[15].

Source

The 100 most-cited articles were published in 27 different journals (Table 2).

The Journal of Clinical Oncology (n=26), *Annals of Surgery* (n=10) and *New England Journal of Medicine* (n=9) published the top-3 ranked articles. Journals were classified into five main categories. Fifty-one articles were published in oncology-specific journals, 17 articles in general-specialty journals, 15 articles in surgery-specific journals, 8 articles in gastroenterology and hepatology-specific journals and 9 articles in various other journals. The journal impact factors ranged from 2.234 to 74.699 (median, 27.603; IQR 9.727-32.956). A moderately strong correlation was found between impact factor and total number of citations reported in a given journal (Spearman's coefficient = 0.552, p < 0.001), and the number of annual citations strongly correlated with the total number of citations (Spearman's coefficient = 0.715, p < 0.001).

The majority of the articles originated in the United States (US) with 38 publications, Japan and Germany, both with 15 publications and the United Kingdom with 9 articles, which was ranked third (Figure 1).

Study Design and Themes

The most frequent study design was the RCT (n=42), followed by the prospective trial (n=17), retrospective study (n=17) and laboratory investigation (n=15). Observational studies accounted for only 9% (9/100) of all studies.

The most common themes were therapies (n=59), followed by pathogenesis or clinical presentation (n=34) and imaging (n=7). Among the therapeutic trials, 22 pertained to chemotherapy, 19 to chemoradiotherapy and 14 to surgery (Figure 2).

Therapies

The citations were categorized into five types of treatment based on the treatment's purpose, which represented the main areas of research in esophageal cancer: (1) definitive treatment (n=20), (2) perioperative treatment (n=3), (3) preoperative treatment (n=19), (4) postoperative treatment (n=2) and (5) salvage treatment (n=15).

The largest category was radical treatment (20 articles). Six articles on the use of radical chemoradiotherapy for ESCC and/or esophageal adenocarcinoma were published in 1997-2007. Among these, one study published in 1999 explored the T4 and/or M1 lymph node in ESCC. Three citation classics, the RTOG 85-01 (two articles published) and RTOG 94-05 studies, reported the effect of concurrent chemoradiotherapy for locally advanced esophageal cancer (1997-2002). Two studies examined chemoradiotherapy with/without surgery in patients with ESCC (2005-2007) and the remaining 14 articles were related to surgery (1991-2012). Two articles were published in 1991 and 1995 on surgical approaches for esophageal cancer in Japan (i.e., three-field versus two-field lymphadenectomy). Five studies focused on the prognostic factors after surgery for esophageal cancer, including the classification of EGJ, surgical technique, histologic tumor type, tumor length, lymph node status and the number of lymph nodes removed (2000-2008). Four studies focused on the very early stage of esophageal cancer (2005-2008) and three articles pertained to minimally invasive esophagectomy (2006-2012). Three articles were about perioperative chemotherapy versus surgery alone for patients with locally advanced adenocarcinoma of the esophagus, EGJ and gastric cancers and ESCC (1988-2011).

Only two articles pertained to postoperative therapy. Macdonald et al. reported advantages of adjuvant chemoradiotherapy for adenocarcinoma of the esophagus or gastric cancer, and Ando et al. studied the value of postoperative chemotherapy for ESCC (2001-2003).

Seven studies explored optimal salvage chemotherapy regimens for advanced gastric cancer and/or esophageal cancer, especially adenocarcinoma (1997-2014). The article (known as the ToGA study), on the use of trastuzumab combined with chemotherapy for the treatment of HER2-positive advanced gastric or EGJ cancer, was published in 2010. The article (known as the REAL-3 study) on the use of panitumumab, an epidermal growth-factor receptor (EGFR) inhibitor, combined with chemotherapy in patients with EGFR positive advanced esophagogastric cancer, was published in 2013. Three articles assessed the value of the vascular EGFR inhibitor in patients with advanced gastric cancer during 2014-2016. The use of immunotherapy for advanced gastric and EGJ cancers has increased in recent years, producing two recent articles. One 1993 study reported the use of metal stents for palliation of esophageal obstruction.

Nineteen citations pertained to preoperative treatment. Among these, 12 articles reviewed the use of neoadjuvant concurrent chemoradiotherapy for esophageal cancer, 6 articles were about preoperative chemotherapy and 1 examined the value of preoperative radiotherapy.

Pathogenesis or Clinical Presentation

A total of 34 citations focused on tumor pathogenesis or clinical presentation. Among these, 16 reported clinical or pathological characteristics of esophageal cancer. Among the 18 pathogenesis-related studies, 9 focused on the etiology of exogenous factors, such as obesity, alcohol intake, tobacco smoking, nutrition deficiencies, biotoxins, medicines and gastroesophageal reflux. The remaining 9 articles were related to gene levels, such as *p53*, *microRNA*, *SOX2*, *MTS1/CDK4I* and *PLCE1*.

Imaging

Seven articles pertained to imaging (2000-2011). Among these, 5 explored the predictors of response to chemotherapy or chemoradiotherapy among patients with esophageal cancer using positive emission tomography. One study investigated the utility of positive emission tomography for the staging of patients with potentially operable esophageal carcinoma. The remaining study focused on the early detection of superficial squamous cell carcinoma in the head and neck regions and esophagus using narrow band imaging.

Temporal Trends

There has been a sharp increase in the number of cited articles since the early 1990s. The peak period with the largest number of cited articles was 2005-2008 (n=23), with a steep decline afterwards (Figure 3A). This increase was largely attributable to studies pertaining to therapies (Figure 3B), especially those focusing on surgery, chemoradiotherapy and chemotherapy (Figure 3C). Furthermore, immunotherapy, which was a promising treatment was developing rapidly and produced 2 of the most-cited articles within two years. Since the 1990s, RCTs have increased continuously and steadily. Prospective studies have also increased gradually with a decrease in retrospective studies, which finally reached its peak during 2005-2008 (Figure 3D).

Discussion

Citation analysis can be a useful tool for identifying publications that have a high scientific impact. A bibliometric analysis of the most-cited articles highlights the most influential articles, trending topics and prolific institutions that contribute to the evolution of a scientific subspecialty. Our study depicts the top 100 citation classics that have played a significant role in bolstering progress in the field of esophageal cancer.

In our analysis, the types of pathology found in the patients in most of the studies were adenocarcinoma with or without squamous cell carcinoma, while some of the other studies involving esophageal squamous cell carcinoma were from Japan and a few were from Germany and France. This

finding also reflects the characteristics of the distribution of esophageal cancer. The research mostly pertained to clinical treatment, followed by pathogenesis or clinical presentation. With developments in the field of medicine, the numbers of RCTs and prospective studies of multidisciplinary treatments are booming, thereby providing more evidence-based rationales for clinicians' treatment decisions.

Analyses of the citation classics showed that more than half of the 100 most-cited articles were published in oncology-specific journals, and 45% of the articles were published in journals with very high impact factors, including *Japan Clinical Oncology*, *Annals of Surgery* and the *New England Journal of Medicine*. Most of the remaining articles were published in journals with a relatively low impact factor. Thus, the median impact factor was 27.603. Although the articles published in top journals are cited more frequently, the articles published in top journals, such as the *New England Journal of Medicine* are relatively rare. Therefore, the correlation between the impact factor and total number of citations of classic papers in this study was not strong. However, a strong correlation was found between the annual and total numbers of citations, indicating the influence of the research reported in the classic papers in the field is persistent and has not been diluted by time.

Most of the classic citations were from the US, which is consistent with the results of most other cancer-related studies. This likely reflects a bias of US authors to submit studies for publication in US-based journals and of US reviewers toward articles from authors and studies based in the US^[16]. Of note, we did not identify articles in languages other than English; thus, we have not represented the entire body of literature that could possibly be relevant to the field of esophageal cancer. That said, this same bias toward English-language articles, made clear by past research revealing that non-English-language articles have low acceptance and citation rates, reduces the likelihood of increasing the number of citations in non-English-language articles^[17, 18].

The most-cited articles focused mostly on optimal clinical treatment in RCTs along with therapeutic studies. Among these, the classic articles on radical chemoradiotherapy were the RTOG 85-01^[19, 20] and RTOG 94-05 studies,^[21] which established guidelines for locally advanced esophageal cancer. The studies from Japan revealed that three-field lymphadenectomy has better local control and overall survival than two-field lymphadenectomy^[22-25]. However, three-field lymphadenectomy could only be performed in a hospital; thus, it has not been adopted worldwide. Furthermore, the persistence and the recurrence rate of esophageal cancer were high (24-58%^[19-21, 26-30]), and the 5-year overall survival was low (5-25%^[31]) after radical chemoradiotherapy or surgery alone. This finding has promoted multidisciplinary treatment studies, which include surgery combined with chemotherapy or chemoradiotherapy^[32-37]. Due to the backwardness of radiotherapy technology and the high incidence of surgical complications in earlier years, most of the prospective preoperative chemoradiotherapy studies had insufficient sample sizes or controversial results. In 2012, a Dutch study (known as the CROSS study) confirmed that the use of neoadjuvant chemoradiotherapy for esophageal cancer has better overall survival and disease free survival than surgery alone, which had been recommended as standard treatment for those with locally advanced esophageal cancer^[15]. The long-term follow-up results further confirmed the value of preoperative chemoradiotherapy^[38]. Since then, neoadjuvant chemoradiotherapy for esophageal cancer has entered a new era.

Three citation classics in perioperative chemotherapy mainly focused on adenocarcinoma of the esophagus or stomach^[13, 39, 40], which might not have been suitable for esophageal squamous cell carcinoma. Similarly, the RCT of postoperative chemoradiotherapy also focused on adenocarcinoma of the esophagus or stomach^[14]. Postoperative chemotherapy only improved the disease free survival for patients with ESCC^[41]. Based on the citation classics, no recommendations have been made for adjuvant therapy after radical esophagectomy for ESCC.

Salvage treatment studies have gradually changed from chemotherapy^[42-44] to targeted therapy^[45-48], with the discovery of molecular checkpoints. Of note, immunotherapy has also attracted much attention in recent years, opening a new door to the treatment of esophageal cancer. At present, the role of immunotherapy in neoadjuvant, adjuvant or radical therapy is still unclear, and many studies are ongoing.

Although bibliometric analysis can provide a comprehensive understanding of the important studies on esophageal cancer, citation analysis has drawn criticism owing to the effects of time^[16, 49, 50]. Some hypothesize that older studies have more time to accumulate citations, making them more likely to end up on the list of citation classics. Articles that have become "landmark" studies may be cited less often over time as their conclusions become more commonplace, a phenomenon referred to as "obliteration by incorporation"^[16, 50]. To mitigate the effect of time in this way, the number of annual citations was introduced.

However, the time lag between publication and accumulation of sufficient citations for incorporation into a list of citation classics, such as our top-100 classics, must be acknowledged, and one cannot predict which of the more recent articles will rise to be included as a citation classic and within what time frame. For this reason, fields must periodically update their list of classics in keeping with this trend.

Abbreviations

EGFR, epidermal growth-factor receptor

ESCC, esophageal squamous cell carcinoma

EGJ, esophagogastric junction

HER2, human epidermal growth factor receptor 2

RCT, randomized controlled trial

US, United States

Declarations

Ethics approval and consent to participate: Not applicable

Consent for publication: Not applicable

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Tables

Table 1. The 100 most-cited articles on esophageal cancer ranked in order of the number of citations received.

Rank	Article	Country	Total number of citations	Number of annual citations	Tumor type	Study design	Theme	Treatment
1	Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. New England Journal of Medicine 2006; 355: 11-20.	UK	3,641	260.07	AEG+G	RCT	Chemotherapy	Perioperative
2	Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. New England Journal of Medicine 2001; 345: 725-730.	USA	2,513	132.26	AEG+G	RCT	Chemoradiotherapy	Postoperative
3	Preoperative Chemoradiotherapy for Esophageal or Junctional Cancer. New England Journal of Medicine 2012; 366: 2074-2084.	Netherlands	2,351	293.88	Ade+ESCC	RCT	Chemoradiotherapy	Preoperative
4	Symptomatic gastroesophageal reflux as a risk factor for esophageal adenocarcinoma. New England Journal of Medicine 1999; 340: 825-831.	Sweden	2,129	101.38	AEG+G	Case-control study	Pathogenesis/Clinical presentation	-
5	Rising incidence of adenocarcinoma of the esophagus and gastric cardia. Jama 1991; 265: 1287-1289.	USA	2,005	69.14	AEG+G	Cross-sectional study	Pathogenesis/Clinical presentation	-
6	Capecitabine and oxaliplatin for advanced esophagogastric cancer. New England Journal of Medicine 2008; 358: 36-46.	UK	1,537	128.08	AEG+G	RCT	Chemotherapy	Salvage
7	A comparison of multimodal therapy and surgery for esophageal adenocarcinoma. New England Journal of Medicine 1996; 335: 462-467.	Ireland	1,523	63.46	AE	RCT	Chemoradiotherapy	Preoperative
8	Chemoradiotherapy of locally advanced esophageal cancer - Long-term follow-up of a prospective randomized trial (RTOG 85-01). Jama-Journal of the American Medical Association 1999; 281: 1623-1627.	USA	1,319	62.81	Ade+ESCC	RCT	Chemoradiotherapy	Radical treatment
9	Pathologic assessment of tumor regression after preoperative chemoradiotherapy of esophageal carcinoma. Clinicopathologic correlations. Cancer 1994; 73: 2680-2686.	France	1,247	47.96	ESCC	Retrospective study	Chemoradiotherapy	-
10	Ramucirumab monotherapy for previously treated	USA	1,173	195.50	AEG+G	RCT	Chemotherapy	Salvage

	advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): an international, randomised, multicentre, placebo-controlled, phase 3 trial. Lancet 2014; 383: 31-39.							
11	Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): a double-blind, randomised phase 3 trial. Lancet Oncology 2014; 15: 1224-1235.	Germany	1,095	182.50	AEG+G	RCT	Chemotherapy	Salvage
12	Chemoradiotherapy followed by surgery compared with surgery alone in squamous-cell cancer of the esophagus. New England Journal of Medicine 1997; 337: 161-167.	France	1,049	45.61	ESCC	RCT	Chemoradiotherapy	Preoperative
13	Perioperative Chemotherapy Compared With Surgery Alone for Resectable Gastroesophageal Adenocarcinoma: An FNCLCC and FFCD Multicenter Phase III Trial. Journal of Clinical Oncology 2011; 29: 1715-1721.	France	1,043	115.89	AE	RCT	Chemotherapy	Perioperative
14	Surgical resection with or without preoperative chemotherapy in oesophageal cancer: a randomised controlled trial. Lancet 2002; 359: 1727-1733.	UK	1,024	56.89	Ade+ESCC	RCT	Chemotherapy	Preoperative
15	INT 0123 (radiation therapy oncology group 94-05) phase III trial of combined-modality therapy for esophageal cancer: High-dose versus standard-dose radiation therapy. Journal of Clinical Oncology 2002; 20: 1167-1174.	USA	1,017	56.50	Ade+ESCC	RCT	Chemoradiotherapy	Radical treatment
16	Chemotherapy followed by surgery compared with surgery alone for localized esophageal cancer. New England Journal of Medicine 1998; 339: 1979-1984.	USA	993	45.14	Ade+ESCC	RCT	Chemotherapy	Preoperative
17	Randomized trial of preoperative chemoradiation versus surgery alone in patients with locoregional esophageal carcinoma. Journal of Clinical	USA	988	52.00	Ade+ESCC	RCT	Chemoradiotherapy	Preoperative

	Oncology 2001; 19: 305-313.							
18	The role of overdiagnosis and reclassification in the marked increase of esophageal adenocarcinoma incidence. Journal of the National Cancer Institute 2005; 97: 142-146.	USA	934	62.27	AE	Cross-sectional study	Pathogenesis/Clinical presentation	-
19	Phase III trial of trimodality therapy with cisplatin, fluorouracil, radiotherapy, and surgery compared with surgery alone for esophageal cancer: CALGB 9781. Journal of Clinical Oncology 2008; 26: 1086-1092.	USA	881	73.42	Ade+ESCC	RCT	Chemoradiotherapy	Preoperative
20	Chemoradiation with and without surgery in patients with locally advanced squamous cell carcinoma of the esophagus. Journal of Clinical Oncology 2005; 23: 2310-2317.	Germany	845	56.33	ESCC	RCT	Chemoradiotherapy	Radical treatment
21	Minimally invasive versus open oesophagectomy for patients with oesophageal cancer: a multicentre, open-label, randomised controlled trial. Lancet 2012; 379: 1887-1892.	Netherlands	811	101.38	Ade+ESCC	RCT	Surgery	Radical treatment
22	Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): long-term results of a randomised controlled trial. Lancet Oncology 2015; 16: 1090-1098.	Netherlands	802	160.40	Ade+ESCC	RCT	Chemoradiotherapy	Preoperative
23	Chemoradiation followed by surgery compared with chemoradiation alone in squamous cancer of the esophagus: FFCD 9102. Journal of Clinical Oncology 2007; 25: 1160-1168.	France	772	59.38	ESCC	RCT	Chemoradiotherapy	Radical treatment
24	Randomized trial comparing epirubicin, cisplatin, and fluorouracil versus fluorouracil, doxorubicin, and methotrexate in advanced esophagogastric cancer. Journal of Clinical Oncology 1997; 15: 261-267.	UK	747	32.48	AE	RCT	Chemotherapy	Salvage
25	Surgery alone versus chemoradiotherapy followed by surgery for resectable cancer of the oesophagus: a randomised controlled phase III trial. Lancet	Australia	698	46.53	Ade+ESCC	RCT	Chemoradiotherapy	Preoperative

	Oncology 2005; 6: 659-668.							
26	SOX2 is an amplified lineage-survival oncogene in lung and esophageal squamous cell carcinomas. Nature Genetics 2009; 41: 1238-U1105.	USA	644	58.55	ESCC	Laboratory investigation	Pathogenesis/Clinical presentation	-
27	A controlled trial of an expansile metal stent for palliation of esophageal obstruction due to inoperable cancer. New England Journal of Medicine 1993; 329: 1302-1307.	Germany	635	23.52	Ade+ESCC	RCT	Metal stent	Salvage
28	Phase III Comparison of Preoperative Chemotherapy Compared With Chemoradiotherapy in Patients With Locally Advanced Adenocarcinoma of the Esophagogastric Junction. Journal of Clinical Oncology 2009; 27: 851-856.	Germany	623	56.64	AE	RCT	Chemoradiotherapy	Preoperative
29	A Randomized Trial Comparing Postoperative Adjuvant Chemotherapy with Cisplatin and 5-Fluorouracil Versus Preoperative Chemotherapy for Localized Advanced Squamous Cell Carcinoma of the Thoracic Esophagus (JCOG9907). Annals of Surgical Oncology 2012; 19: 68-74.	Japan	585	73.13	ESCC	RCT	Chemotherapy	Preoperative
30	Long-Term Results of a Randomized Trial of Surgery With or Without Preoperative Chemotherapy in Esophageal Cancer. Journal of Clinical Oncology 2009; 27: 5062-5067.	UK	581	52.82	Ade+ESCC	RCT	Chemotherapy	Preoperative
31	Nivolumab in patients with advanced gastric or gastro-oesophageal junction cancer refractory to, or intolerant of, at least two previous chemotherapy regimens (ONO-4538-12, ATTRACTION-2): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2017; 390: 2461-2471.	Japan	562	187.33	AEG+G	RCT	New agents_immunotherapy	Salvage
32	PET to assess early metabolic response and to guide treatment of adenocarcinoma of the oesophagogastric junction: The MUNICON phase II trial. Lancet Oncology 2007; 8: 797-805.	Germany	551	42.38	AE	Prospective study	Imaging	-
33	Prediction of response	Germany	545	28.68	AE	Prospective	Imaging	-

	to preoperative chemotherapy in adenocarcinomas of the esophagogastric junction by metabolic imaging. Journal of Clinical Oncology 2001; 19: 3058-3065.					study		
34	Clinical significance of programmed death-1 ligand-1 and programmed death-1 ligand-2 expression in human esophageal cancer. Clinical Cancer Research 2005; 11: 2947-2953.	Japan	541	36.07	ESCC	Laboratory investigation	Pathogenesis/Clinical presentation	-
35	Progress report of combined chemoradiotherapy versus radiotherapy alone in patients with esophageal cancer: An intergroup study. Journal of Clinical Oncology 1997; 15: 277-284.	USA	536	23.30	Ade+ESCC	RCT	Chemoradiotherapy	Radical treatment
36	Phase III trial in metastatic gastroesophageal adenocarcinoma with fluorouracil, leucovorin plus either oxaliplatin or cisplatin: A study of the arbeitsgemeinschaft internistische onkologie. Journal of Clinical Oncology 2008; 26: 1435-1442.	Germany	506	42.17	AEG+G	RCT	Chemotherapy	Salvage
37	Extended transthoracic resection compared with limited transhiatal resection for adenocarcinoma of the mid/distal esophagus - Five-year survival of a randomized clinical trial. Annals of Surgery 2007; 246: 992-1001.	Netherlands	506	38.92	AE	RCT	Surgery	Radical treatment
38	Adenocarcinoma of the esophagogastric junction - Results of surgical therapy based on anatomical/topographic classification in 1,002 consecutive patients. Annals of Surgery 2000; 232: 353-360.	Germany	500	25.00	AE	Retrospective study	Surgery	Radical treatment
39	Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. Lancet 2010; 376: 687-697.	South Korea	494	49.40	AEG+G	RCT	Chemotherapy	Salvage
40	An endoscopic biopsy protocol can differentiate high-grade dysplasia from early adenocarcinoma in Barrett's esophagus.	USA	480	17.78	AE	Prospective study	Pathogenesis/Clinical presentation	-

	Gastroenterology 1993; 105: 40-50.							
41	Surgery plus chemotherapy compared with surgery alone for localized squamous cell carcinoma of the thoracic esophagus: A Japan Clinical Oncology Group Study - JCOG9204. Journal of Clinical Oncology 2003; 21: 4592-4596.	Japan	471	27.71	ESCC	RCT	Chemotherapy	Postoperative
42	Simultaneous occurrence of fumonisin B1 and other mycotoxins in moldy corn collected from the People's Republic of China in regions with high incidences of esophageal cancer. Applied and Environmental Microbiology 1994; 60: 847-852.	USA	470	18.08	ESCC	Laboratory investigation	Pathogenesis/Clinical presentation	-
43	Pre-operative radiotherapy prolongs survival in operable esophageal carcinoma: a randomized, multicenter study of pre-operative radiotherapy and chemotherapy. The second Scandinavian trial in esophageal cancer. World Journal of Surgery 1992; 16: 1104-1110.	Norway	465	16.61	ESCC	RCT	Radiation	Preoperative
44	Randomized, Double-Blind, Placebo-Controlled Phase III Trial of Apatinib in Patients With Chemotherapy-Refractory Advanced or Metastatic Adenocarcinoma of the Stomach or Gastroesophageal Junction. Journal of Clinical Oncology 2016; 34: 1448-1454.	China	460	115.00	AEG+G	RCT	Chemotherapy	Salvage
45	Frequent somatic mutation of the MTS1/CDK4I (multiple tumor suppressor/cyclin-dependent kinase 4 inhibitor) gene in esophageal squamous cell carcinoma. Cancer Research 1994; 54: 3396-3397.	Japan	459	17.65	ESCC	Laboratory investigation	Pathogenesis/clinical presentation	-
46	Epirubicin, oxaliplatin, and capecitabine with or without panitumumab for patients with previously untreated advanced oesophagogastric cancer (REAL3): a randomised, open-label phase 3 trial. Lancet Oncology 2013; 14: 481-489.	UK	458	65.43	AEG+G	RCT	Chemotherapy	Salvage
47	Long-term results and risk factor analysis for recurrence after curative	Germany	455	37.92	AE	Prospective study	Surgery	Radical treatment

	endoscopic therapy in 349 patients with high-grade intraepithelial neoplasia and mucosal adenocarcinoma in Barrett's oesophagus. Gut 2008; 57: 1200-1206.							
48	A randomized study of chemotherapy, radiation therapy, and surgery versus surgery for localized squamous cell carcinoma of the esophagus. Cancer 1994; 73: 1779-1784.	France	450	17.31	ESCC	RCT	Chemoradiotherapy	Preoperative
49	Prospective study of risk factors for esophageal and gastric cancers in the Linxian General Population Trial cohort in China. International Journal of Cancer 2005; 113: 456-463.	USA	449	29.93	ESCC	Cohort study	Pathogenesis/Clinical presentation	-
50	Endoscopic submucosal dissection of early esophageal cancer. Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association 2005; 3: S67-70.	Japan	446	29.73	ESCC	Prospective study	Surgery	Radical Treatment
51	The incidence of adenocarcinoma in Barrett's esophagus: A prospective study of 170 patients followed 4.8 years. American Journal of Gastroenterology 1997; 92: 212-215.	USA	443	19.26	AE	Cohort study	Pathogenesis/Clinical presentation	-
52	Intratumor Heterogeneity Characterized by Textural Features on Baseline F-18-FDG PET Images Predicts Response to Concomitant Radiochemotherapy in Esophageal Cancer. Journal of Nuclear Medicine 2011; 52: 369-378.	France	442	49.11	Ade+ESCC	Prospective study	Imaging	-
53	Exome and whole-genome sequencing of esophageal adenocarcinoma identifies recurrent driver events and mutational complexity. Nature Genetics 2013; 45: 478-U437.	USA	438	62.57	AE	Laboratory investigation	Pathogenesis/Clinical presentation	-
54	Frequent mutation of the p53 gene in human esophageal cancer. Proceedings of the National Academy of Sciences of the United States of America 1990; 87: 9958-9961.	USA	429	14.30	ESCC	Laboratory investigation	Pathogenesis/Clinical presentation	-
55	Improvement in the results of surgical treatment of advanced	Japan	427	21.35	ESCC	Retrospective study	Surgery	Radical treatment

	squamous esophageal carcinoma during 15 consecutive years. Annals of Surgery 2000; 232: 225-232.							
56	Results of a nationwide study on the three-field lymph node dissection of esophageal cancer. Oncology 1991; 48: 411-420.	Japan	417	14.38	ESCC	Retrospective study	Surgery	Radical treatment
57	Increased populations of regulatory T cells in peripheral blood and tumor-infiltrating lymphocytes in patients with gastric and esophageal cancers. Clinical Cancer Research 2003; 9: 4404-4408.	Japan	413	24.29	ESCC	Laboratory investigation	Pathogenesis/Clinical presentation	-
58	Safety and Efficacy of Pembrolizumab Monotherapy in Patients With Previously Treated Advanced Gastric and Gastroesophageal Junction Cancer Phase 2 Clinical KEYNOTE-059 Trial. Jama Oncology 2018; 4.	USA	407	203.50	AEG+G	Prospective study	New agents_immunotherapy	Salvage
59	Obesity, alcohol, and tobacco as risk factors for cancers of the esophagus and gastric cardia: adenocarcinoma versus squamous cell carcinoma. Cancer Epidemiology Biomarkers & Prevention 1995; 4: 85-92.	USA	405	16.20	Ade+ESCC	Case-control study	Pathogenesis/Clinical presentation	-
60	Prospective randomized trial comparing mitomycin, cisplatin, and protracted venous-infusion fluorouracil (PV1 5-FU) with epirubicin, cisplatin, and PV15-FU in advanced esophagogastric cancer. Journal of Clinical Oncology 2002; 20: 1996-2004.	UK	398	22.11	Ade+ESCC	RCT	Chemotherapy	Salvage
61	Utility of positron emission tomography for the staging of patients with potentially operable esophageal carcinoma. Journal of Clinical Oncology 2000; 18: 3202-3210.	Belgium	392	19.60	Ade+ESCC	Prospective study	Imaging	-
62	Curative endoscopic resection of early esophageal adenocarcinomas (Barrett's cancer). Gastrointestinal Endoscopy 2007; 65: 3-10.	Germany	391	30.08	AE	Prospective study	Surgery	Radical treatment
63	Histologic tumor type is an independent prognostic parameter in esophageal cancer: Lessons from more than 1,000 consecutive resections at a single	Germany	391	20.58	Ade+ESCC	Retrospective study	Surgery	Radical treatment

	center in the Western world. Annals of Surgery 2001; 234: 360-367.							
64	The Number of Lymph Nodes Removed Predicts Survival in Esophageal Cancer: An International Study on the Impact of Extent of Surgical Resection. Annals of Surgery 2008; 248: 549-554.	USA	381	31.75	Ade+ESCC	Retrospective study	Surgery	Radical treatment
65	miR-145, miR-133a and miR-133b: tumor-suppressive miRNAs target FSCN1 in esophageal squamous cell carcinoma. International Journal of Cancer 2010; 127: 2804-2814.	Japan	381	38.10	ESCC	Laboratory investigation	Pathogenesis/Clinical presentation	-
66	Specialized intestinal metaplasia, dysplasia, and cancer of the esophagus and esophagogastric junction: Prevalence and clinical data. Gastroenterology 1999; 116: 277-285.	USA	379	18.05	AE	Retrospective study	Pathogenesis/Clinical presentation	-
67	Prognostic significance of activated CD8(+) T cell infiltrations within esophageal carcinomas. Cancer Research 2001; 61: 3932-3936.	Germany	378	19.89	Ade+ESCC	Laboratory investigation	Pathogenesis/Clinical presentation	-
68	Time course of tumor metabolic activity during chemoradiotherapy of esophageal squamous cell carcinoma and response to treatment. Journal of Clinical Oncology 2004; 22: 900-908.	Germany	371	23.19	ESCC	Prospective study	Imaging	-
69	A shared susceptibility locus in PLCE1 at 10q23 for gastric adenocarcinoma and esophageal squamous cell carcinoma. Nature Genetics 2010; 42: 764-U751.	USA	369	36.90	Ade+ESCC	Laboratory investigation	Pathogenesis/Clinical presentation	-
70	Use of aspirin and other nonsteroidal anti-inflammatory drugs and risk of esophageal and gastric cancer. Cancer Epidemiology Biomarkers & Prevention 1998; 7: 97-102.	USA	367	16.68	Ade+ESCC	Case-control study	Pathogenesis/Clinical presentation	-
71	Expression of survivin in esophageal cancer: Correlation with the prognosis and response to chemotherapy. International Journal of Cancer 2001; 95: 92-95.	Japan	362	19.05	ESCC	Laboratory investigation	Pathogenesis/Clinical presentation	-
72	Complete response to neoadjuvant chemoradiotherapy in esophageal carcinoma is associated with	USA	356	23.73	Ade+ESCC	Retrospective study	Chemoradiotherapy	Preoperative

	significantly improved survival. Journal of Clinical Oncology 2005; 23: 4330-4337.							
73	Long-term results of RTOG trial 8911 (USA intergroup 113): A random assignment trial comparison of chemotherapy followed by surgery compared with surgery alone for esophageal cancer. Journal of Clinical Oncology 2007; 25: 3719-3725.	USA	349	26.85	Ade+ESCC	RCT	Chemotherapy	Preoperative
74	Metabolic imaging predicts response, survival, and recurrence in adenocarcinomas of the esophagogastric junction. Journal of Clinical Oncology 2006; 24: 4692-4698.	Germany	347	24.79	AE	Prospective study	Imaging	-
75	Multivariate prognostic factor analysis in locally advanced and metastatic esophagogastric cancer-pooled analysis from three multicenter, randomized, controlled trials using individual patient data. Journal of Clinical Oncology 2004; 22: 2395-2403.	UK	347	21.69	Ade+ESCC	Retrospective study	Chemotherapy	Salvage
76	Multicenter phase II study of irinotecan, cisplatin, and bevacizumab in patients with metastatic gastric or gastroesophageal junction adenocarcinoma. Journal of Clinical Oncology 2006; 24: 5201-5206.	USA	346	24.71	AEG+G	Prospective study	Chemotherapy	Salvage
77	Adenocarcinoma of the esophagogastric junction and Barrett's esophagus. Gastroenterology 1995; 109: 1541-1546.	USA	345	13.80	AE	Case-control study	Pathogenesis/Clinical presentation	-
78	Early esophageal cancer - Pattern of lymphatic spread and prognostic factors for long-term survival after surgical resection. Annals of Surgery 2005; 242: 566-575.	Germany	339	22.60	Ade+ESCC	Retrospective study	Surgery	Radical treatment
79	Prognostic factors for the survival of patients with esophageal carcinoma in the US - The importance of tumor length and lymph node status. Cancer 2002; 95: 1434-1443.	USA	339	18.83	Ade+ESCC	Retrospective study	Surgery	Radical treatment
80	MicroRNA expression profiles of esophageal cancer. Journal of Thoracic and Cardiovascular Surgery 2008; 135: 255-260.	USA	339	28.25	Ade+ESCC	Laboratory investigation	Pathogenesis/Clinical presentation	-
81	Esophageal cancer:	USA	337	16.85	Ade+ESCC	Retrospective	Pathogenesis/Clinical	-

	Results of an American College of Surgeons patient care evaluation study. Journal of the American College of Surgeons 2000; 190: 562-572.					study	presentation	
82	Three-field lymph node dissection for squamous cell and adenocarcinoma of the esophagus. Annals of Surgery 2002; 236: 177-183.	USA	336	18.67	Ade+ESCC	Prospective study	Pathogenesis/Clinical presentation	-
83	Endoscopic biopsy can detect high-grade dysplasia or early adenocarcinoma in Barrett's esophagus without grossly recognizable neoplastic lesions. Gastroenterology 1988; 94: 81-90.	USA	336	10.50	AE	Prospective study	Pathogenesis/Clinical presentation	-
84	Nutrition intervention trials in Linxian, China: multiple vitamin/mineral supplementation, cancer incidence, and disease-specific mortality among adults with esophageal dysplasia. Journal of the National Cancer Institute 1993; 85: 1492-1498.	China	335	12.41	ESCC	RCT	Pathogenesis/Clinical presentation	Nutrition intervention
85	Nutrient intake and risk of subtypes of esophageal and gastric cancer. Cancer Epidemiology Biomarkers & Prevention 2001; 10: 1055-1062.	USA	333	17.53	Ade+ESCC	Retrospective study	Pathogenesis/Clinical presentation	-
86	Early Detection of Superficial Squamous Cell Carcinoma in the Head and Neck Region and Esophagus by Narrow Band Imaging: A Multicenter Randomized Controlled Trial. Journal of Clinical Oncology 2010; 28: 1566-1572.	Japan	332	33.20	ESCC	RCT	Imaging	-
87	Principles of surgical treatment for carcinoma of the esophagus: analysis of lymph node involvement. Annals of surgery 1981; 194: 438-446.	Japan	331	8.49	ESCC	Retrospective study	Pathogenesis/Clinical presentation	
88	Cancer of the Esophagus and Esophagogastric Junction Data-Driven Staging for the Seventh Edition of the American Joint Committee on Cancer/International Union Against Cancer Cancer Staging Manuals. Cancer 2010; 116: 3763-3773.	USA	331	33.10	Ade+ESCC	Retrospective study	Pathogenesis/Clinical presentation	-
89	Genome-wide association study of esophageal squamous cell carcinoma in	China	331	33.10	ESCC	Laboratory investigation	Pathogenesis/Clinical presentation	-

	Chinese subjects identifies susceptibility loci at PLCE1 and C20orf54. Nature Genetics 2010; 42: 759-U746.							
90	MicroRNA Expression in Squamous Cell Carcinoma and Adenocarcinoma of the Esophagus: Associations with Survival. Clinical Cancer Research 2009; 15: 6192-6200.	USA	331	30.09	Ade+ESCC	Laboratory investigation	Pathogenesis/Clinical presentation	-
91	Definitive chemoradiotherapy for T4 and/or M1 lymph node squamous cell carcinoma of the esophagus. Journal of Clinical Oncology 1999; 17: 2915-2921.	Japan	330	15.71	ESCC	Retrospective study	Chemoradiotherapy	Radical Treatment
92	MET Amplification Identifies a Small and Aggressive Subgroup of Esophagogastric Adenocarcinoma With Evidence of Responsiveness to Crizotinib. Journal of Clinical Oncology 2011; 29: 4803-4810.	USA	328	36.44	AE	Laboratory investigation	Pathogenesis/Clinical presentation	-
93	Only pathologic complete response to neoadjuvant chemotherapy improves significantly the long term survival of patients with resectable esophageal squamous cell carcinoma - Final report of a randomized, controlled trial of preoperative chemotherapy versus surgery alone. Cancer 2001; 91: 2165-2174.	Italy	326	17.16	ESCC	RCT	Chemotherapy	Preoperative
94	Docetaxel versus active symptom control for refractory oesophagogastric adenocarcinoma (COUGAR-02): an open-label, phase 3 randomised controlled trial. Lancet Oncology 2014; 15: 78-86.	UK	324	54.00	AE	RCT	Chemotherapy	Salvage
95	Mortality and morbidity rates, postoperative course, quality of life, and prognosis after extended radical lymphadenectomy for esophageal cancer. Comparison of three-field lymphadenectomy with two-field lymphadenectomy. Annals of Surgery 1995; 222: 654-662.	Japan	323	12.92	ESCC	Prospective study	Surgery	Radical treatment
96	Time trends incidence of both major histologic types of esophageal carcinomas in selected countries, 1973-1995. International Journal of Cancer 2002; 99: 860-868.	France	323	17.94	Ade+ESCC	Cross-sectional study	Pathogenesis/Clinical presentation	-

97	Preoperative chemoradiation followed by transhiatal esophagectomy for carcinoma of the esophagus: final report. Journal of Clinical Oncology 1993; 11: 1118-1123.	USA	321	11.89	Ade+ESCC	Prospective study	Chemoradiotherapy	Preoperative
98	Randomized clinical trial of preoperative and postoperative adjuvant chemotherapy with cisplatin, vindesine, and bleomycin for carcinoma of the esophagus. The Journal of thoracic and cardiovascular surgery 1988; 96: 242-248.	USA	319	9.97	Ade+ESCC	RCT	Chemotherapy	Perioperative
99	Three-field lymphadenectomy for carcinoma of the esophagus and gastroesophageal junction in 174 R-0 resections: Impact on staging, disease-free survival, and outcome - A plea for adaptation of TNM classification in upper-half esophageal carcinoma. Annals of Surgery 2004; 240: 962-974.	Belgium	315	19.69	Ade+ESCC	Retrospective study	Pathogenesis/Clinical presentation	-
100	Minimally invasive esophagectomy: Thoracoscopic mobilization of the esophagus and mediastinal lymphadenectomy in prone position - Experience of 130 patients. Journal of the American College of Surgeons 2006; 203: 7-16.	India	314	22.43	ESCC	Prospective study	Surgery	Radical Treatment

AE, adenocarcinoma; AEG, adenocarcinoma of the esophagogastric junction; G, gastric adenocarcinoma; ESCC, esophageal squamous cell carcinoma; ADE, adenocarcinoma of the esophagus; RCT, randomized controlled trial; USA, United States of America; UK, United Kingdom

Table 2. Journals in which the 100 most-cited articles were published.

Abbreviated journal name (International Organization for Standardization)	Journal category	Number of articles published	Average number of citations per paper	Impact factor
J Clin Oncol	Oncology	26	547	32.956
Ann Surg	Surgery	10	385	10.130
N Engl J Med	General	9	1819	74.699
Lancet Oncol	Oncology	6	655	33.752
Lancet	General	5	813	60.392
Cancer	Oncology	5	539	5.742
Nature Genet.	Genetics&Heredity	4	446	27.603
Gastroenterology	Gastroenterology&Hepatology	4	385	17.373
Int. J. Cancer	Oncology	4	379	5.145
Clin Cancer Res	Oncology	3	428.3	10.107
Cancer epidemiol. Biomarkers Prev.	Public, Environmental & Occupation Health	3	368.3	4.344
Cancer Res	Oncology	2	418.5	9.727
JNCI-J Natl Cancer Inst	Oncology	2	634.5	11.577
JAMA-J Am Med Assoc	General	2	1662	45.540
J. Am. Coll. Surg.	Surgery	2	325.5	4.590
J.Thorac. Cardiovasc. Surg.	Surgery	2	329	4.451
Gut	Gastroenterology & Hepatology	1	455	19.819
Ann. Surg. Oncol.	Oncology	1	585	4.061
Am. J. Gastroenterol.	Gastroenterology & Hepatology	1	443	10.171
Appl. Enviro. Microbiol.	Microbiology Biotechnology & Applied microbiology	1	470	4.016
Gastrointest. Endosc.	Gastroenterology & Hepatology	1	391	6.890
J. Nucl. med.	Radiology, nuclear medicine & medical imaging	1	442	7.887
PNAS	General	1	429	9.580
World J. Surg.	Surgery	1	465	2.234
Clin. Gastroenterol. Hepatol.	Gastroenterology & Hepatology	1	446	8.549
JAMA Oncol.	Oncology	1	407	24.799
Oncology	Oncology	1	417	2.642

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Figures

Figure 1

Countries of origin of the 100 most-cited articles.

Figure 2

Distributions of the 100 most-cited articles by study design and theme.

Figure 3

Trends in esophageal cancer reported in citation classics over time. (A) Total number of citation classics by epoch. (B) Trends in themes reported in citation classics by epoch. (C) Trends in therapies reported in citation classics by epoch. (D) Trends in study designs of citation classics by epoch.

Figure 4

Timeline of important historical advances in esophageal cancer. AE, adenocarcinoma of the esophagus; AEGJ, adenocarcinoma of the esophagogastric junction; GAC, gastric adenocarcinoma; ESCC, esophageal squamous cell carcinoma; HER2, human epidermal growth factor receptor 2.