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# Hyperthermic Intraperitoneal Chemotherapy: A Holistic Investigation of Global Outputs with Bibliometric Analysis

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**Abstract**

**Background:** Hyperthermic intraperitoneal administration of chemotherapy (HIPEC) targets microscopic residues remaining after complete cytoreduction.
**Objectives:** We systematically presented the development process of the HIPEC treatment regimen, the most remarkable publications on this topic, the most productive countries, and the future of treatment in the coming years.
**Methods:** The source of our study was the Web of Science (WoS) database which included the Korean Journal Database, core collection index, Russian Science Citation Index, and Sci ELO citation index.
**Results:** We reached a total of 3,343 publications by analyzing the WoS database using the keyword of "Hyperthermic intraperitoneal chemotherapy". When the citations of the documents written about HIPEC were evaluated, we found that the highest citation was made in 2019. Co-citation analysis showed that there were 27,724 authors investigating the issue of HIPEC. The most active university was determined as Wake Forest University, USA. Collaboration and citation collaboration was observed between Wake Forest University, the University of Pittsburgh, and the University of Texas. The intersection point of all researcher countries was the USA. While reviewing the articles on HIPEC, we also identified new trends and topics in this regard. Ovarian cancers, gastric cancers, and colorectal cancers were found to be the types of cancer that had the strongest relationship with HIPEC.
**Conclusion:** HIPEC therapies should be considered an area of research that has been studied, published, and cited by surgeons, oncologists, and pharmacologists interested in the treatment of tumors with peritoneal spread.

*Keywords:* Bibliometry, Cancer, Hyperthermic intraperitoneal chemotherapy

## 1. Background

Peripheral neuropathy is one of the major complications of diabetes (1), leading to progressive loss of vibration, temperature, touch, and proprioception (2), lower limb somatosensory impairment, postural problems, and risk of falls (When peritoneal malignancies originate from the lining of the peritoneal cavity, they are called primary peritoneal cancer, and when they spread from a different area into the peritoneum, they are called secondary peritoneal cancer. While primary peritoneal cancers are rarely observed, secondary peritoneal cancers are more common. Most secondary cancers arise from the ovarian or gastrointestinal tract (1).

While most ovarian tumors originate from the coelomic epithelium, they can rarely stem from germ cells and follicular cells. Epithelial ovarian tumors are malignancies with high mortality and peritoneal spread. The main treatment principle of epithelial ovarian cancer consists of cytoreductive surgery and a treatment regimen containing carboplatin/paclitaxel. One of the most important prognostic factors is debulking surgery (2). However, despite elective surgical treatment and appropriate chemotherapy regimens, peritoneal relapses are frequently observed.

Aggressive cytoreductive surgeries and intraperitoneal chemotherapies have been used to improve survival time and quality of life in the treatment of peritoneal spread cancers. Intraperitoneal administration of chemotherapy targets microscopic residues remained after complete cytoreduction. The advantage of intraperitoneal chemotherapy is described in terms of pharmacokinetics as follows. The peritoneal-plasma barrier allows a high concentration gradient of blood drainage between the peritoneal cavity and systemic circulation. Blood drainage from the peritoneal cavity provides a 'first pass' effect in the liver through the portal system, increases as intra-hepatic concentrations, and decreases systemic toxicity (3). The intraperitoneal chemotherapy used for peritoneal malignancy is between 41 and 43°C, which accelerates the death of cancer cells (4).

Hyperthermic intraperitoneal chemotherapy (HIPEC) treatments were first used in the treatment of colorectal cancers, and then the idea was found to be effective in ovarian cancer recurrences. In patients with ovarian cancer with extensive peritoneal involvement, the addition of HIPEC to intermittent cytoreductive surgery has been shown to increase survival time and reduce recurrence (5). However, the results of some other studies show that the benefits of HIPEC treatment are controversial in

ovarian cancer and that it does not contribute to the standard treatment regimen (6).

## 2. Objectives

In this study, we systematically presented the development process of the HIPEC treatment regimen, the most remarkable publications on this topic, the most productive countries, and the future of treatment in the coming years.

## 3. Methods

The source of our study was the Web of Science (WoS) database which included the Korean Journal Database, core collection index, Russian Science Citation Index, and Sci ELO citation index. The articles indexed between 1991 and 2019 were included in our research in the database; however, the studies of 2020 were not included since the effect factors were not clear yet. The search process in the databases was performed using the following keyword: "Hyperthermic intraperitoneal chemotherapy". Gunnmap free open web-based application was used to visualize global research productivity. VOSviewer 2019 program was used to determine the scientific relevance of the data.

## 4. Results

*4.1. General Features and Global Productivity:*

We reached a total of 3,343 publications by analyzing the WoS database using the keyword "hyperthermic intraperitoneal chemotherapy". In our study, we excluded 198 studies of 2020 from evaluation since the citations were not yet completed. We listed the date of the remaining 3,143 articles published in the past by 2019, and we observed that the first article was published in 1991. The first article was a pilot study in which rectal cancer local recurrence, involving 14 patients, was treated with a combination of surgery and HIPEC (7). The articles were written in 12 different languages, among which the most widely used language was English, which accounted for about 95% of all articles.

Most of the documents (67.7%) were research articles, followed by reviews and meeting abstracts (Table 1). We analyzed the distribution of the documents written about HIPEC in the branches of science and observed that there were studies in 75 different fields in total. We found that the branch of science that carried out the most studies was oncology, and 62.2% of all documents were written by oncologists. The oncology area was followed by surgery, gastroenterology and hepatology, obstetrics, and gynecology in descending order (Table 2). The number of documents written about HIPEC was increasing every year. Since 2003, a large number of documents were published annually, and the most productive year was 2019 (Figure 1). A total of 435 articles were published in 2019; although the majority of these publications were research articles, the rate of review articles was higher this year than in other years. The most cited article in 2019 was the recommendations of the European Society for Medical Oncology and the European Society of Gynecological Oncology on ovarian cancer. It was emphasized that HIPEC treatment should not be the first-line treatment in epithelial ovarian cancers (8).

**Table 1**. Publication types of hyperthermic intraperitoneal chemotherapy literature between 1991 and 2019

| Research areas | Number of publications | % of 3,143 |
|---|---|---|
| **Article** | 2,127 | 67.7 |
| **Review** | 409 | 13.0 |
| **Meeting abstract** | 358 | 11.4 |
| **Proceedings paper** | 141 | 4.5 |
| **Editorial material** | 117 | 3.7 |
| **Letter** | 91 | 2.9 |
| **Book chapter** | 24 | 0.7 |
| **Correction** | 18 | 0.5 |
| **Early access** | 5 | 0.1 |
| **News item** | 2 | 0.06 |

**Table 2.** Top ten research areas of documents in hyperthermic intraperitoneal chemotherapy according to Web of Science database between 1991 and 2019

| Research areas | Number of publications | % of 3,143 |
|---|---|---|
| **Oncology** | 1,959 | 62.2 |
| **Surgery** | 1,532 | 48.7 |
| **Gastroenterology/hepatology** | 318 | 10.1 |
| **Obstetrics gynecology** | 180 | 5.7 |
| **Radiology/nuclear medicine** | 136 | 4.2 |
| **General ınternal medicine** | 118 | 3.7 |
| **Pharmacology** | 92 | 2.9 |
| **Research/experimental medicine** | 55 | 1.7 |
| **Hematology** | 38 | 1.2 |
| **Pediatrics** | 35 | 1.1 |

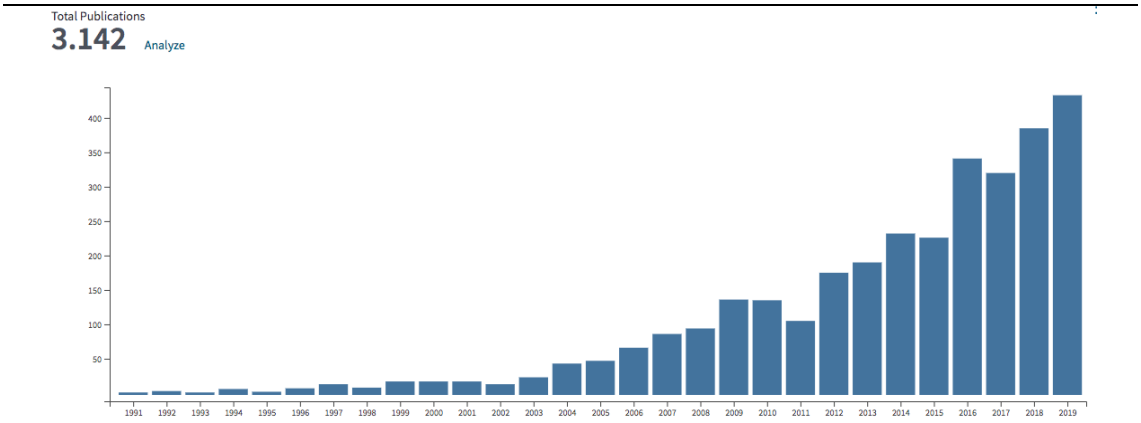


**Figure 1.** Graph of publications about HIPEC by year

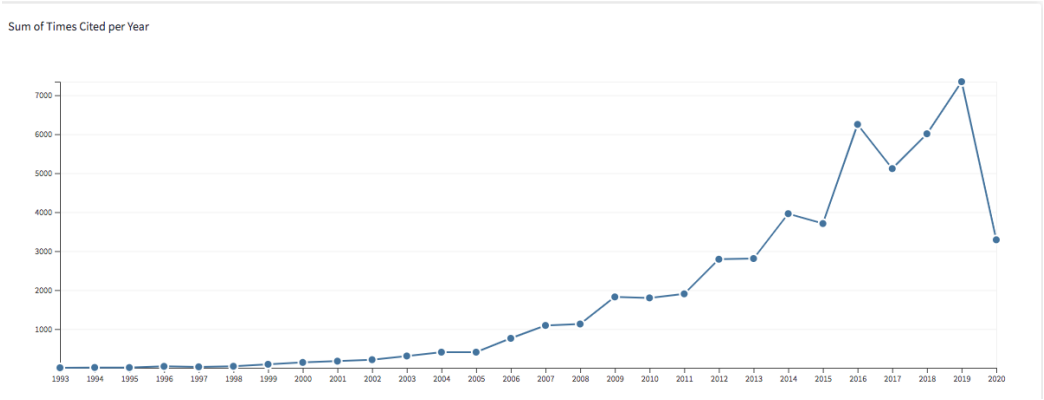


**Figure 2.** Graph of citations about HIPEC by year

When the citations of the documents written about HIPEC were evaluated, we found that the highest citation was made in 2019. The listing of the articles in all the years revealed that the article that received the most citation was the research that was published in 2003 comparing HIPEC and systemic chemotherapy in colorectal cancer patients (9). The most cited article on HIPEC treatment in ovarian cancer was published in 2018. This article was a multicentre, phase three study involving 245 patients in total. It was shown in this research that the addition of HIPEC treatment to cytoreductive surgery increased long-term survival (10).

We evaluated the countries in which the articles were written about HIPEC and found that the most productive countries were the United States, France, and Italy. About 30.4% of all publications were produced in the USA, and the sum of the three most productive countries made up 53.3% of all publications (Figure 3). We found that the

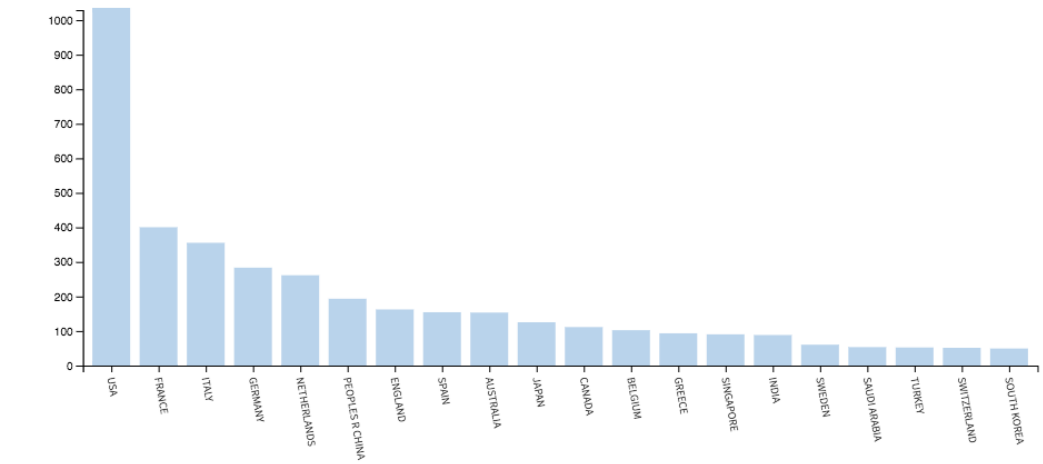


**Figure 3.** Charts of the top ten publishing countries on HIPEC

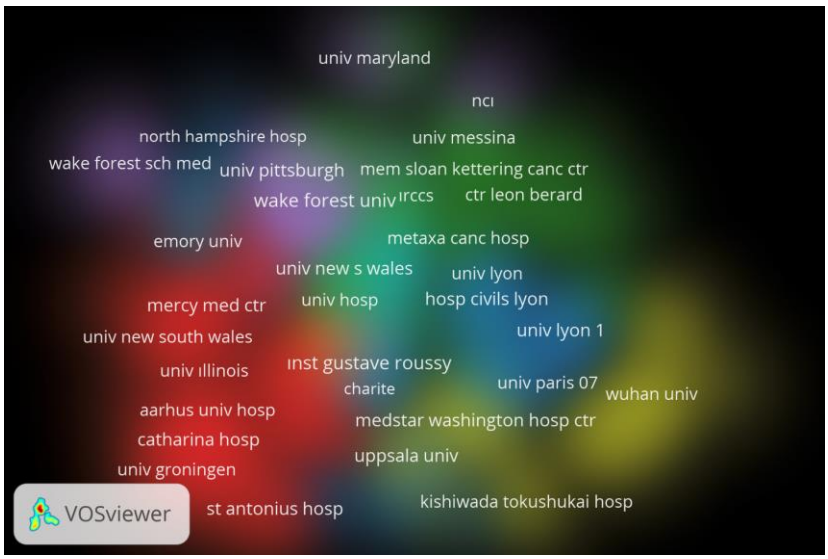


**Figure 4.** HIPEC publication density according to the universities

productivity of African countries and Central Asian countries was very low on HIPEC. The most productive universities were in North America and Europe (Figure 4).

*4.2. Productivity of Authors and Institutions:*

We compared authors' productivity, institutions, and H-Index. In this regard, Glehen O, from the University of Lyon, Lyon, France, was found to be the most productive researcher. The 10 most productive authors and countries are presented in Table 3. We also compared the productivity of universities and organizations in the WoS database. Accordingly, the most productive university was Wake Forest University, North Carolina, USA, which hosted 104 publications in the field of HIPEC (Table 4).

*4.3. Authorship and Institutions Co-citation*

Co-citation analysis showed that there were 27,724 authors investigating the issue of HIPEC. Organizations that published at least 10 documents about HIPEC and received 10 citations were classified; as a result, 124 out of a total of 2,480 organizations were found to meet these requirements. Among these 124 organizations, the most active one was determined as Wake Forest University. Collaboration and citation collaboration were observed between Wake Forest University, the University of Pittsburgh, and the University of Texas. Organizations belonging to the European Union countries were cooperating among themselves. Collaborations were observed between the University of Lyon, Gustave Roussy, and the Netherlands Cancer Institute.

Authors' collaborations were evaluated, and a total of 10,823 authors with at least 10 publications on HIPEC were separated. After this filtering, 187 active authors were identified, and their cooperation was evaluated among themselves. Collaboration clustering around 5 active authors was detected. Of these five writers, David Morris, Edward Levine, and

**Table 3.** First ten authors by record count in hyperthermic intraperitoneal chemotherapy literature between 1991 and 2019

| Authors | Institution | Record count | % of 3,142 | H-index |
|---|---|---|---|---|
| **Glehen O.** | University of Lyon, Italy | 143 | 4.5 | 33 |
| **Deraco M.** | IRCCS Foundation National Cancer Institute Milan, Italy | 131 | 4.1 | 18 |
| **Sugerbaker P.H.** | MedStar Washington Hospital Center<br>Washington, DC, USA | 128 | 4.0 | 54 |
| **Levine E.A.** | Wake Forest Baptist Medical Center<br>Dept Surg Oncol<br>Winston Salem, NC, USA | 125 | 3.9 | 49 |
| **Baratti D.** | IRCCS Foundation National Cancer Institute Milan, Italy | 109 | 3.4 | 8 |
| **Shen P.** | Wake Forest Baptist Medical Center<br>Dept Surg Oncol<br>Winston Salem, NC, USA | 106 | 3.3 | 35 |
| **Kasamura S.** | IRCCS Foundation National Cancer Institute Milan, Italy | 105 | 3.3 | 8 |
| **Morris D.L.** | University of New South Wales Sydney<br>St George Clin Sch<br>Sydney, Nsw, Australia | 96 | 3.0 | 53 |
| **Elias D.** | Dept Surg Oncol Gustave Roussy, Villejuif, France | 86 | 2.7 | 72 |
| **Steward J.H** | University of Illinois System<br>Canc Ctr<br>Chicago, USA | 75 | 2.3 | 43 |

**Table 4.** Top ten organizations by the number of hyperthermic intraperitoneal chemotherapy literature

| Institutions | Number of publications | % of 3,142 |
|---|---|---|
| **Unicancer** | 184 | 5.8 |
| **CHU-Lyon** | 170 | 5.4 |
| **Wake Forest University** | 154 | 4.9 |
| **Fondazione IRCCS Istituto Nazionale Tumori Milan** | 140 | 4.4 |
| **University of Texas System** | 136 | 4.3 |
| **Gustave Roussy** | 128 | 4.0 |
| **UTMD Anderson Cancer Center** | 124 | 3.9 |
| **Netherlands Cancer Institute** | 116 | 3.6 |
| **St George Hospital** | 112 | 3.5 |
| **University of New South Wales Sydney** | 108 | 3.4 |

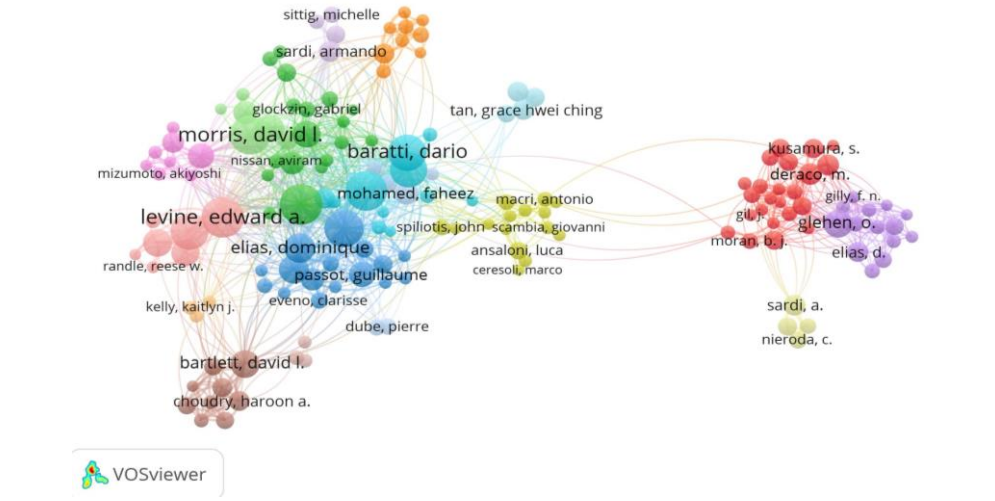


**Figure 5.** Intensity map of the cooperation analysis of the authors

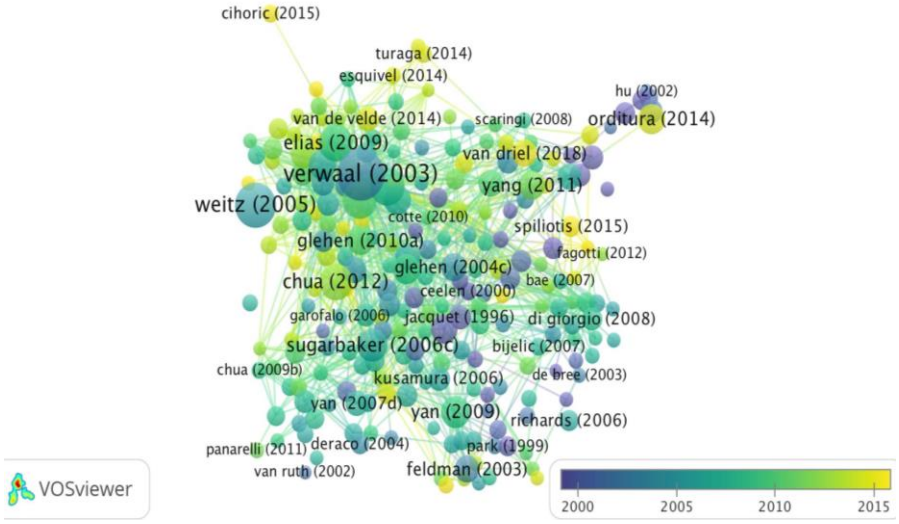


**Figure 6.** Network visualization map of co-citation analysis of active authors

Marcello Deraco were the most active and collaborative ones (Figures 5 and 6).

*4.4. Significant Publications*

Articles written about HIPEC were reviewed and the most cited articles, the average number of citations per year, authors, and publishers were examined. The document by Vervaal et al., comparing the treatment of peritoneal carcinomatosis from colorectal cancer in 2003, was the first in terms of the total number of citations and the average number of citations per year. The 10 most cited articles are presented in Table 5. The citation relations between the articles were indicative of the tendencies of the publishers and the authors. The authors of the two most cited articles also cited each other in Verwaal and Weitz's articles. When the citations of the articles were examined on a yearly basis, it was observed that the most cited articles were written between 2000 and 2010 (11-20) (Table 5).

**Table 5.** Top ten most cited manuscripts about hyperthermic intraperitoneal chemotherapy

| No | Article | Author | Journal name/published | TC | ACY |
|---|---|---|---|---|---|
| **1** | Randomized trial of cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy and palliative surgery in patients with peritoneal carcinomatosis of colorectal cancer (11) | Verwaal, VJ; van Ruth, S; de Bree, E; et al. | Journal of Clinical Oncology, 2003 | 1,182 | 65.6 |
| **2** | Colorectal cancer (12) | Weitz, J; Koch, M; Debus, J; et al. | Lancet, 2005 | 821 | 51.3 |
| **3** | 8-year follow-up of randomized trial: cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy in patients with peritoneal carcinomatosis of colorectal cancer (13) | Verwaal, Vic J.; Bruin, Sjoerd; Boot, Henk; et al. | Annals of Surgical Oncology, 2008 | 563 | 43.3 |
| **4** | Peritoneal colorectal carcinomatosis treated with surgery and perioperative intraperitoneal chemotherapy: Retrospective analysis of 523 patients from a multicentric French study (14) | Elias, Dominique; Gilly, Francois; Boutitie, Florent; et al. | Journal of Clinical Oncology, 2010 | 553 | 50.2 |
| **5** | Complete cytoreductive surgery plus intraperitoneal chemohyperthermia with oxaliplatin for peritoneal carcinomatosis of colorectal origin (15) | Elias, Dominique; Lefevre, Jeremie H.; Chevalier, Julie; et al. | Journal of Clinical Oncology, 2009 | 513 | 42.7 |
| **6** | Early- and long-term outcome data of patients with pseudomyxoma peritonei from appendiceal origin treated by a strategy of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (16) | Chua, Terence C.; Moran, Brendan J.; Sugarbaker, Paul H.; et al. | Journal of Clinical Oncology, 2012 | 471 | 52.3 |
| **7** | New standard of care for appendiceal epithelial neoplasms and pseudomyxoma peritonei syndrome (17) | Sugarbaker, PH | Lancet Oncology, 2006 | 390 | 26 |
| **8** | Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for malignant peritoneal mesothelioma: multi-institutional experience (18) | Yan, Tristan D.; Deraco, Marcello; Baratti, Dario; et al. | Journal of Clinical Oncology, 2009 | 356 | 29.6 |
| **9** | Peritoneal carcinomatosis of colorectal origin- incidence and current treatment strategies (19) | Koppe, MJ; Boerman, OC; Oyen, WJG; et al. | Annals of Surgery, 2006 | 324 | 21.6 |
| **10** | Should the Treatment of peritoneal carcinomatosis by cytoreductive surgery and hyperthermic intraperitoneal chemotherapy still be regarded as a highly morbid procedure? A systematic review of morbidity and mortality (20) | Chua, Terence C.; Yan, Tristan D.; Saxena, Akshat; et al. | Annals of Surgery, 2006 | 321 | 26.5 |

TC: Total citation; ACY: Average citations per year

**Table 6.** First fifteen journals by the number of publications and citations on hyperthermic intraperitoneal chemotherapy

| Journal name | No | % of 522 | C |
|---|---|---|---|
| **Annals of Surgical Oncology** | 491 | 15.6 | 9,565 |
| **European Journal of Surgical Oncology** | 175 | 5.5 | 3,461 |
| **Journal of Surgical Oncology** | 137 | 4.3 | 3,417 |
| **International Journal of Hyperthermia** | 77 | 2.4 | 575 |
| **Journal of Clinical Oncology** | 72 | 2.2 | 4,200 |
| **International Journal of Gynecological Cancer** | 54 | 1.7 | 330 |
| **World Journal of Surgical Oncology** | 43 | 1.3 | 376 |
| **Diseases of the Colon Rectum** | 40 | 1.2 | 668 |
| **European Journal of Cancer** | 38 | 1.2 | 684 |
| **Pleura and Peritoneum** | 38 | 1.2 | 114 |
| **British Journal of Surgery** | 37 | 1.1 | 1,142 |
| **World Journal of Gastroenterology** | 37 | 1.1 | 1,174 |
| **Indian Journal of Surgical Oncology** | 36 | 1.1 | 151 |
| **Surgical Oncology Oxford** | 36 | 1.1 | 279 |
| **Anticancer Research** | 35 | 1.1 | 433 |

No: Number of publications; C: Citations (without self-citations)

### *4.5. Productivity of Journals*

Journals containing publications on HIPEC were examined in terms of the number of publications and citations they received. Fifteen journals with the largest number of articles are presented in Table 6 with their publication numbers and citations. A total of 556 journals published on HIPEC were examined, and 54 most active journals with at least 10 articles were found. It was observed that the journal Annals of Surgical Oncology published 15% of the articles on HIPEC. The 2019 impact factor of this journal was 3.7, and its effectiveness on surgical oncology seemed to be high (Figure 7).

### 4.6. *International Collaboration*

When the studies published by countries on HIPEC were examined, the most active country was determined as the USA. Collaborations of countries on research were also examined. The intersection point of all researcher countries was the USA. France, Germany, and Belgium were the countries that cooperated most with the USA. A collaborative cluster was formed around Italy. In this cluster, Australia, Canada, and Turkey were also included. Eastern countries had formed a separate cooperation network and China was at the center of this network (Figure 8).

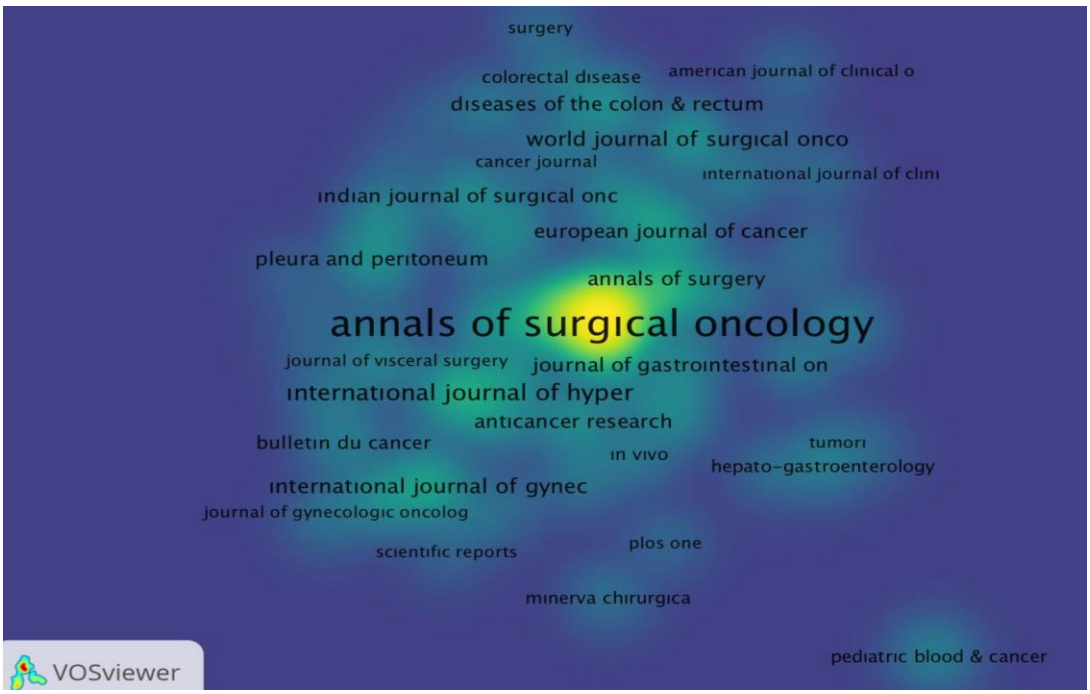


**Figure 7.** Density visualization of productivity of journals

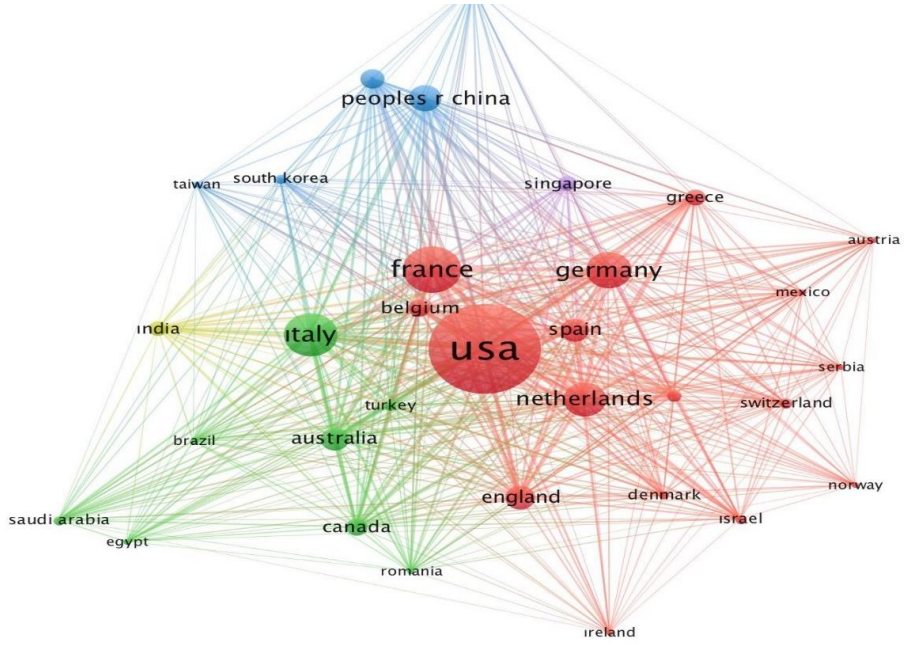


**Figure 8.** Network visualization of productivity of countries

*4.7. Trend Topics*

While reviewing the articles on HIPEC, we alsoidentified new trends and topics in this regard. Frequently used keywords in the articles on HIPEC, the frequency of these words, and their interrelationships would provide insight into new research topics. The words cytoreductive surgery and peritoneal carcinomatosis identified the subjects with the strongest association with HIPEC. Ovarian cancers, gastric cancers, and colorectal cancers were found to be the types of cancer that had the strongest relationship with HIPEC. The most frequently repeated chemotherapeutic agents in the articles on HIPEC were observed as Paclitaxel, Cisplatin, and Mitomycin (Figure 9).

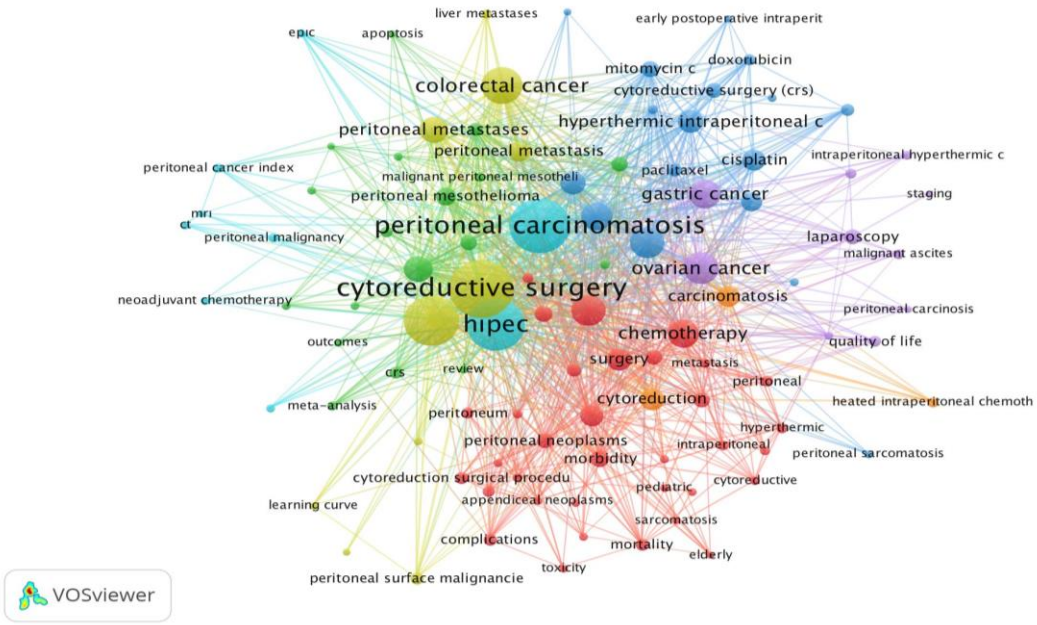


**Figure 9.** Network visualization map of relationships between the most commonly used trend keywords

## 5. Discussion

Spread patterns, survival rates, and treatment modalities of cancers that spread to the peritoneal surface vary according to the organs from which they originated. Ovarian cancers are also among the female malignancies that spread to the peritoneum surface, with low survival rates, and the eighth rank among cancer-related deaths (21). The use of HIPEC has increased in ovarian cancer and other cancers with peritoneal spread. While providing cytoreductive excision of peritoneal spreading tumors, ways to increase the effectiveness of chemotherapy were investigated. Intraperitoneal chemotherapies were used as well as systemic chemotherapies, and increased efficacy was demonstrated at 41-43°C (22). Although it was observed that the use of HIPEC in colorectal cancers, other cancers of the gastrointestinal system, and cancers has increased over the years, there are no global studies on this subject.

Since HIPEC is used in all tumors with peritoneal involvement, clinicians who do research on this subject will benefit from the results of our article. The effectiveness of medical research data and cooperation options of physicians dealing with especially gastrointestinal system cancers and gynecological oncology were clearly emphasized. The fact that the documents published about HIPEC were mainly research articles and the low number of reviews were deficiencies for the method used for about 30 years. Among the 2020 publications that we did not include in our research, there were 60 reviews. The 2020 publications were mostly produced in the fields of medical oncology, gastrointestinal oncology, and gynecological oncology. The gynecological Oncology Journal was the most productive journal.

There are many hypotheses explaining the observation of cancer recurrences after cytoreductive surgery and HIPEC procedures. In a recent review evaluating the effects of HIPEC treatments in the microenvironment, it has been mentioned that immune stimulation can increase the resistance of endothelial and mesenchymal cells (23). There are also various inconsistencies regarding the standardization of HIPEC protocols applied in gynecological oncology centers. In a review, where HIPEC experiences and current literature were shared, it was emphasized that the team working in the center and dealing with this procedure required gynecologists, pharmacologists, perfusionists, and trained nurses. It was recommended that the entire team had to be trained in medical practices for the prevention and extraction of chemotherapeutic agents during application. The same center recommended the use of crystalloid, furosemide for diuresis before HIPEC, and sodium thiosulfate for protection against nephrotoxicity. It was emphasized that Cisplatin experiences were positive in HIPEC application, especially in patients with epithelial ovarian cancer (24).

Gynecological oncology results of HIPEC procedures were compared in different studies. In an article in which HIPEC applications in primary epithelial ovarian cancer were evaluated and 35 studies were compiled, inconsistencies between the data were mentioned. In this article, it was mentioned that the findings of only one study showed that the HIPEC procedure was beneficial in interval cytoreductive surgery (25). Multicenter randomized controlled studies are required to standardize HIPEC

procedures and determine their effectiveness in epithelial ovarian cancer. There were also studies evaluating cytoreductive surgeries and HIPEC applications in patients with peritoneal spread endometrial cancer. In a recent article conducted on 43 participants, HIPEC applications in addition to surgery showed an increase in survival rate (26).

There were studies evaluating the efficacy of HIPEC use in epithelial ovarian cancers; however, none of the randomized controlled studies demonstrated that adding HIPEC at the time of cytoreductive surgery increased survival in cases of recurrent cancer and stage 4 disease (27). However, some prospective cohort studies and randomized controlled studies showed that the combination of cytoreductive surgery and HIPEC reduced recurrence and offered positive effects on survival (28). There were also cases where HIPEC treatment was applied after laparoscopic cytoreductive surgeries. Laparoscopic cytoreduction + HIPEC combination was compared with laparotomic combination in a study carried out on 825 cases, in which different tumor-originated peritoneal metastases were evaluated. There was no difference between the two groups in terms of surgery times, blood transfusions, and postoperative morbidity-mortality. Hospitalization time and transition to adjuvant chemotherapy were found to be shorter in the laparoscopy group (29). Single port laparoscopic cytoreductive surgery and HIPEC treatments of low-grade peritoneal malignancies were also shown to be useful new approaches (30).

Various recommendations and regulations have been made regarding the management of gynecological cancers during the COVID-19 pandemic process. These recommendations included approaches to the use of HIPEC regimens. Neoadjuvant chemotherapy options should be considered when determining care in the period after cytoreductive surgery in advanced cancer cases. It seems logical to avoid HIPEC applications during the pandemic period due to the limitations of intensive care and postoperative care (31).

Bibliometric analysis provides a global perspective for scientists doing research on a specific subject (32). Performing bibliometric analysis with up-to-date, correct keywords and correct databases ensures objective data. The globality of bibliometric analysis helps to orient towards multidisciplinary approaches and correct research areas. Although bibliometric analyzes in obstetrics and gynecology have increased in recent years, there is no bibliometric analysis in the literature about gynecological oncology and HIPEC.

## 6. Conclusion

HIPEC therapies should be considered an area of research that has been studied, published, and cited by surgeons, oncologists, and pharmacologists interested in the treatment of tumors with peritoneal spread. HIPEC treatments are generally applied as combined models supporting cytoreductive surgeries, and research on this subject has increased in the last decade. The results of our study would benefit both oncologists and surgeons and enable them to predict in which direction HIPEC applications will evolve in peritoneal tumors and what research is needed with the support of current literature.

## Acknowledgments

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## Footnotes

**Conflicts of Interest:** None.

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