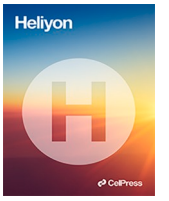
Heliyon 9 (2023) e15309

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



Research article

Global research trends in immunotherapy for head and neck neoplasms: A scientometric study

Zhou Jiang, Chenzhou Wu, Yiming Zhao, Qi Zhan, Kunyu Wang, Yi Li *

State Key Laboratory of Oral Diseases, National Clinical Research Center for Oral Diseases, Dept. of Head and Neck Oncology, West China Hospital of Stomatology, Sichuan University, Chengdu, Sichuan, 610041, PR China

A R T I C L E I N F O

Keywords:
Scientometric
Immunotherapy
Head and neck neoplasms
Head and neck squamous cell carcinoma
Nivolumab
PD-1

A B S T R A C T

In recent decades, the traditional treatment of head and neck neoplasms has reached a bottleneck with limited improvement in overall survival. Nevertheless, the emerging field of immunotherapy has shown promise. Literature on research into immunotherapy for head and neck neoplasms was retrieved from WoSCC. Citespace was used as a scientometric analysis tool for text mining and visualization of the scientific literature. This analysis included 1915 documents. Recently, the annual number of publications and citations has been growing rapidly. 'Oncology' was the most popular research area. The most dominant institution and country were the University of Pittsburgh and the USA. Ferris RL was not only the most prolific but also the most cited author, demonstrating a strong influence and reputation. Of the ten core journals identified in this field, *Cancer Research* ranked first. 'Regulatory T cell', 'PD-1' and 'biomarker' were regarded as current hotspots, while 'recurrent' and 'nivolumab' were considered as trending keywords. The most cited reference was Ferris RL (2016). Notably, the front trends and future directions in the field may lie in the clinical practice of combination therapy of immunotherapy plus other therapies, the mechanism of impaired immune surveillance, and the improvement in resistance to immunotherapeutic agents. It is firmly believed that the present scientometric analysis has provided both a macroscopic and microscopic overview of research into immunotherapy for head and neck neoplasms, which will assist researchers and oncologists to better understand this discipline and thus promote further development and policies in this field.

1. Introduction

1.1. Immunotherapy for head and neck neoplasms

Head and neck neoplasms are the sixth most common malignant tumors in the world, with approximately 830,000 patients developing head and neck neoplasms each year [1]. It is a general term for a class of cancers with a similar incidence and treatment plan, including oral cancer, pharyngeal cancer, laryngeal cancer, nasal cancer, salivary gland tumor and many other types [2]. More than 90% of head and neck cancers are diagnosed as head and neck squamous cell carcinoma (HNSCC), a malignancy with heterogeneity in anatomy and biology. Major risk factors include smoking, alcohol consumption, and human papillomavirus (HPV) infection

* Corresponding author. Dept. of Head and Neck Oncology, West China Hospital of Stomatology, Sichuan University, No.14, The 3rd section of Renminnan Avenue, Chengdu, Sichuan, 610041, China.
E-mail address: liyi1012@163.com (Y. Li).

https://doi.org/10.1016/j.heliyon.2023.e15309
Received 22 December 2022; Received in revised form 1 April 2023; Accepted 3 April 2023
Available online 13 April 2023

[3,4]. 70%–80% of head and neck cancer patients have locally advanced or metastatic disease when diagnosed, and are more likely to relapse after receiving multiple treatments including surgery, radiotherapy and chemotherapy. The 5-year survival rate of patients diagnosed with HNSCC has not much improved substantially over the past few decades, remaining at around 50% to 60% [5].

Although the traditional therapeutic methods have made some progress in recent years, the prognosis for patients with head and neck neoplasms is still not ideal. At present, patients with localized or early head and neck malignancies are mainly treated by surgery or radiotherapy alone, and the curative effect of surgery or radiotherapy for such patients is basically the same. However, patients with locally advanced head and neck malignancies still need to receive combined chemotherapy after surgery [6]. Some patients still have a high risk of peripheral nerve invasion, vascular invasion or lymph node metastasis after surgery, and need further adjuvant radiotherapy or concurrent radiotherapy and chemotherapy [7]. After radiotherapy, patients are at high risk of microbial infection and invasion [8,9]. There is due to two reasons: firstly, patients' skin and mucosa are damaged by radiotherapy and the physiological barrier is incomplete [10]. Secondly, bone marrow suppression and neutropenia occur after radiotherapy, leading to a decline in patients' immune function [11,12]. In addition, the failure of radiotherapy may also be due to radiation-induced damage to vascular endothelial cells, which accelerates the process of atherosclerosis [13]. Stroke caused by carotid artery stenosis associated with radiotherapy for head and neck tumors is one of the most serious complications of radiotherapy, seriously threatening the life safety of patients [14].

Head and neck tumors are late diagnosed and are prone to recurrence, a serious worldwide health problem. However, immunotherapy is bringing new hope to head and neck cancer patients. Under normal conditions, the immune system can recognize and eliminate tumor cells in the tumor microenvironment to actively play the role of immune killer. However, in order to survive and grow, tumor cells evade surveillance through a variety of mechanisms that inhibit the immune system. Inhibition of tumor antigen expression is the main mechanism of tumor immune escape. Studies have shown that in HNSCC it is very common for tumor cells to reduce tumor antigen expression by downregulating the expression of human leukocyte antigen and antigen processing machinery [15]. In addition, tumor cells can achieve immunosuppression by releasing cells or chemical factors that bind to inhibitory receptors on the surface of immune cells [16].

Immunotherapy, with low toxicity and high specificity, has been gradually applied in the clinical treatment of a variety of tumors, including head and neck neoplasms [17]. Tumor immunotherapy can control and eliminate tumors by restarting and restoring immune response, including monoclonal antibody immune checkpoint inhibitors (ICIs), therapeutic antibodies, cancer vaccines, cell therapy and small molecule inhibitors [18]. Programmed cell death protein 1 (PD-1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) binding to their ligands are the two main mechanisms of immune checkpoint inhibition, which play an important role in the early and late stages of the tumor immune response [18,19]. Blocking antibodies against the two pathways have also been developed and applied. PD-1 can inhibit the proliferation and differentiation of T cells and induce the activated T cells to transform into ineffective T cells or to undergo apoptosis [20]. Pembrolizumab and nivolumab, two PD-1 inhibitors, have been approved by the US Food and Drug Administration (FDA) for recurrent or metastatic head and neck neoplasms [21]. According to the POLARIS-02 study, torepalimab, as the first listed PD-1 ICI for the treatment of malignant melanoma in China, has manageable safety, long-lasting clinical response and significant effect in the treatment of nasopharyngeal carcinoma [22]. It was approved by the State FDA in February 2021 for the treatment of recurrent or metastatic nasopharyngeal carcinoma. Similarly, as an inhibitory receptor, CTLA-4 can inhibit T cell activation by competitively binding CD80/CD86 on the surface of antigen-presenting cells and then transmitting the inhibitory signal to T cells. In the immunotherapy of head and neck tumors, CTLA-4 inhibitors are mainly being explored as combination therapy [23]. In a mouse model of oral cancer, when a PD-1 inhibitor was used alone, the tumor regression rate was 54%. After a double block of PD-1 and CTLA-4, the tumor regression rate reached 71% [24]. The double block showed stronger anti-tumor activity. Lymphocyte activating gene-3 (LAG-3) is another important negative immune checkpoint that has a synergistic effect with PD-1/PD-L1 on immunosuppression [25,26]. Therefore, LAG-3 is expected to become a new immune target for the treatment of head and neck tumors. Moreover, a variety of tumor vaccine therapeutic methods including protein/peptide vaccine and DNA vaccine have been developed, but there are still many shortcomings, such as weak immunogenicity and tumor antigen limitation [27–29]. Among them, the protein/peptide-activated dendritic cell vaccine has attracted considerable attention due to its strong immune activity, but its therapeutic effect in head and neck neoplasms needs further clinical verification. Single cytokine therapy and cell-derived systemic immunotherapy are also in clinical trials. IRX-2 is a compound cytokine biological agent derived from homologous cells that has multiple immunomodulatory effects [30]. The main active components of IRX-2 include interleukin-2 and interleukin-1 β、γ interferon and tumor necrosis factor-α [31]. IRX-2 has been demonstrated to induce lymphocyte infiltration into primary tumors in HNSCC [32]. Studies have found that IRX-2 can improve the 2-year overall survival rate of patients with HNSCC (32% to 61%) [33]. In patients with locally advanced HNSCC who received IRX-2 and immunoadjuvant therapy prior to surgery, 74% of patients achieved tumor remission or stability [34].

1.2. Scientometrics

Scientometrics is a quantitative analysis of the literature in a scientific field by means of mathematical statistics to provide a macroscopic overview of the historical evolution, current hotspots and front trends in the research field, as well as insights into specific objects of interest, such as the most cited reference and author [35,36]. Based on the above literature review on immunotherapy for head and neck neoplasms, it is not difficult to find the overall survival rate has improved to some extent through a lot of effort and progress. Therefore, it is quite necessary to conduct a scientometric study on global research trends in immunotherapy for head and neck neoplasms, and the results were presented with mapping knowledge domains, a form of visualization, from which relevant investigators will reveal a wealth of valuable information and promote further development of the discipline. Meanwhile, the relevant

policies regarding research collaboration and funding allocation may increase in response to new findings from this study.

2. Material and methods

The primary data were retrieved on July 28, 2021 by two researchers from Thomson Reuters' Web of Science Core Collection (WoSCC), the preferred database source for Citespace (5.8. R1 version) used as the scientometric analysis tool in this study, but the editions only covered Science Citation Index Expanded required for the following literature search [37]. The search strategies were specifically described in the appendix and the time span was set from 1900 to 2020. Language was set to "all". After removing meeting abstracts, editorial materials, letters and other types of documents, a total of 1915 documents (1400 articles and 515 reviews) were ultimately retained and then were exported in a form of the plain text file containing the full record and cited references. Subsequently, Citespace, developed by Chaomei Chen, served as a scientometric analysis software for text mining and visualiation in scientific literature [38] (Fig. 1).

As the first document in the field of immunotherapy for head and neck neoplasms was published in 1975, the time slice of the primary data was set from January 1975 to December 2020. As mentioned above, the results were presented in a visual form called mapping knowledge domains, such as cluster views consisting of nodes and links. The largest node was referred to as the landmark node, while the most central node was termed as the hub node [38]. Each node represented the object of analysis in this study, such as a WoS category, institution, country, author, journal, keyword or cited reference. Each link indicated the relationship between two analysis objects, such as the co-occurrence of categories or keywords, the co-operation of institutions, countries or authors, and the co-citation of authors, journals and references [39]. The top 50 annual levels of the most occurring or cited items were selected to form a cluster view, and each level may contain multiple qualified nodes. If a cluster view was overly complex or discrete, the cluster network could be pruned by removing nonsignificant or ignorable nodes, to generate more accurate results [40]. Cluster networks were characterized by the fact that all nodes could be divided into different clusters with respective labels selected from the index terms of their own citers by a log-likelihood ratio test performed by Citespace [41]. The label of a cluster can well summarize and represent all nodes within it. In addition, burst detection could be performed to discover keywords, cited references and other items with a sudden increase in citations over a period of time, which could well reflect hotspots and trends in a scientific field [38,42].

3. Results

3.1. General analysis

A total of 1915 documents (1400 articles and 515 reviews) on research into immunotherapy for head and neck neoplasms from 1900 to 2020 were collected, with a total citation count of 46,546 times (40,996 citations excluding self-citations), an average citation count of 24.31 times, and an H-index of 88. The main language is English, accounting for 96.50%, with the rest being mainly German and French. In this research field, the first paper entitled "Immunologic aspects of human thyroid cancer. Humoral and cell-mediated immunity, and a trial of immunotherapy" was published in 1975. As the annual number of publications and citations is shown in Fig. 2 by year from 1975 to 2020, it is observed that the distribution can be divided into three periods. In the first period 1975–1990, research into immunotherapy for head and neck neoplasms was in an initial stage with few scientific outputs. Then, this field stepped into the development period 1991–2015 and came into focus, but the annual number of publications did not exceed 100 or the annual number

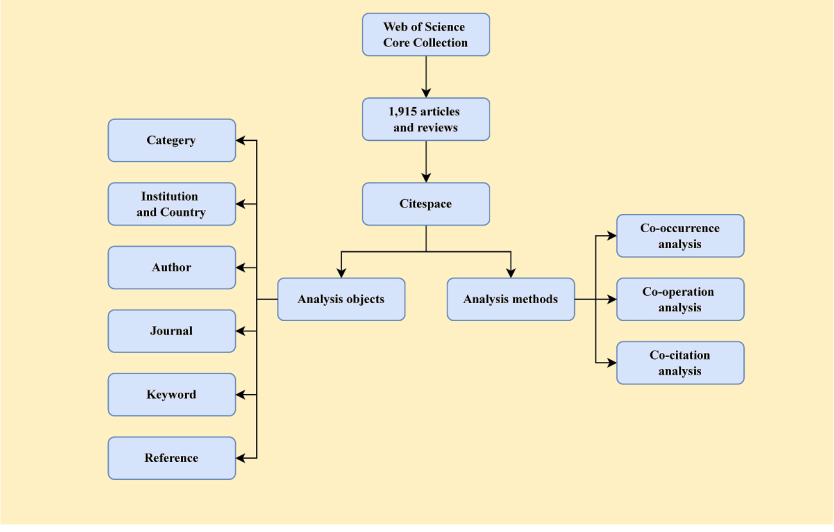


Fig. 1. The workflow of the study.

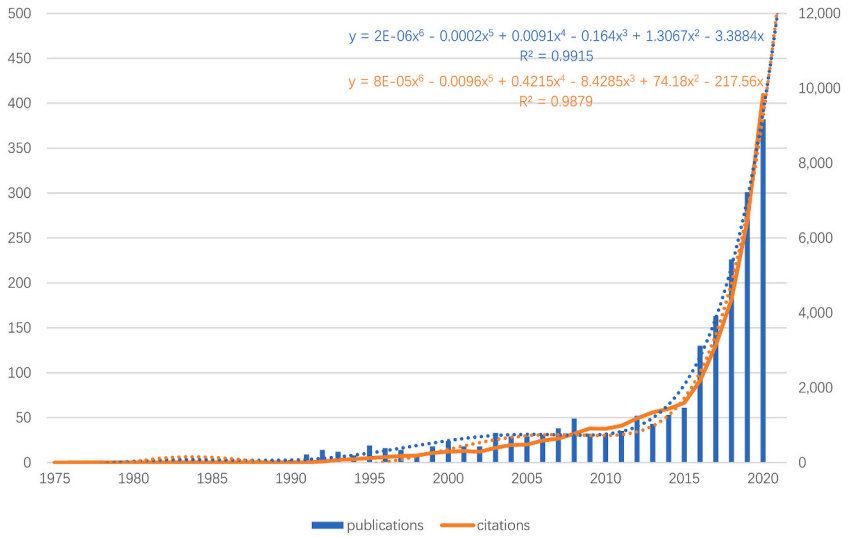


Fig. 2. The distribution of publications and citations from 1975 to 2020. The annual number of publications and citations from 1975 to 2020 in this field showed a trend of continuous and rapid growth, and the distribution can be divided into three periods: initial period (1975–1990), development period (1991–2015) and boom period (2016–2020). The dotted lines are the trend lines, whose equations are shown at upper right corner.

of citations did not exceed 2000 until 2016, the key turning point. The last period 2016–2020 could be called the boom period, since there was an obvious and tremendous growth in both publications and citations, suggesting that immunotherapy for head and neck neoplasms has attracted increasing attention and that a lot of breakthroughs and advances have been made in recent years.

3.2. Category analysis

A total of 45 research areas were identified in the co-occurrence analysis of WOS categories. 1026 publications belonged to 'oncology', accounting for 38.73% of the total, followed by 'immunology' (287), 'otorhinolaryngology' (163), 'medicine, research & experimental' (157) and 'dentistry, oral surgery & medicine' (128). 'Oncology' was shown to be the most popular and central category. More importantly, research into immunotherapy for head and neck neoplasms was an interdisciplinary field that had attracted a wide range of attention.

3.2.1. Institution and country analysis

The co-operation analysis of institutions revealed that the University of Pittsburgh played a leading role in immunotherapy research on head and neck neoplasms, contributing 77 publications and partnering with 41 other institutions. Notably, 47 papers were published in the last five years (2016–2020). Based on the most cited articles from this institution, it is found that the institution has made important achievements mainly in the following three aspects. 1) Reviews on immunological principles related to head and neck cancer, including the concept of cancer immunosurveillance, immune escape and tumor-induced immune suppression [43,44]. 2) The establishment of the long-term efficacy and safety profile of nivolumab [45]. 3) Identification of the mechanisms underlying the clinical response of cancer patients treated with tumor antigen-targeted monoclonal antibodies [46].

Among 43 countries involved in the co-operation network of immunotherapy research on head and neck neoplasms, the USA was the most active and dominant country, contributing a total of 730 publications as well as collaborating with up to 29 other countries. The rest of the top five most productive countries are China (351), Germany (243), Japan (219) and Italy (108). A sudden increase in the number of citations over a period of time was referred to as bursts, which could symbolize and emphasize the influence of the scientific outputs of a single entity [42]. For example, the USA experienced a period of citation bursts from 1991 to 2003 with the strongest citation bursts, followed by Japan (1992–2015) and Germany (1999–2011), whereas China and Italy had no bursts.

3.3. Author analysis

A total of 721 authors constituted the co-operation network of research into immunotherapy for head and neck neoplasms. Among them, Ferris RL played a central and important role, collaborating with up to 46 other authors worldwide and having an output of 40 publications. Consistent with the institution analysis above, the most active author came from the University of Pittsburgh, the most active institution.

Nevertheless, the number of citations is more valuable than publications in assessing the influence of an author in a scientific field. The co-citation analysis of authors indicated that Ferris RL was also the most cited one among approximately 1081 authors, with a total of 449 co-citations and the strongest bursts period 2017–2020, followed by Seiwert TY (269), Vermorken JB (220), Topalian SL (213)

and Rosenberg SA (195). On the other hand, Whiteside TL, at the center of the co-citation network, was co-cited with up to 103 other authors, despite she had a relatively low output of 151 publications. Unfortunately, her highly cited papers could not be traced through Citespace in this analysis.

3.4. Journal analysis

76 out of 1915 papers were published on *Oral Oncology*, however, the influence and authority of a journal are determined by the number of its citations rather than its publications. The co-citation analysis of journals showed that 282 journals were co-cited 29,785 times altogether. Based on Bradford's law, core journals in the field of immunotherapy for head and neck neoplasms were identified as follows: *Cancer Research*, *Clinical Cancer Research*, *Journal of Clinical Oncology*, *New England Journal of Medicine*, *International Journal of Cancer*, *Journal of Immunology*, *Nature*, *Proceedings of the National Academy of Sciences of the United States of America*, *Science* and *British Journal of Cancer*. Notably, *Cancer* had relatively fewer citations than the top ten core journals, but it enjoyed the strongest citation bursts from 1988 to 2013, during which time it developed rapidly and received a great deal of attention.

3.5. Keyword analysis

In order to obtain significant results, redundant and ignorable keywords were omitted, and the merged network of keywords was pruned according to Citespace's settings. As shown, the co-occurrence network of keywords consisted of 367 nodes and 821 links between nodes. Each node represented a keyword, and the size of the node indicated the frequency of the keyword. Undoubtedly, 'immunotherapy' was the most frequent keyword in the field of immunotherapy for head and neck neoplasms, also known as the landmark node, and it usually co-occurred with 'cell', 'cancer patient', '*in vivo*', 'mice' and 'ok-432'. On the other hand, the most central keyword is 'monoclonal antibody' in the middle of the co-occurrence network of keywords, also known as the hub node. Based on the strength of the relationships between the keywords, a total of 367 keywords were grouped into 14 clusters with different labels shown in Fig. 3, which were selected from the title terms of their own citers using a log-likelihood ratio test performed by Citespace. It was found that cluster #0, labelled 'cancer tissue', was up to date, which could well reflect the front trends in the field. The most frequent and hotly debated keywords in this cluster were 'regulatory T cell', 'PD-1' and 'biomarker'.

In addition, a number of critical citing references were identified that covered as many keywords as possible in cluster #0, which highlighted the specific cutting-edge advances in the field. For instance, De Costa AM et al. reviewed potential immunotherapeutic approaches for HNSCC patients that have been shown to be effective and mature in the treatment of other solid malignancies and summarized the advances and deficiencies associated with such approaches [47]. Moreover, Schuler PJ et al. pointed out that the prospects of immunotherapy-related clinical trials had dramatically shifted from antibody-based growth factor inhibition to immune checkpoint modulation, and the combination of immunotherapy with other types of therapeutic approaches, such as radiotherapy and chemotherapy, is promising and beneficial for head and neck cancer patients [48]. Furthermore, Böttcher A et al. established gene expression profiling of circulating natural killer cells in HNSCC and introduced a couple of candidate genes for further investigation, such as some down-regulated cytokine receptors: CCR7, IL-7R, and CXCR, which may account for the impaired immune surveillance that results in HNSCC [49].

Besides, 'dendritic cell' was detected as the top ranked keyword by bursts, with the strongest burst of 26.96, highlighting that it is one of the research hotspots and made a breakthrough in the period 2002–2015 in Fig. 4a. In the above analysis, the evolution of the discipline was divided into three periods: the initial period (1975–1990), the development period (1991–2015) and the boom period (2016–2020). However, no significant research trends were observed in the initial period, as the number of publications in this period was too low to perform a burst detection or to generate a visual map. In the development period, the research trends mainly fall on 'interleukin 2' and 'recombinant interleukin 2', which lasted for more than eleven years (Fig. 4b), whereas in the boom period, the strongest burst keywords were 'hpv associated', 'dendritic cell', 'antitumor immunity' and 'oropharyngeal cancer' (Fig. 4c). Notably,

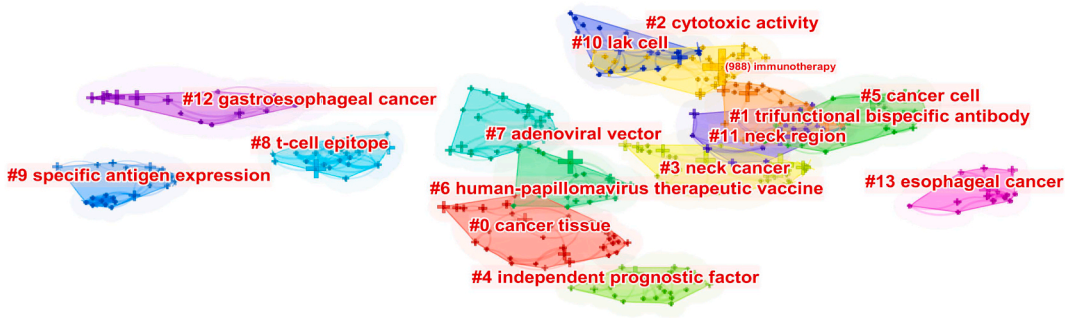


Fig. 3. The co-occurrence network of keywords. Each node represents a keyword, and each link between two nodes represents the co-occurrence relationship between two keywords. In this network, a total of 367 keywords were divided into 14 clusters from #0 to #13 with respective theme label. It was found that cluster #0 labelled 'cancer tissue' was up to date, which could well reflect the front trends in this field. And 'immunotherapy' was the most popular keyword, with a co-occurrence count of 988.

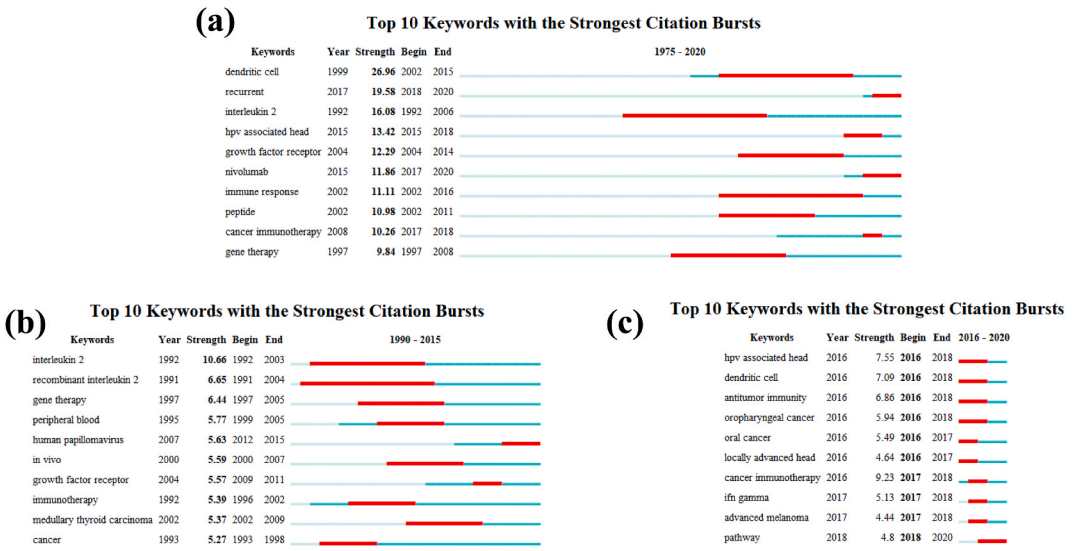


Fig. 4. Top 10 keywords with the strongest citation burst. From 1975 to 2020, 'dendritic cell' was the strongest burst keyword with a strength value of 26.96 (a), and the latest burst keywords were 'recurrent' and 'nivolumab' also known as trending keywords. From 1990 to 2015, 'interleukin 2' and 'recombinant interleukin 2' were the strongest burst keywords (b), while from 2016 to 2020, the strongest burst keywords were 'hpv associated', 'dendritic cell', 'antitumor immunity' and 'oropharyngeal cancer'.

the most recent burst keywords were 'recurrent' and 'nivolumab', also known as trending keywords, which indicate current and future research directions in the field of immunotherapy for head and neck neoplasms.

3.6. Reference analysis

The 1915 documents retrieved from WoSCC, also known as citing references, constituted the research front in the field of immunotherapy for head and neck neoplasms, while the intellectual base comprised their cited references. Similarly, the co-citation network of references was pruned by Citespace in order to produce more significant results. The top 10 cited references with the most citations were listed below, and the top ranked was 'Ferris RL (2016)' with a citation count of 205 (Table 1). In this article, Ferris RL et al. demonstrated that treatment with nivolumab compared with standard single-agent therapy such as methotrexate, docetaxel, or

Table 1
The top 10 most cited references.

Rank	Cited Reference	Citation count	Journal	IF	Author	Year
1	Nivolumab for Recurrent Squamous-Cell Carcinoma of the Head and Neck	205	*NEW ENGL J MED*	175.3	Ferris RL	2106
2	Safety and clinical activity of pembrolizumab for treatment of recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-012): an open-label, multicentre, phase 1b trial	115	*LANCET ONCOL*	53.88	Seiwert TY	2016
3	Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries	99	*CA-CANCER J CLIN*	285.5	Bray F	2018
4	Pembrolizumab versus methotrexate, docetaxel, or cetuximab for recurrent or metastatic head-and-neck squamous cell carcinoma (KEYNOTE-040): a randomised, open-label, phase 3 study	89	*LANCET*	201.5	Cohen EEW	2019
5	Comprehensive genomic characterization of head and neck squamous cell carcinomas	70	*NATURE*	68.74	Lawrence MS	2015
6	The blockade of immune checkpoints in cancer immunotherapy	68	*NAT REV CANCER*	69.25	Pardoll DM	2012
7	Pembrolizumab for Platinum- and Cetuximab-Refractory Head and Neck Cancer: Results From a Single-Arm, Phase II Study	63	*J CLIN ONCOL*	49.84	Bauml J	2017
8	Pembrolizumab in Patients With Advanced Triple-Negative Breast Cancer: Phase Ib KEYNOTE-012 Study	63	*J CLIN ONCOL*	49.84	Nanda R	2016
9	Nivolumab vs investigator's choice in recurrent or metastatic squamous cell carcinoma of the head and neck: 2-year long-term survival update of CheckMate 141 with analyses by tumor PD-L1 expression	62	*ORAL ONCOL*	5.45	Ferris RL	2018
10	Pembrolizumab alone or with chemotherapy versus cetuximab with chemotherapy for recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-048): a randomised, open-label, phase 3 study	54	*LANCET*	201.5	Burtness B	2019

cetuximab led to longer overall survival in patients with recurrent HNSCC after platinum chemotherapy [50].

By clustering, the network was divided into 12 clusters with different labels, and cluster #7, labelled 'neoadjuvant', was the most recent (mean year = 2017). Therefore, a couple of key citing references were traced, covering as many cited references in this cluster as possible, which could well represent the research front in this field. For example, Galvis MM et al. validated the efficacy and safety of immunotherapy for HNSCC patients, especially for HPV- and PD-L1- positive ones through a systematic review and meta-analysis [51]. In recent years, great importance has benn attached to major breakthroughs, predictive biomarkers and future perspectives of immunotherapy for HNSCC [52–54]. However, a majority of patients presented resistance to immunotherapeutic agents, such as ICIs, Napolitano M et al. provided a practical guide to assist clinical oncologists in the best candidate selection of patients for immunotherapy [55]. The application of ICIs in the treatment of head and neck neoplasms are listed in Table 3.

In addition, 'Bonner JA (2006)' was the most cited reference by bursts, with a burst of 10.94 in the period 2006–2007 (Table 2). Bonner JA found that in the locoregional treatment of head and neck cancer, concomitant high-dose radiotherapy plus cetuximab improved locoregional control and reduced mortality without increasing the common toxic effects of radiotherapy [56]. On the other hand, 'Ward MJ (2014)' and 'Lyford-Pike S (2013)' were the latest burst cited references, indicating their significant importance as theoretical backgrounds in the field of immunotherapy for head and neck neoplasms. Their studies mainly focused on the prediction of tumor-infiltrating lymphocytes for outcomes in HPV positive oropharyngeal cancer and the role of the PD-1/PD-L1 pathway in immune resistance of HPV positive HNSCC, respectively [57,58].

4. Conclusions

A total of 1915 documents related to immunotherapy research on head and neck neoplasms were retrieved from WoSCC, with the first article published in 1975. The annual number of publications and citations from 1975 to 2020 in this field showed a continuous and rapid growth trend, and the distribution can be divided into three periods: the initial period (1975–1990), the development period (1991–2015) and the boom period (2016–2020), the latter symbolizing that immunotherapy for head and neck neoplasms has become a popular and intriguing research topic and has made substantial progress in the last five years.

In the field of immunotherapy for head and neck neoplasms, 'oncology' was the most popular research area. Among the 298 institutions, the University of Pittsburgh played a leading role in collaborative research. The USA was also the most active and dominant country. Ferris RL was not only the most productive author in collaborative research but also the most cited author, with a strong influence and reputation in the field. Furthermore, core journals were identified in this field according to Bradford's law: *Cancer Research*, *Clinical Cancer Research*, *Journal of Clinical Oncology*, *New England Journal of Medicine*, *International Journal of Cancer*, *Journal of Immunology*, *Nature*, *Proceedings of the National Academy of Sciences of the United States of America*, *Science* and *British Journal of Cancer*. *Cancer* was also notable for having the strongest citation bursts from 1988 to 2013.

As the most frequent keyword, 'immunotherapy' usually co-occurred with 'cell', 'cancer patient', '*in vivo*', 'mice' and 'ok-432'. However, the most central keyword was 'monoclonal antibody'. Among 14 keyword clusters, it was cluster #0 labelled 'cancer tissue' that best reflected the leading trends in the field, and the most heated keywords in this cluster were 'regulatory T cell', 'PD-1' and 'biomarker'. Similarly, among 12 cited reference clusters, 'neoadjuvant' was the most recent. Beyond that, 'Ferris RL (2016)' was the most cited reference, which laid the foundation for research in the field of immunotherapy for head and neck neoplasms.

A major limitation of this study was that the authors' works were not available through Citespace. In particular, information on the research directions and main contributions of highly cited authors was missing. In addition, bibliometrics focuses more on articles already published in peer-reviewed journals and their citation analysis, ignoring ongoing scientific research, and therefore the measurement system is not sufficiently comprehensive in its coverage.

In conclusion, based on the above analysis of keywords and cited references, especially burst detection, 'recurrent' and 'nivolumab' were considered as trending keywords, and emerging front trends and future research priorities may lie in the following directions. 1) The efficacy and safety of combination therapy of immunotherapy and other types of therapy, such as surgery, radiotherapy and chemotherapy, for head and neck neoplasms. 2) The underlying mechanisms of impaired immune surveillance of tumor-infiltrating immune cells, such as natural killer cells. 3) The improvements in the resistance to immunotherapeutic agents, such as ICIs. As this study is the first bibliometric analysis on global research trends in immunotherapy for head and neck neoplasms, it is believed that the present study would greatly assist relevant scientific researchers and clinical oncologists to better understand the field of immunotherapy for head and neck neoplasms and thereby promote the further development and policies of the discipline.

Declarations

Author contribution statement

Zhou Jiang: Analyzed and interpreted the data; Wrote the paper.
Yi Li: Conceived and designed the experiments
Chenzhou Wu: Analyzed and interpreted the data.
Yiming Zhao: Analyzed and interpreted the data; Wrote the paper.
Qi Zhan: Contributed reagents, materials, analysis tools or data.
Kunyu Wang: Contributed reagents, materials, analysis tools or data.

Table 2
The top 10 cited references with the strongest citation bursts.

Rank	Cited reference	Strength of bursts	Beginning year	Ending year
1	Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck	10.94	2007	2013
2	Human papillomavirus and survival of patients with oropharyngeal cancer	8.29	2013	2017
3	A unique subset of $CD4^{+}CD25highFoxp3+$ T cells secreting interleukin-10 and transforming growth factor-beta1 mediates suppression in the tumor microenvironment	7.21	2010	2014
4	Platinum-based chemotherapy plus cetuximab in head and neck cancer	6.20	2010	2016
5	Vaccination against HPV-16 oncoproteins for vulvar intraepithelial neoplasia	6.18	2013	2014
6	Improved survival with ipilimumab in patients with metastatic melanoma	5.94	2013	2016
7	Immune suppression in head and neck cancers: a review	5.94	2013	2016
8	Prognostic value of tumor-infiltrating $CD4^{+}$ T-cell subpopulations in head and neck cancers	5.28	2010	2014
9	Tumour-infiltrating lymphocytes predict for outcome in HPV-positive oropharyngeal cancer	4.54	2016	2020
10	Evidence for a role of the PD-1:PD-L1 pathway in immune resistance of HPV-associated head and neck squamous cell carcinoma	4.25	2013	2020

Table 3
The application of ICIs in the treatment of head and neck neoplasms.

Target	Drug	Application in the treatment of head and neck neoplasms	Advantages	Shortcomings
PD-1/PD-L1	Pembrolizumab [1]	1) previous first-line systemic treatment failure, locally advanced or metastatic esophageal squamous cell carcinoma (ESCC) (comprehensive positive score (CPS) $\geq$ 10) 2) the first-line treatment of metastatic or unresectable recurrent HNSCC	Complement the traditional treatment of HNSCC and improve the median overall survival rate and objective response rate	10%–30% adverse reaction
	Nivolumab [2]	Platinum-containing regimen treatment failure, recurrent or metastatic HNSCC		
	Camrelizumab [3–5]	1) previous first-line chemotherapy failure, locally advanced or metastatic ESCC 2) previous second-line or chemotherapy failure, advanced nasopharyngeal carcinoma		
	Toripalimab [6]	Previous second-line or systemic treatment failure, recurrent or metastatic nasopharyngeal carcinoma		
CTLA-4	Tremelimumab [7,8]	Low or no PD-L1 tumor cell expression, recurrent or metastatic HNSCC	As combination therapy	Limited evidence of anti-CTLA4 activity of single drug in HNSCC

1. de Sousa, L.G.,R. Ferrarotto, *Pembrolizumab in the first-line treatment of advanced head and neck cancer*. Expert Rev Anticancer Ther, 2021. **21**(12): p. 1321–1331.
2. Ferris, R.L., G. Blumenschein, Jr., J. Fayette et al. Nivolumab for Recurrent Squamous-Cell Carcinoma of the Head and Neck. N Engl J Med, 2016. 375(19): p. 1856–1867.
3. Zhang, W., C. Yan, X. Gao et al. Safety and Feasibility of Radiotherapy Plus Camrelizumab for Locally Advanced Esophageal Squamous Cell Carcinoma. Oncologist, 2021. 26(7): p. e1110-e1124.
4. Zhou, C., C. Shangguan, M. Shi et al. Camrelizumab and metronomic capecitabine for patients with treatment-refractory solid tumors (McCREST trial). Future Oncol, 2022. 18(23): p. 2495–2503.
5. Mo, D.C., J.F. Huang, P.H. Luo et al., PD-1/PD-L1 inhibitor plus chemotherapy versus standard of care in the first-line treatment for recurrent or metastatic head and neck squamous cell carcinoma. Eur Arch Otorhinolaryngol, 2023. 280(1): p. 1–9.
6. Yamamoto, S.,K. Kato, JUPITER-06 establishes immune checkpoint inhibitors as essential first-line drugs for the treatment of advanced esophageal squamous cell carcinoma. Cancer Cell, 2022. 40(3): p. 238–240.
7. Ferris, R.L., R. Haddad, C. Even et al. Durvalumab with or without tremelimumab in patients with recurrent or metastatic head and neck squamous cell carcinoma: EAGLE, a randomized, open-label phase III study. Ann Oncol, 2020. 31(7): p. 942–950.
8. Siu, L.L., C. Even, R. Mesía et al. Safety and Efficacy of Durvalumab With or Without Tremelimumab in Patients With PD-L1–Low/Negative Recurrent or Metastatic HNSCC: The Phase 2 CONDOR Randomized Clinical Trial. JAMA Oncology, 2019. 5(2): p. 195–203.

Data availability statement

Data included in article/supp. material/referenced in article.

Funding

This work was supported by The National Natural Science Foundation of China [Grant No. 81972546 to Y.L.].

Conflict of interests

Authors declare no conflict of interests.

Acknowledgment

Zhou Jiang especially wishes to thank Mayday, whose songs have given him powerful spiritual support during the period of writing.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e15309.

References

[1] F. Bray, J. Ferlay, I. Soerjomataram, et al., Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries, CA A Cancer J. Clin. 68 (6) (2018) 394–424.
[2] L.Q.M. Chow, Head, Neck Cancer, N. Engl. J. Med. 382 (1) (2020) 60–72.
[3] Comprehensive genomic characterization of head and neck squamous cell carcinomas, Nature 517 (7536) (2015) 576–582.
[4] C. Leemans, B. Braakhuis, R. Brakenhoff, The molecular biology of head and neck cancer, Nat. Rev. Cancer 11 (1) (2011) 9–22.
[5] D. de Boer, A. Brink, M. Buijze, et al., Establishment and genetic landscape of precancer cell model systems from the head and neck mucosal lining, Mol. Cancer Res. : MCR 17 (1) (2019) 120–130.
[6] A.C. Chi, T.A. Day, B.W. Neville, Oral cavity and oropharyngeal squamous cell carcinoma–an update, CA A Cancer J. Clin. 65 (5) (2015) 401–421.
[7] A.F. Alfouzan, Radiation therapy in head and neck cancer, Saudi Med. J. 42 (3) (2021) 247–254.
[8] M.E. Gaubatz, A.R. Bukatko, M.C. Simpson, et al., Racial and socioeconomic disparities associated with 90-day mortality among patients with head and neck cancer in the United States, Oral Oncol. 89 (2019) 95–101.
[9] S.N. Hamilton, E. Tran, E. Berthelet, et al., Early (90-day) mortality after radical radiotherapy for head and neck squamous cell carcinoma: a population-based analysis, Head Neck 40 (11) (2018) 2432–2440.
[10] M.L. Gillison, A.M. Trotti, J. Harris, et al., Radiotherapy plus cetuximab or cisplatin in human papillomavirus-positive oropharyngeal cancer (NRG Oncology RTOG 1016): a randomised, multicentre, non-inferiority trial, Lancet 393 (10166) (2019) 40–50.
[11] M.D. Olson, K.M. Van Abel, R.N. Wehrs, et al., Ewing sarcoma of the head and neck: the Mayo Clinic experience, Head Neck 40 (9) (2018) 1999–2006.
[12] M.E. Shaul, Z.G. Fridlender, Tumour-associated neutrophils in patients with cancer, Nat. Rev. Clin. Oncol. 16 (10) (2019) 601–620.
[13] A. Greco, A. Gallo, A. De Virgilio, et al., Carotid stenosis after adjuvant cervical radiotherapy in patients with head and neck cancers: a prospective controlled study, Clin. Otolaryngol. 37 (5) (2012) 376–381.
[14] A.S. Scott, L.A. Parr, P.A.S. Johnstone, Risk of cerebrovascular events after neck and supraclavicular radiotherapy: a systematic review, Radiother. Oncol. 90 (2) (2009) 163–165.
[15] C. Wickenhauser, D. Bethmann, M. Kappler, et al., Tumor microenvironment, HLA class I and APM expression in HPV-negative oral squamous cell carcinoma, Cancers 13 (4) (2021).
[16] C.T. Allen, N.P. Judd, J.D. Bui, et al., The clinical implications of antitumor immunity in head and neck cancer, Laryngoscope 122 (1) (2012) 144–157.
[17] V. Dogan, T. Rieckmann, A. Munscher, et al., Current studies of immunotherapy in head and neck cancer, Clin. Otolaryngol. 43 (1) (2018) 13–21.
[18] R.O. Dillman, Cancer immunotherapy, Cancer Biother. Radiopharm. 26 (1) (2011) 1–64.
[19] B. Rowshanravan, N. Halliday, D.M. Sansom, CTLA-4: a moving target in immunotherapy, Blood 131 (1) (2018) 58–67.
[20] J.R. Brahmer, S.S. Tykodi, L.Q. Chow, et al., Safety and activity of anti-PD-L1 antibody in patients with advanced cancer, N. Engl. J. Med. 366 (26) (2012) 2455–2465.
[21] S. Subramaniam, C. Paterson, J. McCaul, Immunotherapy in the management of squamous cell carcinoma of the head and neck, Br. J. Oral Maxillofac. Surg. 57 (10) (2019) 957–966.
[22] F. Wang, X. Wei, J. Feng, et al., Efficacy, safety, and correlative biomarkers of toripalimab in previously treated recurrent or metastatic nasopharyngeal carcinoma: a phase II clinical trial (POLARIS-02), J. Clin. Oncol. : Off. J. Am. Soci. Clin. Oncol. 39 (7) (2021) 704–712.
[23] L.L. Siu, C. Even, R. Mesía, et al., Safety and efficacy of Durvalumab with or without tremelimumab in patients with PD-L1–low/negative recurrent or metastatic HNSCC: the phase 2 CONDOR randomized clinical trial, JAMA Oncol. 5 (2) (2019) 195–203.
[24] S. Dorta-Estremera, V.L. Hegde, R.B. Slay, et al., Targeting interferon signaling and CTLA-4 enhance the therapeutic efficacy of anti-PD-1 immunotherapy in preclinical model of HPV+ oral cancer, J. ImmunoTher. Cance. 7 (1) (2019) 252.
[25] A.K. Mishra, T. Kadoishi, X. Wang, et al., Squamous cell carcinomas escape immune surveillance via inducing chronic activation and exhaustion of CD8+ T Cells co-expressing PD-1 and LAG-3 inhibitory receptors, Oncotarget 7 (49) (2016) 81341–81356.
[26] W.-W. Deng, L. Mao, G.-T. Yu, et al., LAG-3 confers poor prognosis and its blockade reshapes antitumor response in head and neck squamous cell carcinoma, OncoImmunology 5 (11) (2016) e1239005.
[27] Q. Li, M. Prince, J. Moyer, Immunotherapy for head and neck squamous cell carcinoma, Oral Oncol. 51 (4) (2015) 299–304.
[28] N. Bloy, A. Buqué, F. Aranda, et al., Trial watch: naked and vectored DNA-based anticancer vaccines, OncoImmunology 4 (5) (2015) e1026531.
[29] Y. Choi, S. Hur, T. Kim, et al., A phase II, prospective, randomized, multicenter, open-label study of GX-188e, an HPV DNA vaccine, in patients with cervical intraepithelial neoplasia 3, Clin. Cancer Res. : Off. J. Am. Assoc. Canc. Res. 26 (7) (2020) 1616–1623.
[30] N.L. Berinstein, G.T. Wolf, P.H. Naylor, et al., Increased lymphocyte infiltration in patients with head and neck cancer treated with the IRX-2 immunotherapy regimen, Cancer Immunol. Immunother. 61 (6) (2012) 771–782.
[31] G. Wolf, J. Moyer, M. Kaplan, et al., IRX-2 natural cytokine biologic for immunotherapy in patients with head and neck cancers, OncoTargets Ther. 11 (2018) 3731–3746.
[32] G.T. Wolf, W.E. Fee Jr., R.W. Dolan, et al., Novel neoadjuvant immunotherapy regimen safety and survival in head and neck squamous cell cancer, Head Neck 33 (12) (2011) 1666–1674.
[33] B. Schilling, M. Harasymczuk, P. Schuler, et al., IRX-2, a novel immunotherapeutic, enhances functions of human dendritic cells, PLoS One 8 (2) (2013), e47234.
[34] G. Wolf, S. Liu, E. Bellile, et al., Tumor infiltrating lymphocytes after neoadjuvant IRX-2 immunotherapy in oral squamous cell carcinoma: interim findings from the INSPIRE trial, Oral Oncol. 111 (2020), 104928.
[35] C. Chen, M. Song, Visualizing a field of research: a methodology of systematic scientometric reviews, PLoS One 14 (10) (2019) e0223994.
[36] C. Chen, Science mapping: a systematic review of the literature, J. Data Infor. Sci. 2 (2) (2017) 1–40.
[37] J. Nicolaisen, Bibliometrics and citation analysis: from the science citation index to cybermetrics, J. Am. Soc. Inf. Sci. Technol. 61 (1) (2010) 205–207.

[38] C. Chen, CiteSpace II: detecting and visualizing emerging trends and transient patterns in scientific literature, J. Am. Soc. Inf. Sci. Technol. 57 (3) (2006) 359–377.
[39] R.R. Braam, H.F. Moed, A.F.J. van Raan, Mapping of science by combined co-citation and word analysis. II: dynamical aspects, J. Am. Soc. Inf. Sci. 42 (4) (1991) 252–266.
[40] C. Chen, Searching for intellectual turning points: progressive knowledge domain visualization, Proc. Natl. Acad. Sci. U. S. A. 101 (Suppl 1) (2004) 5303–5310.
[41] C. Chen, F. Ibekwe-SanJuan, J. Hou, The structure and dynamics of cocitation clusters: a multiple-perspective cocitation analysis, J. Am. Soc. Inf. Sci. Technol. 61 (7) (2010) 1386–1409.
[42] C. Chen, CiteSpace : a Practical Guide for Mapping Scientific Literature, 2016.
[43] R.L. Ferris, Immunology and immunotherapy of head and neck cancer, J. Clin. Oncol. 33 (29) (2015) 3293–3304.
[44] T.L. Whiteside, Exosomes and tumor-mediated immune suppression, J. Clin. Invest. 126 (4) (2016) 1216–1223.
[45] R.L. Ferris, G. Blumenschein Jr., J. Fayette, et al., Nivolumab vs investigator's choice in recurrent or metastatic squamous cell carcinoma of the head and neck: 2-year long-term survival update of CheckMate 141 with analyses by tumor PD-L1 expression, Oral Oncol. 81 (2018) 45–51.
[46] R.L. Ferris, E.M. Jaffee, S. Ferrone, Tumor antigen-targeted, monoclonal antibody-based immunotherapy: clinical response, cellular immunity, and immunoescape, J. Clin. Oncol. 28 (28) (2010) 4390–4399.
[47] A.M. De Costa, M.R. Young, Immunotherapy for head and neck cancer: advances and deficiencies, Anti Cancer Drugs 22 (7) (2011) 674–681.
[48] P.J. Schuler, S. Laban, J. Doescher, et al., Novel treatment options in head and neck cancer, Oncol. Res. Treat. 40 (6) (2017) 342–346.
[49] A. Böttcher, J. Ostwald, D. Koczan, et al., Gene expression profiling of circulating natural killer cells in head and neck squamous cell carcinoma, Cancer Genomics Proteomics 10 (5) (2013) 197–207.
[50] R.L. Ferris, G. Blumenschein Jr., J. Fayette, et al., Nivolumab for recurrent squamous-cell carcinoma of the head and neck, N. Engl. J. Med. 375 (19) (2016) 1856–1867.
[51] M.M. Galvis, G.A. Borges, T.B. Oliveira, et al., Immunotherapy improves efficacy and safety of patients with HPV positive and negative head and neck cancer: a systematic review and meta-analysis, Crit. Rev. Oncol. Hematol. 150 (2020), 102966.
[52] C. Borel, A.C. Jung, M. Burgy, Immunotherapy breakthroughs in the treatment of recurrent or metastatic head and neck squamous cell carcinoma, Cancers 12 (9) (2020).
[53] V. Cristina, R.G. Herrera-Gómez, P. Szturz, et al., Immunotherapies and future combination strategies for head and neck squamous cell carcinoma, Int. J. Mol. Sci. 20 (21) (2019).
[54] N. Gavrielatou, S. Doumas, P. Economopoulou, et al., Biomarkers for immunotherapy response in head and neck cancer, Cancer Treat Rev. 84 (2020), 101977.
[55] M. Napolitano, F.M. Schipilliti, L. Trudu, et al., Immunotherapy in head and neck cancer: the great challenge of patient selection, Crit. Rev. Oncol. Hematol. 144 (2019), 102829.
[56] J.A. Bonner, P.M. Harari, J. Giralt, et al., Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck, N. Engl. J. Med. 354 (6) (2006) 567–578.
[57] M.J. Ward, S.M. Thirdborough, T. Mellows, et al., Tumour-infiltrating lymphocytes predict for outcome in HPV-positive oropharyngeal cancer, Br. J. Cancer 110 (2) (2014) 489–500.
[58] S. Lyford-Pike, S. Peng, G.D. Young, et al., Evidence for a role of the PD-1:PD-L1 pathway in immune resistance of HPV-associated head and neck squamous cell carcinoma, Cancer Res. 73 (6) (2013) 1733–1741.