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Treatment options for oropharyngeal carcinoma — An umbrella review

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Abstract: Introduction: Our umbrella review aimed to summarize and revisit the evidence from all of the meta-analyses and systematic reviews regarding the treatments of oropharyngeal squamous cell carcinoma (OPSCC).
Materials and Methods: Major medical databases such as PubMed, Scopus, Embase, Web of Science, Google Scholar, Cochrane Library, BIOSIS, and EBSCO were searched. The overall search process was conducted in 3 stages.
Results: Finally, a total of 28 studies met the inclusion criteria and were included in this study. Out of those 28 meta-analyses, a total of 315 primary studies were screened in order to extract the data and perform the statistical analysis. In total, data from 22,619 patients was analyzed.
Conclusion: The main objective of the present umbrella review was to summarize and analyze all of the evidence-based data provided by numerous meta-analyses and systematic reviews regarding the treatment of OPSCC. Our study delivers the most up-to-date and evidence-based results regarding the different therapeutic modalities of this malignancy in one concise review, making it the ultimate tool for physicians treating OPSCC.

Keywords: oropharyngeal carcinoma, squamous cell carcinoma, human papillomavirus, cancer, treatment.

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Introduction

The frequency of oropharyngeal squamous cell carcinoma (OPSCC) has been rising for the last decades, mainly due to increased human papillomavirus (HPV) infections. Numerous studies have reported a significant increase in HPV-induced OPSCC,

which is the main contributor to the increase in OPSCC in developed countries. HPV is said to be responsible for over 70% of OPSCC in Europe and the United States, and the number of cases is excepted to rise in the future [1]. The most common cancer of the oropharynx is squamous cell carcinoma (<95% of cases) which arises from the mucosal surface of the oral cavity. Advances in treatments have led to an improvement in survival outcomes over the past three decades, but, despite significant technical advances, oral cancer still has a significant mortality rate, with over 140,000 deaths recorded, representing nearly half of the incident cases (48%) [2]. Interestingly, HPV-positive OPSCC has shown to have a significantly better clinical response to primary treatment and a more desirable prognosis compared to the HPV-negative OPSCC [3].

Historically, OPSCC has been managed primarily with surgery and/or radiotherapy, both of which have evolved in the last decades. Chemotherapy- and immunotherapy-based strategies are usually used for patients with advanced diseases [3]. These days, old surgical approaches that involve large incisions and mandibulotomies are not preferred by most healthcare institutions because of their substantially high mortality and morbidity. In order to decrease the potential morbidity which is associated with these older, more invasive surgical approaches, transoral approaches were developed within the last decades. These include transoral robotic surgery (TORS), transoral laser microsurgery (TLM), or other conventional transoral techniques [4]. Radiotherapy (RT) may be used alone, in combination (adjuvant) with surgery, or combined with chemotherapy (CT). RT is usually used alone for tumors of smaller caliber, or for patients who are not qualified for surgical treatment [5]. When used preoperatively, the main goal is to kill cancer cells and shrink the tumor. Similarly, postoperative RT destroys residual cancer cells that may remain in the affected area [5]. Furthermore, numerous variations of this therapy have been developed. These include fractionation (hyperfractionation and accelerated fractionation), accelerated RT, continuous hyperfractionated accelerated RT, intensity-modulated RT (IMRT), and image-guided RT. CT, similarily to RT, may be used as "induction" therapy, to shrink a tumor prior to surgery or RT, concurrently with RT, as a "radiosensitizer" to improve the efficacy of RT, or it may be provided adjuvant following surgery or RT [2, 6]. Immunotherapeutic agents, when compared to conventional cytotoxic chemotherapies, have the potential to minimize toxicities due to their selectivity to cancer cells. The majority of head and neck cancers (80%–90%) share a common characteristic — mainly that the epidermal growth factor receptors (EGFR) are overexpressed. Therefore, making treatments that specifically target EGFR, such as monoclonal antibodies (mAbs), is logical for head and neck cancers, such as OPSCC. These mAbs against the EGFR include cetuximab, panitumumab, and nimotuzumab, amongst others [7].

Numerous original studies have been conducted regarding various treatments for OPSSC. This has consequently led to meta-analyses and systematic reviews being presented to compare the efficacy and potential complications associated with the different treatment modalities. However, the quality of the evidence provided by these meta-analyses and systematic reviews depends mainly on the quality of the primary studies used. Furthermore, the amount of information presented by these various reviews is incredibly large, and it may pose problems for physicians that wish to get a clear and evidence-based picture of the treatment of OPSCC. Therefore, our umbrella review aimed to summarize and revisit the evidence from all of the meta-analyses and systematic reviews regarding the treatments of OPSCC. Our study delivers the most up-to-date and evidence-based results regarding the different therapeutic modalities of this malignancy in one concise review, making it the ultimate tool for physicians treating OPSCC.

Materials and Methods

Search strategy

In order to perform this umbrella review, a systematic search was conducted in which all meta-analyses and systematic reviews regarding the treatment of the OPSCC were looked for. Major medical databases such as PubMed, Scopus, Embase, Web of Science, Google Scholar, Cochrane Library, BIOSIS, and EBSCO were searched. The overall search process was conducted in 3 stages. (1) In the first step, all mentioned medical databases were searched using the following search terms: (((oropharyngeal) OR (pharyngeal) OR (oropharynx) OR (tonsillar)) AND ((carcinoma) OR (cancer))). The search phrases were established using the Boolean technique. Neither date, language, article type, nor text availability conditions were applied. (2) Subsequently, the mentioned databases were searched through once again using another set of search phrases: (a) (oropharyngeal carcinoma[Title/Abstract]) AND (treatment [Title/Abstract]); (b) (oropharyngeal carcinoma[Title/Abstract]) AND (surgery [Title/Abstract]); (c) (oropharyngeal carcinoma[Title/Abstract]) AND (chemotherapy [Title/Abstract]); (d) (oropharyngeal carcinoma [Title/Abstract]) AND (immunotherapy [Title/Abstract]); (e) (oropharyngeal carcinoma [Title/Abstract]) AND (radiotherapy [Title/Abstract]); (f) (oropharyngeal carcinoma [Title/Abstract]) AND (transoral robotic surgery [Title/Abstract]); (g) (oropharyngeal carcinoma [Title/Abstract]) AND (TORS [Title/Abstract]). (3) Later, an additional, manual search was also performed throughout all references from the initial submitted studies. During this study, the rules for conducting umbrella reviews designated by Fusar-Poli *et al.* and by Bonczar and Ostrowski *et al.* were taken into account [8, 9]. Furthermore, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines

were followed, as significant similarities in methodology between meta-analysis and umbrella reviews can be observed. In order to minimize the bias and the potential double consideration of the results, authors conducted all statistical analyses based on the results of all of the primary studies, from all of the meta-analyses. Therefore, after the initial search, all primary studies of all meta-analyses were screened in order to perform statistical analyses.

Eligibility assessment and data extraction

The inclusion criteria were established as follows: meta-analysis or systematic reviews conducted using systematic methods, with extractable data on the treatment of the OPSCC. The exclusion criteria were the following: systematic reviews or meta-analyses without any systematic search; systematic reviews or meta-analyses including case studies in their statistical analysis; and narrative or expert reviews, abstracts, or letters to the editor.

The eligibility assessment and data extraction of data from qualified studies (both all meta-analyses, systematic reviews, and all primary studies) were performed by two independent reviewers. Quantitative and qualitative data regarding the treatment of the OPSCC were extracted. Any discrepancies between studies identified by the two reviewers were resolved by contacting the authors of the original studies wherever possible or by consensus involving a third reviewer.

Quality assessment

Subsequently, the methodological quality of all meta-analyses submitted was assessed by two independent reviewers. For this purpose, A MeaSurement Tool to Assess Systematic Reviews 2 (AMSTAR 2) [10] and a ROBIS tool were used [11]. Any disagreements among the authors about the assessment of the studies were resolved by consensus with a third author. Additionally, Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) working group classification was used to establish the quality of evidence for each meta-analysis included in this study [12].

Statistical analysis

Statistical analysis was performed using STATISTICA version 13.1 software (StatSoft Inc., Tulsa, OK, USA), MetaXL version 5.3 software (EpiGear International Pty Ltd, Wilston, Queensland, Australia) and Comprehensive Meta-analysis version 4.0 software (Biostat Inc., Englewood, NJ, USA). The heterogeneity in the meta-analyzes submitted was evaluated with the I-squared statistic reported value [13]. The

I-squared statistic was interpreted on a specific scale: (1) 0%–40% as 'might not be important', (2) 30%–60% as 'may represent moderate heterogeneity,' (3) 50%–90% as 'may represent substantial heterogeneity' and (4) 75%–100% as 'may represent considerable heterogeneity'. A p-value <0.05 and confidence intervals (95% CI) were used to determine statistically significant differences between study groups. If the confidence intervals between the groups overlapped, the differences were considered insignificant, while in the reverse situation, the differences were considered statistically significant. Only data from the primary studies were taken into consideration during the statistical analysis.

Results

Search Results

A total of 856 studies were initially identified from databases. After removing duplicate records, 313 articles were screened and qualified for further evaluation. Of these, 234 were excluded, and 79 were evaluated for eligibility. Furthermore, 39 studies were excluded due to their irrelevance to our study and 12 because they were a narrative review. Finally, a total of 28 studies met the inclusion criteria and were included in this study [2, 4, 5, 7, 14–37]. Out of those 28 meta-analyses, a total of 315 primary studies were screened in order to extract the data and perform the statistical analysis. In total, data from 22,619 patients was analyzed. A flow chart summarizing the overall data collection process can be found in Fig. 1. The qualitative characteristics of the meta-analyses submitted are gathered in Table 1.

Transoral robotic surgery vs. open surgical treatment

New statistical outcomes regarding the risks and consequences of the TORS treatment for the OPSCC were evaluated. TORS has been evaluated in several categories regarding comparison to open surgical treatment, the localization of cancer, and the outcomes of the treatment itself. The complete results can be found in Table 2 and in Fig. 2.

Surgery and Radiotherapy

New statistical outcomes regarding the risks and consequences of the surgical and radiotherapeutic treatment for the OPSCC were evaluated. Surgery was evaluated in categories regarding total mortality, overall survival, and complications. Radiotherapy was evaluated in categories of postoperative locoregional control, postoperative total mortality, and several regarding the IMRT itself. The complete results can be found in Table 3.

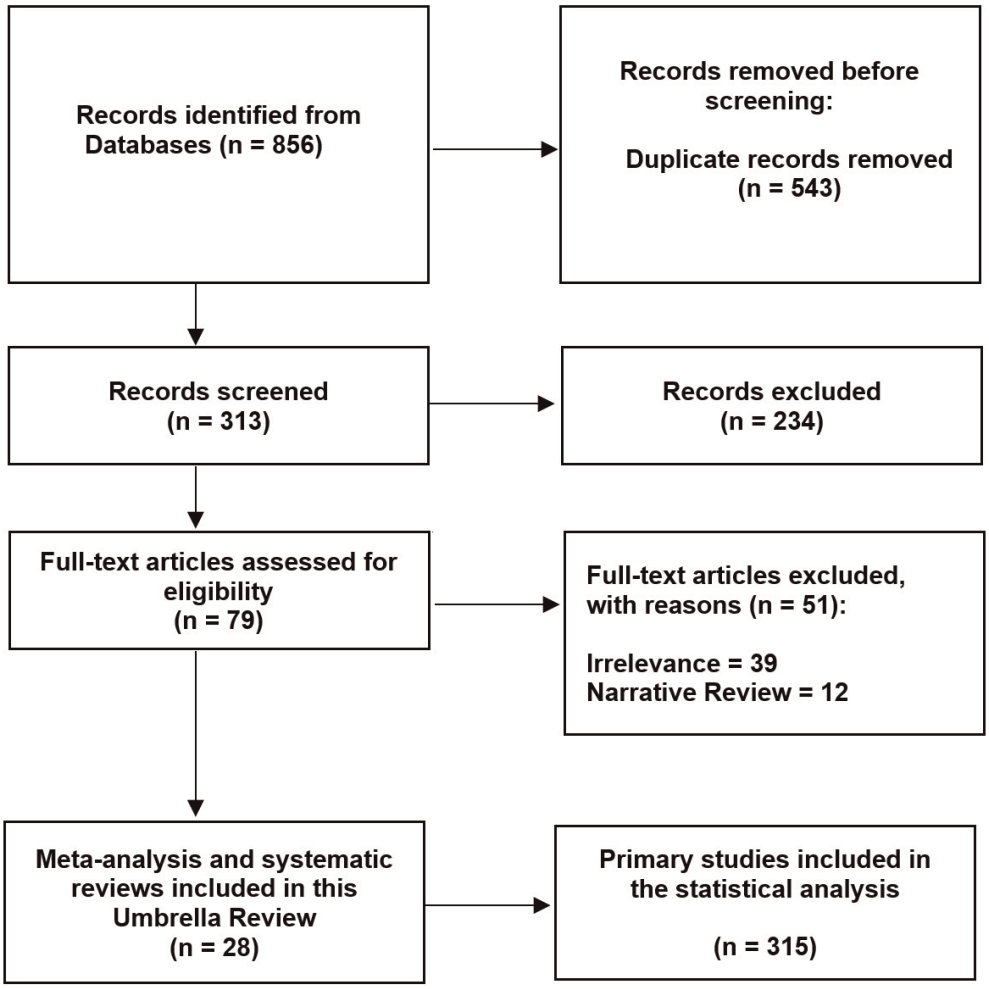

Fig. 1. Flow diagram presenting process of collecting data included in this Umbrella Review.

Chemotherapy and Immunotherapy

A comparison of specific chemotherapeutic methods for the treatment of OPSCC with one another was performed in categories like overall survival, progression-free survival, locoregional control, and total mortality. The usage of mAbs and tyrosine kinase inhibitors in treating OPSCC was also evaluated. Additionally, complications of immunotherapy in the treatment of OPSCC were also established. The complete and detailed results can be found in Table 4. Results regarding chemo- and immunotherapy are illustrated in Fig. 2.

Table 1. Characteristics of the studies included in this Umbrella Review.

First Author	Year	Continent	Country
Nicolas S. Poupore	2022	North America	USA
Daniel D. Sharbel	2022	North America	USA
Fasil Mathews	2022	North America	USA
Ambika Parmar	2021	North America	USA
Craig A. Bollig	2020	North America	USA
Armando De Virgilio	2020	Europe	Italy
Dong Ah Park	2020	Asia	Republic of Korea
Daniela Alterio	2020	Europe	Italy
Eva Stein	2020	North America	USA
Ahmed S. Ibrahim	2019	Africa	Egypt
Philippe Gorphe	2019	Europe	France
Vishal M. Bulsara	2018	Australia	Australia
Parul Sinha	2018	North America	USA
S.S. Kao	2018	Australia	Australia
Sharan Chakkyath Jayaram	2016	Europe	United Kingdom
Pai Pang	2016	Asia	China
Benoît Morisod	2016	Europe	Switzerland
Kelvin K.W. Chan	2015	North America	Canada
D.H. Yeh	2015	North America	Canada
Katherine A. Hutcheson	2015	North America	USA
Kate Kelly	2014	North America	Canada
Maximilian Moergel	2011	Europe	Germany
Pierre Blanchard	2011	Europe	France
Susan Furness	2011	Europe	United Kingdom
Anne-Marie Glenn	2010	Europe	United Kingdom
Susan Furness	2010	Europe	United Kingdom
Clemens Klug	2008	Europe	Austria
R.J. Oliver	2007	Europe	United Kingdom

Table 2. Statistical results of this umbrella review regarding the comparison of risks in transoral robotic surgery (TORS) versus open surgery in treatment of the oropharyngeal carcinoma and the comparison of risks in the TORS treatment of the oropharyngeal carcinoma at the base of the tongue (BOT) and in the tonsil area. Statistical results of this umbrella review regarding the early TORS outcomes and overall functional TORS outcomes.

Category	Higher Chances In	OR	Lower Limit	Upper Limit	Z-Value	p-Value
OPEN vs TORS						
Disease-free Survival	TORS	2.18	1.14	4.16	2.35	0.02
Recurrence	Open	0.63	0.26	1.50	–1.05	0.30
Mortality	Open	0.69	0.23	2.06	–0.67	0.50
Hematoma	TORS	1.88	0.50	7.05	0.94	0.35
Chyle Leakage	Open	0.80	0.21	3.01	–0.33	0.74
Marginal Nerve Palsy	TORS	4.83	0.83	28.05	1.75	0.08
Pharyngocutaneous fistula	Open	0.25	0.04	1.52	–1.51	0.13
Positive Margin	Open	0.73	0.37	1.47	–0.87	0.38
Seroma	Open	0.88	0.41	1.90	–0.33	0.74
Wound Infection	Open	0.31	0.01	8.27	–0.69	0.49
TORS BOT vs TORS Tonsil						
Total Recurrence	TORS BOT	1.13	0.81	1.57	0.72	0.47
Locoregional Recurrence	TORS BOT	1.18	0.76	1.84	0.75	0.45
Metastatic Recurrence	TORS Tonsil	0.84	0.43	1.66	–0.50	0.62

Category	Pooled Prevalence	LCI	HCI	Q	I^2
Early Tors					
Overall Survival	97.64%	93.61%	99.85%	7.65	21.56
Disease-free Survival	92.33%	84.76%	97.60%	10.78	44.33
Local Recurrence	1.90%	0.18%	4.94%	3.70	0.00
Regional Recurrence	5.76%	1.34%	12.52%	10.47	42.72
Intraoperative complications	1.30%	0.06%	3.64%	3.57	0.00
Postoperative complications	10.31%	2.84%	21.13%	30.78	70.76
Prolonged gastrostomy tube dependence	1.96%	0.32%	4.68%	7.21	0.00
TORS Functional Outcomes					
Percutaneous gastrostomy (Stages 1–4)	8.43%	1.84%	18.44%	9.85	69.54

Table 2. cont.

Category	Pooled Prevalence	LCI	HCI	Q	I^2
Percutaneous gastrostomy (Stages 1–2)	0.58%	0.00%	2.78%	0.00	0.00
Percutaneous gastrostomy (Stages 3–4)	4.15%	0.00%	10.90%	8.58	65.05
Perioperative feeding tube	31.06%	15.74%	48.69%	103.88	93.26
Tracheostomy (Stage 1–4)	16.70%	1.48%	40.47%	100.95	94.06
Tracheostomy (Stage 1–2)	0.58%	0.00%	2.78%	0.00	0.00
Tracheostomy (Stage 3–4)	38.40%	9.82%	71.42%	23.16	91.36

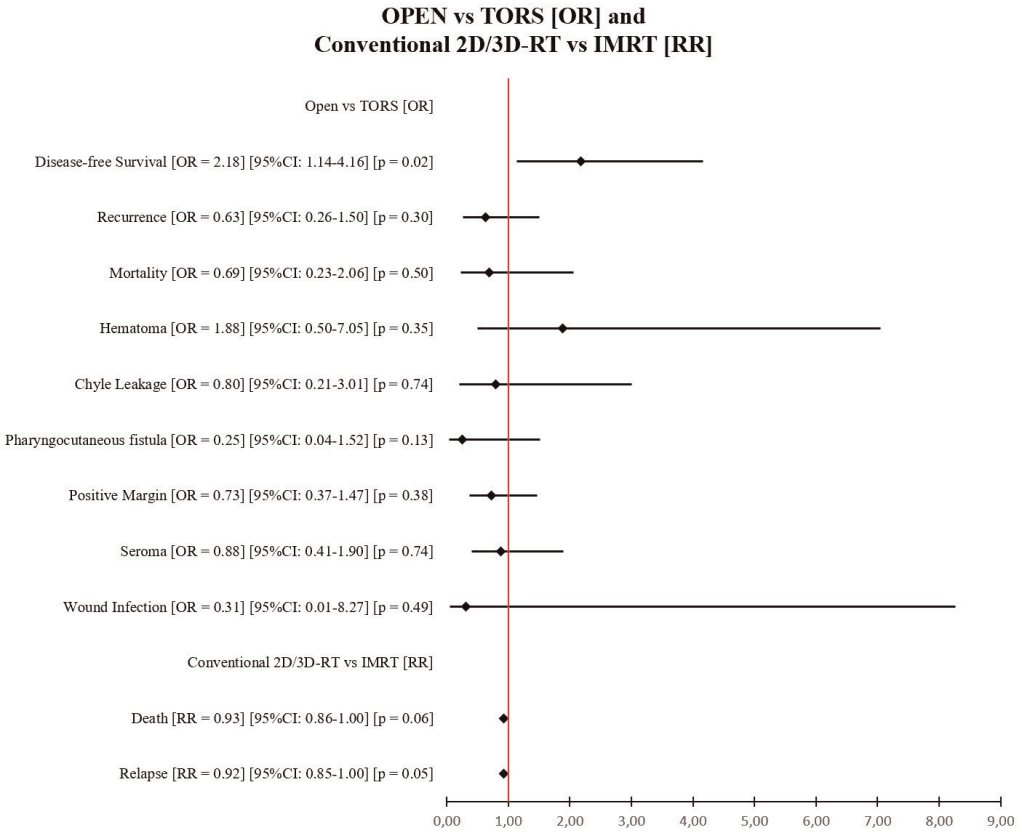

Fig. 2. Forrest plot of some of the results regarding transoral robotic surgery (TORS) in treatment of oropharyngeal squamous cell carcinoma and the results regarding the comparison of conventional 2D/3D-RT versus intensity-modulated radiation therapy (IMRT).

Table 3. Statistical results of this umbrella review regarding an overall survival after the surgical treatment of the oropharyngeal carcinoma and the comparison of risks regarding mortality between treatments and the results regarding the surgical treatment outcomes prevalence. Results of this umbrella review regarding the risks and prevalence of outcomes of radiotherapy in treatment of oropharyngeal carcinoma. LCI — lower confidence interval. HCI — higher confidence interval. Q — Cochran's Q. RN — Radical neck dissection. RT — Radiotherapy. IMRT — intensity-modulated radiation therapy.

SURGERY					
Category	**Hazard Ratio**	**Lower Limit**	**Upper Limit**	**Z-Value**	**p-Value**
Total Mortality					
Surgery + Radiotherapy vs Surgery	0.99	0.92	1.06	–0.28	0.78
Elective RN vs Therapeutic RN	0.84	0.41	1.72	–0.47	0.64
Surgery + Post-operative RT + Cisplatin vs Surgery + Post-operative RT	0.79	0.65	0.95	–2.45	0.01
Category	**Pooled Prevalence**	**LCI**	**HCI**	**Q**	**I^2**
Overall Survival					
1 Year	63.38%	49.84%	75.95%	2.54	60.59
2 Years	52.18%	39.32%	64.90%	39.28	82.18
3 Years	42.04%	31.60%	52.84%	14.80	66.22
5 Years	27.22%	23.22%	31.41%	7.29	3.96
Complications					
Any Complication	48.42%	28.80%	68.29%	228.69	95.63
Bleeding	9.99%	5.57%	15.48%	3.90	23.09
Carotid Artery Rupture	3.96%	0.00%	12.46%	5.21	80.82
Fistula	8.86%	3.06%	16.98%	83.22	87.98
Hematoma	4.91%	0.81%	11.57%	0.28	0.00
Pneumonia	8.97%	4.95%	13.98%	2.57	0.00
Sepsis	4.05%	0.68%	9.54%	0.02	0.00
Wound Complications	14.08%	1.60%	33.61%	70.57	92.91
RADIOTHERAPY					
Category	**HR**	**Lower Limit**	**Upper Limit**	**Z-Value**	**p-Value**
Postoperative Locoregional Control					
Hyperfractionated vs. Conventional	0.74	0.62	0.89	–3.27	0.00

Table 3. cont.

Category	Hazard Ratio	Lower Limit	Upper Limit	Z-Value	p-Value
Hyperfractionated-accelerated vs. Conventional	0.84	0.71	1.01	–1.89	0.06
Hyperfractionated-accelerated-split vs. Conventional	0.86	0.73	1.02	–1.72	0.09
Altered Fractionation vs. Conventional Radiotherapy	0.79	0.71	0.89	–3.95	0.00
Postoperative Total Mortality					
Hyperfractionated-accelerated vs. Conventional	0.87	0.75	1.00	–1.92	0.05
Hyperfractionated-accelerated-split vs. Conventional	1.02	0.90	1.17	0.36	0.72
Accelerated-boost vs. Conventional	0.98	0.72	1.35	–0.11	0.91
Altered Fractionation vs. Conventional	0.86	0.76	0.98	–2.32	0.02
Hyperfractioned vs. Conventional	0.77	0.65	0.91	–3.00	0.00
Neutron vs. Photon Therapy	1.10	0.90	1.34	0.90	0.37
Category	**RR**	**Lower Limit**	**Upper Limit**	**Z-Value**	**p-Value**
Conventional 2D/3D-RT vs IMRT					
Death	0.93	0.86	1.00	–1.87	0.06
Relapse	0.92	0.85	1.00	–1.98	0.05
Category	**Pooled Prevalence**	**LCI**	**HCI**	**Q**	**I^2**
IMRT Overall Survival					
2 Years	96.14%	90.96%	99.33%	2.45	18.31
3 Years	80.97%	72.52%	88.20%	4.66	78.56
5 Years	80.08%	69.32%	89.06%	6.99	85.69
IMRT Disease Free Survival					
2 Years	85.51%	75.10%	93.57%	3.61	44.54
3 Years	78.90%	74.84%	82.69%	18.26	50.71
IMRT Tracheostomy Dependence					
Overall	0.87%	0.00%	2.86%	7.95	62.27
IMRT Feeding Tube Dependence					
Overall	4.14%	2.65%	5.95%	39.36	64.43

Discussion

The anatomy of the head and neck region is highly complex, making surgical treatment of OPSCC challenging [38–45]. Surgical treatment of OPSCC has historically consisted of extensive open surgeries with large incisions and mandibulotomies. However, open operations by mandibulotomies result in complications in 10% to 60% of cases, including severe impairments in normal function, like speech and swallowing [17, 46]. Not all of the open surgical techniques for OPSCC damage the mandible, though. The mandibular preservation method usually combines a visor incision in the neck and mandibular lingual release, which completely spares the mandible. However, when the mandible preservation method and mandibulectomy in oral and oropharyngeal cancer were compared and analyzed in a meta-analysis conducted by Pang *et al.* [25], the findings suggested that the two techniques gave similar clinical outcomes. Due to the significantly high mortality and morbidity which are associated with these old surgical approaches, new minimally invasive techniques, such as TORS, have become the gold standard for OPSCC. TORS is a minimally invasive technique that allows clear visualization of the oropharynx with the help of telescopes and wristed instruments. In the present umbrella review, the open surgical techniques were compared to the minimally invasive ones (Table 2). Our results show that TORS is associated with higher disease-free survival than open approaches. Furthermore, the open techniques are associated with higher mortality, recurrence, and positive margin rates, as well as with numerous other complications, such as; chyle leakage, pharyngocutaneous fistulas, and wound infections, amongst others. This indicates that minimally invasive techniques, such as TORS, are favorable over open-access operations.

As mentioned earlier, RT is another primary treatment modality used for OPSCC. RT may be used alone, as an adjuvant with surgery, or in combination with chemotherapy [47]. There are numerous variations of this therapy, with variable dosing (fractionation, hyperfractionated and accelerated fractionation) and accelerated therapies, where the goal is to overcome tumor cell repopulation during the course of the treatment. Furthermore, the use of neutron therapy was also compared to conventional RT in the past. Our umbrella review shows that the best postoperative locoregional control was obtained with hyperfractionated therapy when compared to conventional RT. However, the postoperative total mortality was also higher in hyperfractionated therapy than in conventional RT. Moreover, the postoperative total mortality was higher in patients who were treated with neutron therapy compared to conventional RT. Hence, conventional therapy, and its variations, are the gold standard for the primary treatment of OPSCC. However, conventional two-dimensional or three-dimensional conformal RT has been associated with significant impairments in function due to local structures being affected [29, 48]. Therefore, IMRT has been getting more attention as a new technique that may help to decrease the toxic effects

associated with conventional RT. This is mainly accomplished by sparing normal tissue while maintaining locoregional control of the malignancy [29]. IMRT generates dose distributions that are more conformal to the target volumes, including tumors, involved lymph nodes, and areas at risk, compared to conventional two-dimensional and three-dimensional RT [49]. This allows dose reductions to normal tissues, thus decreasing toxicity and potentially enhancing locoregional control through dose escalation. Our results show that conventional 2D/3D-RT had a slightly higher risk of death and relapse when compared to IMRT. However, the difference between these two modalities was not statistically significant ($p > 0.05$). Nevertheless, there are some disadvantages associated with IMRT. Because the said therapy is more localized, there might be an increased risk of marginal miss and decreased dose homogeneity. Furthermore, IMRT may be associated with an increased total body dose and increased labor and expense [49].

For advanced OPSCC, more general therapies are used, including CT and IT. CT may be used as an induction therapy, where the main goal is to shrink the tumor before surgery or RT, in combination with RT (as a "radiosensitizer"), or it may be provided in the "adjuvant" setting after surgery or RT [2, 6]. Many chemotherapeutic agents interrupt the life cycle of cancer cells at variable stages. Therefore, combining different agents into a chemotherapy regimen may be more beneficial in inducing cell death than single-agent chemotherapy [2]. Therefore, numerous studies have analyzed the efficacy of different combinations of treatment modalities consisting of various chemotherapeutic agents [50–52]. Our results show that intra-arterial bleomycin and vincristine with surgery give a better overall survival than just surgery alone. Moreover, the addition of carboplatin and 5-fluorouracil to a treatment regimen consisting of RT and surgery gave higher overall survival than RT and surgery alone. However, the addition of chemotherapeutic agents to treatment regimens of OPSCC does not always increase overall survival. Interestingly, the use of methotrexate along with surgery gave a lower overall survival than surgery alone.

Immunotherapy for OPSCC is currently in the spotlight, especially for patients with advanced diseases. Various studies on programmed death-1/programmed death-ligand 1 checkpoint inhibitors have shown to be beneficial to patients with metastatic head and neck squamous cell carcinoma [3]. mAbs, such as nivolumab and pembrolizumab, were approved as the second-line treatment for advanced metastatic head and neck squamous cell carcinoma. Tyrosine kinase inhibitors of several vascular endothelial growth factor (VEGF) receptors, such as lenvatinib, have also been used for head and neck squamous cell carcinomas, including OPSCC [53]. Our results show that adding IT to a treatment regimen consisting mainly of RT may be beneficial because it has a higher 5-year survival (Table 4). However, IT is associated with numerous side effects, including mucositis, dysphagia, rash, and xerostomia, amongst others. The overall risk of these side effects occurring is presented in Table 4.

Table 4. Results of this umbrella review regarding the risks of chemotherapy and immunotherapy in treatment of oropharyngeal carcinoma. RN — Radical neck dissection. RT — Radiotherapy.

CHEMOTHERAPY					
Category	**HR**	**Lower Limit**	**Upper Limit**	**Z-Value**	**p-Value**
Overall Survival					
Cisplatin + 5-FU + CRT (cisplatin) vs. CRT (cisplatin)	0.71	0.37	1.35	–1.05	0.30
Cisplatin + 5-FU + Docetaxel + CRT (cisplatin) vs CRT (cisplatin)	1.08	0.80	1.44	0.49	0.63
Intra-arterial Bleomycin + Vincristine + Surgery vs Surgery	0.67	0.50	0.91	–2.55	0.01
Surgery + CRT (cisplatin) vs surgery + RT	0.79	0.65	0.98	–2.16	0.03
Bleomycin + Vincristine + Surgery + RT vs RT + Surgery	0.67	0.50	0.91	–2.55	0.01
Carboplatin or Cisplatin + 5FU + RT + Surgery vs RT + Surgery	0.90	0.80	1.02	–1.69	0.09
Carboplatin + 5FU + RT + Surgery vs RT + Surgery	0.82	0.66	1.02	–1.79	0.07
Cisplatin + 5FU + RT + Surgery vs RT + Surgery	0.92	0.77	1.10	–0.89	0.37
Intraarterial Methotrexat + RT vs RT	0.69	0.50	0.94	–2.33	0.02
Methotrexat + RT vs RT	0.90	0.72	1.14	–0.88	0.38
Platinum + 5-FU + RT vs RT	0.85	0.70	1.03	–1.61	0.11
Surgery + Adjuvant Chemiotherapy vs Surgery	0.95	0.73	1.22	–0.43	0.67
Surgery + Methotrexate vs Surgery	1.04	0.77	1.42	0.28	0.78
Progression-free Survival					
Cisplatin + 5FU + RT vs RT	0.82	0.62	1.07	–1.49	0.14
Cisplatin + Post-operative RT vs Post-operative RT	0.84	0.66	1.08	–1.35	0.18
LT + chemo vs LT	0.80	0.64	1.00	–1.97	0.05
Surgery + RT + CT vs Surgery + RT	0.88	0.64	1.20	–0.80	0.42
Concomitant CT vs RT	0.77	0.67	0.89	–3.51	0.00

Table 4. cont.

CHEMOTHERAPY					
Category	**HR**	**Lower Limit**	**Upper Limit**	**Z-Value**	**p-Value**
Locoregional Control					
Cisplatin or Carboplatin + 5FU + RT + Surgery vs RT	0.76	0.61	0.94	–2.55	0.01
Cisplatin or Carboplatin + RT vs RT	0.78	0.65	0.94	–2.65	0.01
Cisplatin + 5FU + RT + Surgery vs RT	0.78	0.59	1.03	–1.75	0.08
Concomitant CT vs RT	0.71	0.62	0.82	–4.71	0.00
Total Mortality					
Alternating Cisplatin + 5-FU + RT vs Altered Fractionation RT	0.75	0.54	1.05	–1.65	0.10
Alternating CT + RT vs RT	0.85	0.71	1.01	–1.83	0.07
Bleomycin + RT vs RT	0.74	0.37	1.49	–0.83	0.41
Carboplatin + 5FU + RT vs RT	0.74	0.60	0.92	–2.78	0.01
Cisplatin or Carboplatin + 5FU + RT + Surgery vs RT	0.71	0.62	0.81	–5.12	0.00
Cisplatin or Carboplatin + RT vs RT	0.66	0.57	0.77	–5.40	0.00
Cisplatin + 5FU + RT vs RT	0.69	0.53	0.90	–2.73	0.01
Cisplatin + 5FU + RT + Surgery vs RT	0.68	0.57	0.81	–4.34	0.00
Concomitant CT vs RT	0.76	0.70	0.84	–5.78	0.00
Mitomycin + RT vs RT	0.92	0.76	1.12	–0.81	0.42
Surgery + RT + Cisplatin vs Surgery + RT	0.79	0.65	0.98	–2.16	0.03
Surgery + RT + CT vs Surgery + RT	0.88	0.79	0.99	–2.21	0.03
IMMUNOTHERAPY					
Category	**HR**	**Lower Limit**	**Upper Limit**	**Z-Value**	**p-Value**
Monoclonal Antibodies					
mAb Therapy + RT vs RT (5 Year Survival)	0.73	0.58	0.91	–2.74	0.01
Tyrosine Kinase Inhibitors					
Overall Survival	0.99	0.62	1.57	–0.06	0.95

Table 4. cont.

CHEMOTHERAPY					
Category	**HR**	**Lower Limit**	**Upper Limit**	**Z-Value**	**p-Value**
Progression-free Survival	0.80	0.51	1.28	–0.92	0.36
Locoregional Control	0.86	0.42	1.75	–0.42	0.67
Category	**OR**	**Lower Limit**	**Upper Limit**	**Z-Value**	**p-Value**
Complications					
Any Adverse Event	1.30	0.75	2.28	0.93	0.35
Dysphagia	0.88	0.68	1.15	–0.92	0.36
Dysphagia (Grade 3)	0.87	0.62	1.23	–0.79	0.43
Mucositis	1.43	1.04	1.98	2.18	0.03
Mucositis (Grade 3)	1.49	0.92	2.40	1.63	0.10
Rash	6.95	0.91	53.08	1.87	0.06
Rash (Grade 3)	5.36	1.50	19.16	2.58	0.01
Skin reaction inside portal	0.88	0.67	1.16	–0.92	0.36
Skin reaction inside portal (Grade 3)	1.69	1.25	2.28	3.43	0.00
Skin reaction outside portal	39.54	18.34	85.25	9.38	0.00
Skin reaction outside portal (Grade 3)	8.28	1.09	62.93	2.04	0.04
Xerostomia	0.97	1.43	0.66	–0.15	0.88

The efficacy of different combinations of the aforementioned treatment modalities has been heavily discussed in the literature. As mentioned earlier, the time at which these treatments are given varies considerably. RT may be given alone, prior to surgery, or postoperatively. CT may also be given preoperatively, as an induction therapy, together with RT, or as an adjuvant after surgery or RT. IT is usually used concomitantly with standard therapy, i.e., surgery and/or RT. Our umbrella review shows that the total mortality is very similar in patients receiving surgery and RT when compared to those who only receive surgical treatment. Interestingly, the total mortality was higher in patients that had additional CT (cisplatin) added to a treatment regimen consisting of surgery and post-operative RT when compared to patients that did not receive the additional CT. However, one has to keep in mind that, generally speaking, patients that undergo CT or IT, meaning systemic therapies, tend to have more advanced OPSCC than patients undergoing primary treatments like surgery and RT.

Although the present umbrella review is the most up-to-date and evidence-based study regarding the treatment of OPSCC, some limitations must be discussed. Un-

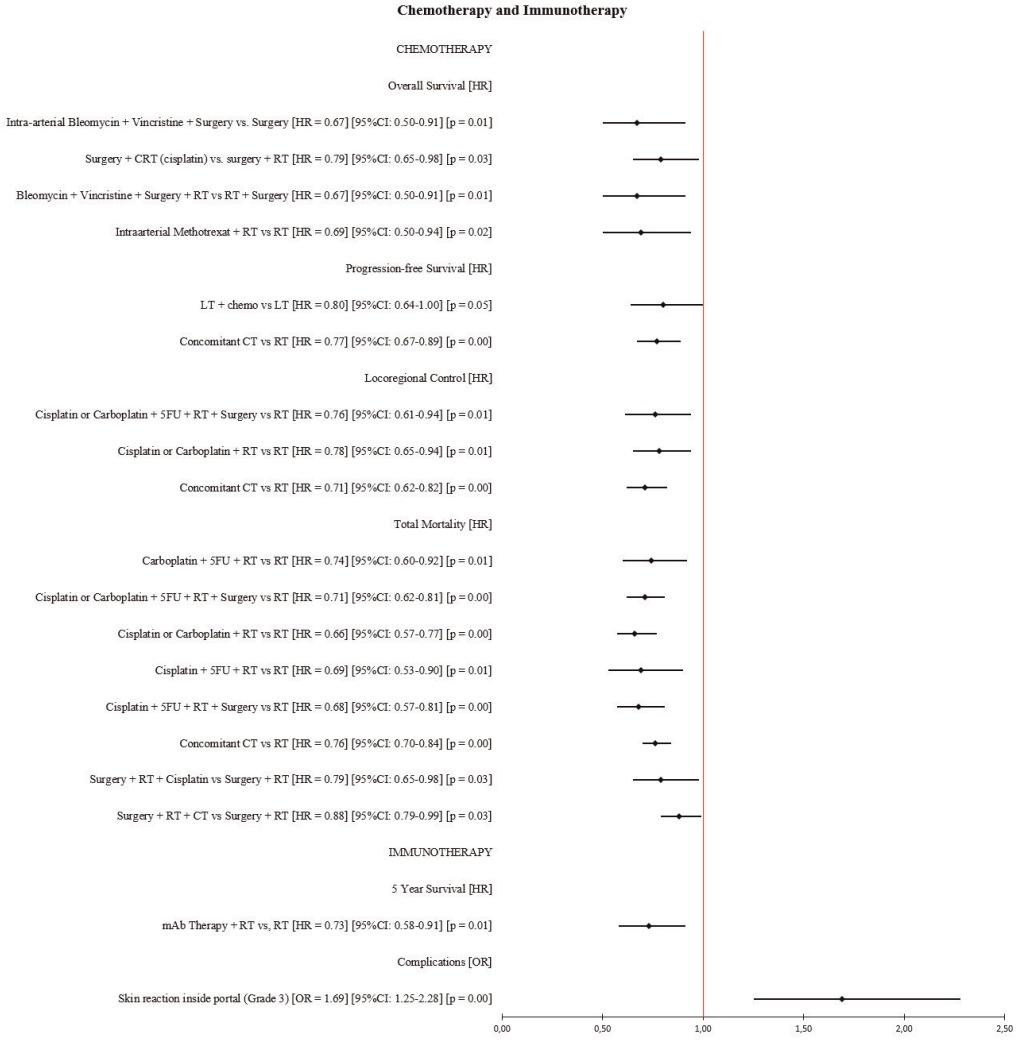

Fig. 3. Statistically significant ($p < 0.05$) results rgarding the chemotherapy and immunotherapy for oropharyngeal squamous cell carcinoma.

fortunately, the differences in treatments between HPV-positive and HPV-negative OPSCC could not be analyzed due to limited data on this topic. This is significant due to the different clinical outcomes which have been associated with these types of OPSCC. Furthermore, the quality of the evidence provided by the present umbrella review depends mainly on the quality of the primary studies used. Although not without limitations, our umbrella review attempts to estimate the risks and benefits of each treatment used for oropharyngeal carcinoma based on the data from the

literature that meet the requirements of evidence-based medicine, at the same time providing physicians with an up-to-date review of the current literature.

These days, the main topic of interest concerning the treatment of OPSCC is the optimization of treatment de-escalation. As shown earlier, the overall treatment of locoregionally advanced head and neck OPSCC involves a multimodality approach that combines surgery, RT, and systematic therapy (CT and IT). These curative strategies are associated with significant acute and chronic long-term toxicities [54]. Due to the higher cure rates and the significant treatment-related morbidity and mortality, de-escalation therapeutic strategies are now being heavily discussed. This de-escalation consists mainly of replacing, reducing, or excluding cytotoxic CT, reducing the dose or volume of RT, and incorporating less-invasive surgical techniques. Some studies have started to show promising results in substantial de-escalations of different treatment modalities for this malignancy [55]. However, only long-term follow-up data will help affirm the efficacy of these strategies. Further research in this area should be performed to guarantee progression in finding the most optimal treatment plan for OPSCC.

Conclusion

The main objective of the present umbrella review was to summarize and analyze all of the evidence-based data provided by numerous meta-analyses and systematic reviews regarding the treatment of OPSCC. Our study delivers the most up-to-date and evidence-based results regarding the different therapeutic modalities of this malignancy in one concise review, making it the ultimate tool for physicians treating OPSCC.

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Conflict of interest

None declared.

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