Brazilian Journal of Clinical Medicine and Review

PCAA PUBLICAÇÕES CIENTÍFICAS DE ACESSO ABERTO

Review

Evaluation of Head and Neck Squamous Cell Cancer Treatment and Outcomes: Low-Dose Nivolumab in Palliative Treatment, A Literature Review

Julia Pastorello [1], Emanuela Lando [2,*]

[1] Department of Medical Oncology, Hospital de Clínicas de Passo Fundo – HCPF, Passo Fundo, Rio Grande do Sul/ SP, Brazil.
[2] Medical Oncology Resident, Hospital de Amor – HA, Barretos, São Paulo/ SP, Brazil.

* Correspondence: manu.lando@hotmail.com.

Abstract: The chemotherapy treatment based on Taxol, paclitaxel is widely used in the treatment of neoplastic conditions in the head and neck, however in the last decades immunotherapy has made a revolution in the context of oncological treatments. The Anti-PDL1 agent, Nivolumab, has been proving to be of great value in the treatment of solid tumors. Through the review method this study aims to synthesize and analyze treatments for advanced head and neck cancer, in addition to critically analyzing existing studies on the use of reduced doses of nivolumab in patients with head and neck cancer. Thus, we aim to elucidate the action of oncological agents used in the treatment of SCC, as well as confirm the superiority of immunotherapeutic treatment in cases of advanced stage SCC.

Keywords: Squamous cell carcinoma; Treatment; Immunotherapy; Oncology.

Citation: Pastorello J, Lando E. Evaluation of Head and Neck Squamous Cell Cancer Treatment and Outcomes: Low-Dose Nivolumab in Palliative Treatment, A Literature Review. Brazilian Journal of Clinical Medicine and Review. 2025:Jan-Dec;03(1):bjcmr14.

https://doi.org/10.52600/2763-583X.bjcmr.2025.3.1.bjcmr14

Received: 12 July 2024
Accept: 1 September 2024
Published: 10 September 2024

1. Introduction

The squamous cell carcinoma, also called squamous cell carcinoma (SCC), is the head and neck neoplasm with the highest incidence, accounting for 90% of all cases. Highly solid tumor with multifactorial etiology, intrinsically associated with smoking, alcoholism, which when associated increase the rate of development of SCC by 40% and exposure to the human papillomavirus HPV-16, is an independent risk factor especially in the oropharyngeal site [1-3]. Regarding the diagnosis of SCC of the oral cavity, this is confirmed through biopsy, most often through nasofibroscopy, the immunohistochemical profile with research for HPV-16 in confirmatory cases is of utmost importance [4-6]. Regarding staging, tomography with contrast of the sinuses, as necessary, in addition to the cervical and thoracic regions, are essential, as they are the main sites of external involvement associated with SCC of the head and neck [2, 7].

The description of treatment must be evaluated according to staging, considering tumor location, organ preservation when possible and association with metastatic activity [8-11]. The platinum agent, especially cisplanitna, which is widely used in chemotherapy and/or chemorapidotherapeutic protocols in various scenarios, draws attention to the treatment of head and neck SCC. chemotherapy against taxanes and especially paclitaxel [12-16]. Regarding the monoclonal antibody agent, cetuximab is associated with high response rates, gain in overall and progression-free survival, today there are formal and restricted periodicities for its use in relation to the treatment of SCC subtype

neoplasia, as well as the institution of protocols based on immunotherapy with anti PD-L1 agents, such as pembrolizumab or nivolumab [17-19]. In essence, through a literature review, the current study aims to evaluate the lines of treatment in advanced head and neck SCC, as well as their impact on the associated prognosis, especially considering immunotherapy treatment in reduced doses with the agent nivolumab, as well as This consequence supports oncological scientific technical development.

2. Literature Review

2.1 Squamous Cell Carcinoma

Squamous cell carcinoma (SCC) of the head and neck is an extremely prevalent carcinogenic subtype, around 90% of all neoplastic manifestations in the head and neck region are related to this subtype. The most affected regions are the oropharynx, oral cavity, hypopharynx and larynx [5, 20]. SCC has been considered a tumor with a multifactorial cause due to the association of somatic causes especially related to smoking, alcoholism, exposure to the human papilloma virus (HPV), as well as genetic factors, such as mutations in EGFR, TP53, HPV-14 and hereditary factors [1, 2].

Among the risk factors mentioned above, the main one in the development of SCC is smoking, since it contains genotoxic polycyclic hydrocarbons, in addition to nitrosamines [1-3, 7]. Studies indicate that smoking cessation reduces the chance of developing SCC among the general population and that the main risk associated with the development of SCC in patients consumers would be the association with alcoholism [7, 21-23]. Considering the mechanism of action of alcohol, since it acts as a solvent in the interaction of the oral mucosa with carcinogenic agents, acetaldehyde stands out, which has the potential to form DNA adducts, in addition to the sum of the interaction between alcohol and smoking increases the chance of developing squamous cell carcinoma by 40% [24, 25].

Regarding the interaction with HPV-16, this is an independent risk factor for SCC, since 25% of all SCC diagnoses are associated, especially with neoplastic conditions in the oropharyngeal region [1, 26]. In relation to other habits, which are related to diet, low BMI, oral hygiene, it is known that healthy eating has a greater chance of reducing the presentation of carcinogenic conditions, as well as low BMI and poor-quality oral hygiene predispose to greater risks in the development of CEC [27-29].

The diagnosis of SCC of the oral cavity largely depends on the type of presentation of the lesion, it is visible whether there is an associated obstructive and/or painful condition, since such findings are generally evidenced before the patient seeks medical attention, however in certain places when such results are often demonstrated and may already be associated with metastatic presentations [6, 20]. Thorough physical examination of the oral cavity, especially in the mucous membrane region beyond the upper aerodigestive tract, is extremely important in differentiating metachronous and/or synchronous lesions. Since the biopsy, most often through nasofibroscopy, at the site of the lesion is what will confirm the neoplastic condition, in addition to the immunohistochemical profile with research for HPV-16 in confirmatory cases [4]. Therefore, after staging with tomography with contrast of the sinuses, as necessary, in addition to the cervical and thoracic regions, they are essential, as they are the main sites of external involvement associated with SCC of the head and neck. More tests such as ultrasound and bone scintigraphy and tomography of the abdomino-pelvic region in certain cases may be requested, however, in extremely restricted cases [2, 7].

In relation to staging, we must consider the TNM criteria, in addition to the site of involvement, as in certain cases, especially in diseases with resectability potential, it may be necessary to perform Magnetic Resonance Imaging and PET-CT, this is indicated when available and when they present extensive lymph node involvement. Furthermore, in certain cases to evaluate possible synchronous esophageal tumors, in around 4% of cases, we can perform upper digestive endoscopy for further evaluation and consequently staging [30, 31].

2.2 SCC Head and Neck Treatment

Regarding the treatment, it must be evaluated according to staging, always considering the tumor location, preservation of the organ when possible and association with metastatic activity, when presented. To carry out treatment for head and weight SCC, we provide surgical treatment, radiotherapy, chemotherapy, concomitant chemotherapy and radiotherapy treatment, in addition to target therapies and immunotherapy in selected cases [11]. The surgery is the main therapeutic option in cases of primary, secondary and recurrent disease, after which assessment of adjuvant methods is necessary [8].

The primary objective of head and neck surgery is to obtain negative margins, since, when possible, this is intrinsically associated with increased free survival in patients, however in certain cases there may be organ dysfunction, changes in the order of speech and masticatory due to the procedure, thus inferring the patient's quality of life [32]. However, it is not always possible to obtain negative margins, in most cases due to infiltration, especially in the vascular region close to the tumor site, consequently contributing to a reduction in the free survival rate [32, 33].

According to radiotherapy treatment, intensity-modulated IMRT radiotherapy, as it is more homogeneous in relation to dosage, is seen as presenting advantages over conventional 2D and 3D conformal radiotherapy, in addition to reducing xerostomia rates in patients [34]. The commonly used accelerated hyperfractionated radiotherapy modality promotes better local control and survival compared to usual fractionation, however it can produce reactions of different degrees of intensity in the oral cavity such as mucositis, corroborating chewing difficulties and in certain cases swallowing. need for strict monitoring of patients during radiotherapy treatment [35-37].

Considering that approximately 60% of patients with HNSCC of the head and neck already present advanced disease at diagnosis, it is extremely important to highlight the main therapeutic approaches imposed in this scenario: Platinum-based chemoradiotherapy concomitant with surgery reserved for cases of recurrence tumor, surgery with neck dissection followed by radiotherapy or adjuvant chemotherapy or induction chemotherapy followed by definitive chemoradiotherapy and/or surgery [10, 11].

The staging, in the face of stages I and II in oropharyngeal tumor site and HPV negative, there is a recommendation to continue surgical or radiotherapy treatment, on the other hand, in cases of positive HPV, the treatment of choice is the combined treatment of radiochemotherapy with cisplatin [15, 16]. In non-oropharyngeal cases of the oral cavity, surgical treatment with neck dissection should initially be instituted if the tumor depth is greater than 4 mm and after evaluating the case regarding adjuvant radiotherapy treatment [38-40].

Furthermore, considering stages I and II of the hypopharyngeal site, radiotherapy and/or radiochemotherapy with cisplatin is recommended, while in tumors of the laryngeal site radiotherapy or chemotherapy treatment is indicated [41, 42]. In stages III and IV without distant metastases, the treatment of choice is surgery, with unilateral or bilateral neck dissection, after adjuvant radiotherapy, especially in stage T2, invasion thickness 4 mm, and compromised resection margin, not subject to enlargement and tumors from stage T3N0 onwards [43-45]. Adjuvant radiotherapy is indicated for patients with intermediate risk factors for recurrence. Adjuvant radiochemotherapy is indicated for patients with compromised margins and/or lymph nodes with extranodal extension, with cisplatin being the chemotherapy of choice at the same time [45, 46].

In relation to the oropharyngeal site in such stages, radiochemotherapy with cisplatin is indicated or in cases of young patients without comorbidities and with large-volume disease, induction chemotherapy treatment with a TPF regimen (cisplatin, 5-FU and docetaxel) can be performed. Afterwards, concomitant radiotherapy with cisplatin or cetuximab or just radiotherapy alone may be considered [47-49]. The surgical procedure in such stages in the oropharynx is reserved for cases of tumor recurrence [47-49].

Regarding the laryngeal tumor site and hypopharynx, we must take into account the associated anatomy, because when there is the possibility of preserving the organ with consequently laryngeal functionality, we can opt for initial radiochemotherapy treatment with cisplatin or induction chemotherapy with a TPF regimen and after radiotherapy alone. , and surgery in this case would be reserved, as in oropharyngeal tumors, for tumor recurrence [50, 51]. However, studies currently indicate a greater tendency towards surgical treatment, considering studies that showed higher overall survival rates in patients who underwent total laryngectomy compared to patients who underwent chemoradiotherapy or radiotherapy alone [52, 53]. In cases where there is no possibility of preserving the organ, initial surgical treatment is the most recommended and only after radiotherapy and/or chemotherapy do they become an option [50, 51].

In relation to stage IV with distant metastasis, an assessment of PD-L1 expression should be carried out, considering the addition of immunotherapy: pembrolizumab or not to the treatment, as well as the possibility of isolated immunotherapy in restricted cases [54]. In the case of an expressed PDL-L1 disease, with a CPS greater than or equal to 1%, we can institute a treatment protocol with carboplatin AUC 5 (Cisplatin 100mg/m^2), 5FU 1000mg/m^2 and pembrolizumab 200 mg every 3 weeks or carboplatin, paclitaxel 175 mg/m^2 and pembrolizumab every 3 weeks or just pembrolizumab monotherapy in certain cases [54, 55]. Thus methotrexate 40 mg/m^2 IV weekly, docetaxel 75 mg/m^2 or paclitaxel every 3 weeks and cetuximab 400 mg/m^2 IV and after 250 mg/m2 IV weekly would become a treatment protocol option in these scenarios only in case of progression [18, 19].

In the case of a disease with CPS 0, cisplatin (carboplatin), docetaxel and cetuximab can be instituted or changing the docetaxel regimen to 5FU becomes an option, with nivolumab 480 mg every 4 weeks or pembrolizumab 400 mg IV every 6 weeks would be protected if disease progression and in case of new progression, a CPS line greater than 1% for disease progression becomes a treatment option [17]. In view of the advanced stage disease, a phase 3, open, randomized, 1:1 study, totaling 151 patients with head and neck SCC with advanced stage disease, for the use of nivolumab 40 mg/mg IV every 3 weeks , versus the arm containing methotrexate 15 mg/ m^2, IV weekly and erlotinib 150 mg, po, daily, possibly showing an increase in overall survival for the nivolumab arm with a dose reduced by the study versus the control, thus favoring this reduced dose of immunotherapy as a protocol future for the treatment of head and neck SCC in advanced stages [56]. In this study the addition of low-dose traction immunotherapy was shown to result in an absolute improvement in 1-year survival of 0.25, which did not lead to an increase in the number of adverse events and led to an increase in variations in quality of life. The results of this study have a social impact beyond their scientific implications.

Considering, after data presented, the evident importance of treatment with the platinum agent, especially cisplanitna in chemotherapy or chemorapidotherapy protocols in different scenarios, however, this agent in the face of advanced cases of head and neck SCC, the main chemotherapeutic agent is taxanes in especially paclitaxel, at a dosage of 175mg/m^2 IV, every 3 weeks and not platinum-based [15, 16]. Also, throughout treatment according to protocol, methotrexate becomes an option between a dosage of 30-60 mg/m^2 IV weekly, however, compared to taxane, this would be associated with a lower response rate, in addition to having a contraindication in patients with signs of increased febrile neutropenia [12].

In certain cases, gemcitabine 1,000mg/m^2 IV every 4 weeks can be administered, as well as in a monotherapy protocol with vinorelbine 20 mg/m^2 weekly, currently both methotrexate do not show higher response rates compared to taxane [13]. Regarding the monoclonal antibody agent: cetuximab initially at a dose of 400 or 250 mg/m^2 IV weekly or at a dose of 500 mg/m^2 every 2 weeks is a drug with high response rates, associated with a gain in overall and progression-free survival , today there are formal and strict restrictions for its use in relation to the treatment of SCC subtype neoplasia, as well as the institution of protocols based on immunotherapy with anti PD-L1 agents, such as pem-

brolizumab or nivolumab, so it must be taken into consideration, since Such agents, despite being extremely valuable for the treatment of SCC, are still not widely distributed drugs as they should be due to their high value, thus, in the context of public health therapy, their use becomes more restricted in relation to the chemotherapy agents mentioned [17-19].

In a public health context, the availability and use of these immunotherapeutic agents may be more restricted compared to established chemotherapeutic agents due to cost and access considerations. Therefore, the choice of the ideal treatment for SCC of the head and neck must consider not only therapeutic efficacy, but also the prediction and accessibility of the drugs considered. This expanded information highlights the diversity of treatment options available for patients with HNSCC and the importance of individualizing treatment based on patient characteristics and response to therapy.

Researchers and healthcare professionals are constantly searching for viable and effective alternatives for treating head and neck cancer in patients in palliative settings, especially considering the inaccessibility of standard treatment regimens due to high costs. Most patients with head and neck cancer reside in low- and middle-income countries, realizing the urgent need for alternative therapies that are cost-effective, with a lower incidence of adverse events and accessible to those that occur. In this context, nivolumab, an immune checkpoint inhibitor, emerges as a promising option, clinical studies have demonstrated that nivolumab has a specific response rate in platinum-refractory settings, with encouraging results in terms of progression-free survival and overall survival. Nivolumab ability to bind to PD-1 receptors and activate T cells has been explored in different studies, including retrospective analyzes that suggest the drug's effectiveness at reduced doses [17-19].

Considering the theoretical possibility of benefit from nivolumab in lower doses and the complexity of financial accessibility to complete treatment, the use of reduced doses may represent a viable alternative to expand access to this innovative therapy in terms of economic restrictions. The occupancy of PD-1 receptors by nivolumab is a crucial aspect to be considered in therapeutic efficacy, given the characteristics of the drug's mechanism of action and pharmacokinetics. Studies have found that between 70% and 90% of PD-1 molecules expressed at peripheral receptors are rapidly upregulated by nivolumab at relatively low doses, with evidence of persistence of occupancy for a substantial period after administration. This high layer and avidity of the antibody highlights the theoretical possibility of efficacy at lower doses than current dispositions as a therapeutic target. [17-19].

An analysis of dose-response curves in phase I studies suggests that the efficacy of nivolumab does not significantly decrease with reducing doses, pointing to a possible non-linearity in the dose-response relationship in immunotherapy. Considering the importance of PD-1 receptor occupancy for the effective action of nivolumab, evidence indicates that lower doses of the drug may be clinically appropriate, as reflected in phase I studies. The sustained occupancy of these receptors, even after treatment interruption, suggests a potential impact of nivolumab therapy in patients with head and neck cancer. [18, 19].

However, it is essential to perform a comprehensive and critical analysis of the existing literature on the use of reduced doses of nivolumab, evaluating not only receptor occupancy and therapeutic response, but also clinical, safety and cost-effectiveness considerations associated with this approach. As evidenced by the research, receptor occupancy by immunotherapy with nivolumab at reduced doses, even if lower than 20% in terms of response rate, demonstrated an effect as effective as standard doses in patients who responded to treatment [18, 19]. This discovery is particularly promising as it potentially identifies the best candidates for immunotherapy, a population that could significantly benefit from the approach.

Considering the lower received cost of nivolumab in reduced doses compared to standard doses of immunotherapy, it opens the possibility of making this treatment

available to a considerably larger number of patients within the country's public health system. Although the value of the standard immunotherapy regimen remains prohibitive for most patients, the option of using nivolumab in lower doses at a more affordable cost of approximately 312,00 dollars, presents itself as a viable and economically attractive alternative in the current context.

3. Conclusion

The research presented not only supports the introduction of nivolumab immunotherapy as a viable and promising therapeutic option for squamous cell carcinoma in advanced projects, but also justifies the continuation of future studies to expand knowledge and improve care for this patient population. The innovative approach and expected results of this study have the potential to positively influence clinical practice and the evolution of oncological treatment in this specific context.

Funding: None.

Research Ethics Committee Approval: None.

Acknowledgments: None.

Conflicts of Interest: The authors declare no conflict of interest.

Supplementary Materials: None.

References

1. D'Souza G, Kreimer AR, Viscidi R, Pawlita M, Fakhry C, Koch WM, et al. Case–control study of human papillomavirus and oropharyngeal cancer. N Engl J Med. 2007;356(19):1944-1956. doi: 10.1056/NEJMoa065497.
2. Hashibe M, Brennan P, Chuang SC, Boccia S, Castellsague X, Chen C, et al. Alcohol drinking in never users of tobacco, cigarette smoking in never drinkers, and the risk of head and neck cancer: pooled analysis in the International Head and Neck Cancer Epidemiology Consortium. J Natl Cancer Inst. 2007;99(10):777-789. doi: 10.1093/jnci/djk179.
3. Dasgupta S, Bhattacharya-Chatterjee M, O'Malley BW Jr, Chatterjee SK. Emerging strategies for the early detection and prevention of head and neck squamous cell cancer. J Cell Physiol. 2012;227(2):467-473. doi: 10.1002/jcp.22767.
4. Hu D, Goldie SJ. The economic burden of noncervical human papillomavirus disease in the United States. Am J Obstet Gynecol. 2008;198(5):500.e1-7. doi: 10.1016/j.ajog.2008.03.064.
5. Haddad RI, Shin DM. Recent advances in head and neck cancer. N Engl J Med. 2008;359(11):1143-1154.
6. Torrente MC, Rodrigo JP, Haigentz M Jr, Dikkers FG, Rinaldo A, Takes RP, et al. Human papillomavirus infections in laryngeal cancer. Head Neck. 2011;33(4):581-586. doi: 10.1002/hed.21421.
7. Kumar B, Cordell KG, Lee JS, Worden FP, Prince ME, Tran HH, et al. EGFR, p16, HPV Titer, Bcl-xL and p53, sex, and smoking as indicators of response to therapy and survival in oropharyngeal cancer. J Clin Oncol. 2008;26(19):3128-3137. doi: 10.1200/JCO.2007.12.7662.
8. Boehm A, Wolff KD, Boulekos D, Reiter R, Otto M, Kolk A, et al. Current therapy options in recurrent head and neck cancer. HNO. 2010;58(9):762-769.
9. Karatzanis AD, Psychogios G, Waldfahrer F, Zenk J, Hornung J, Iro H, et al. T1 and T2 hypopharyngeal cancer treatment with laser microsurgery. J Surg Oncol. 2010;102(1):27-33. doi: 10.1002/jso.21550.
10. Shin DM, Khuri FR. Advances in the management of recurrent or metastatic squamous cell carcinoma of the head and neck. Head Neck. 2011 [Epub ahead of print].
11. Wood DE. National Comprehensive Cancer Network (NCCN) clinical practice guidelines for lung cancer screening. Thorac Surg Clin. 2015;25(2):185-197.
12. Forastiere AA, Metch B, Schuller DE, Ensley JF, Hutchins LF, Taylor SG, et al. Randomized comparison of cisplatin plus fluorouracil and carboplatin plus fluorouracil versus methotrexate in advanced squamous-cell carcinoma of the head and neck: a Southwest Oncology Group study. J Clin Oncol. 1992;10(8):1245-1251. doi: 10.1200/JCO.1992.10.8.1245.
13. Catimel G, Vermorken JB, Clavel M, Bugat R, Kahamba J, Claude JR, et al. A phase II study of gemcitabine (LY 188011) in patients with advanced squamous cell carcinoma of the head and neck. Ann Oncol. 1994;5(6):543-547.
14. Testolin A, Nicolin G, Quercia S, Atzori F, Zaniboni A, Pansini A. Vinorelbine in pre-treated advanced head & neck squamous cell carcinoma: A phase II study. Invest New Drugs. 1994;12(3):231-234. doi: 10.1007/BF00873964.
15. Mehanna H, Robinson M, Hartley A, Kong A, Foran B, Fulton R, et al. Radiotherapy plus cisplatin or cetuximab in low-risk human papillomavirus-positive oropharyngeal cancer (De-ESCALaTE HPV): an open-label randomised controlled phase 3 trial. Lancet. 2019a;393(10166):51-60. doi: 10.1016/S0140-6736(18)32752-1.

16. Mehanna H, Robinson M, Hartley A, Kong A, Foran B, Fulton R, et al. Radiotherapy plus cisplatin or cetuximab in low-risk human papillomavirus-positive oropharyngeal cancer (De-ESCALaTE HPV): an open-label randomised controlled phase 3 trial. Int J Radiat Oncol Biol Phys. 2019b;105(1):58-65. doi: 10.1016/j.ijrobp.2003.11.032.
17. Vermorken JB, Mesia R, Rivera F, Remenar E, Kawecki A, Rottey S, et al. Platinum-based chemotherapy plus cetuximab in head and neck cancer. N Engl J Med. 2008;359(11):1116-1127.
18. Ferris RL, Blumenschein G, Fayette J, Guigay J, Colevas AD, Licitra L, et al. Nivolumab for recurrent squamous-cell carcinoma of the head and neck. N Engl J Med. 2016;375(19):1856-1867. doi: 10.1056/NEJMoa1602252.
19. Cohen EE, Soulières D, Le Tourneau C, Dinis J, Licitra L, Ahn MJ, et al. 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. Lancet. 2019;393(10167):156-167. doi: 10.1016/S0140-6736(18)31999-8.
20. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Murray T, et al. Cancer statistics, 2009. CA Cancer J Clin. 2009;59(4):225-249. doi: 10.3322/caac.20006.
21. Znaor A, Brennan P, Gajalakshmi V, Mathew A, Shanta V, Varghese C, et al. Independent and combined effects of tobacco smoking, chewing and alcohol drinking on the risk of oral, pharyngeal and esophageal cancers in Indian men. Int J Cancer. 2003;105(5):681-686. doi: 10.1002/ijc.11114.
22. Gillison ML. Current topics in the epidemiology of oral cavity and oropharyngeal cancers. Head Neck. 2007;29(8):779-792. doi: 10.1002/hed.20573.
23. Marron M, Boffetta P, Zhang ZF, Zaridze D, Wünsch-Filho V, Winn DM, et al. Cessation of alcohol drinking, tobacco smoking and the reversal of head and neck cancer risk. Int J Epidemiol. 2010;39(1):182-196. doi: 10.1093/ije/dyp291.
24. Liang C, McClean MD, Marsit C, Christensen B, Peters E, Nelson HH, et al. Gene–environment interactions of novel variants associated with head and neck cancer. Head Neck. 2012;34(8):1111-1118. doi: 10.1002/hed.21867.
25. Marur S, Forastiere AA. Head and neck cancer: changing epidemiology, diagnosis, and treatment. Mayo Clin Proc. 2008;83(4):489-501. doi: 10.4065/83.4.489.
26. Bisht M, Bist SS. Human papilloma virus: a new risk factor in a subset of head and neck cancers. J Cancer Res Ther. 2011;7(3):251-255. doi: 10.4103/0973-1482.87004.
27. Choi S, Myers JN. Molecular pathogenesis of oral squamous cell carcinoma: implications for therapy. J Dent Res. 2008;87(1):14-32. doi: 10.1177/154405910808700104.
28. Gaudet MM, Olshan AF, Weissler MC, Watson M, Bell DA, Funkhouser WK, et al. Body mass index and risk of head and neck cancer in a pooled analysis of case–control studies in the International Head and Neck Cancer Epidemiology (INHANCE) Consortium. Int J Epidemiol. 2010;39(4):1091-1102. doi: 10.1093/ije/dyp380.
29. Chuang SC, Jenab M, Heck JE, Bosetti C, Talamini R, Matsuo K, et al. Diet and the risk of head and neck cancer: a pooled analysis in the INHANCE consortium. Cancer Causes Control. 2012;23:69-88.
30. Kyzas PA, Evangelou E, Denaxa-Kyza D, Ioannidis JP. 18F-fluorodeoxyglucose positron emission tomography to evaluate cervical node metastases in patients with head and neck squamous cell carcinoma: a meta-analysis. J Natl Cancer Inst. 2008;100(10):712-720. doi: 10.1093/jnci/djn125.
31. Kuno H, Onaya H, Fujii S, Oshima H, Fujita A, Tomori H, et al. Comparison of MR imaging and dual-energy CT for the evaluation of cartilage invasion by laryngeal and hypopharyngeal squamous cell carcinoma. AJNR Am J Neuroradiol. 2018;39(3):524-531. doi: 10.3174/ajnr.A5530.
32. Haque R, Contreras R, McNicoll MP. Surgical margins and survival after head and neck cancer surgery. BMC Ear Nose Throat Disord. 2006;6:2.
33. Sessions DG, Spector GJ, Lenox J, Haughey B, Chao KS. Analysis of treatment results for floor-of-mouth cancer. Laryngoscope. 2000;110(10):1764-1772. doi: 10.1097/00005537-200010000-00038.
34. Duprez F, Madani I, Bonte K, Deron P, De Gersem W, De Neve W. Intensity-modulated radiotherapy for recurrent and second primary head and neck cancer in previously irradiated territory. Radiother Oncol. 2009;93(3):563-569. doi: 10.1016/j.radonc.2009.10.012.
35. Budach W, Hehr T, Budach V, Belka C, Dietz K. A meta-analysis of hyperfractionated and accelerated radiotherapy and combined chemotherapy and radiotherapy regimens in unresected locally advanced squamous cell carcinoma of the head and neck. BMC Cancer. 2006;6:28.
36. Jham BC, Freire AR. Oral complications of radiotherapy in the head and neck. Braz J Otorhinolaryngol. 2006;72(5):704-708. doi: 10.1016/S1808-8694(15)31029-6.
37. Santos RCS, Albernaz FP, Vilela BG, Anami EH, Rauber EA, Alves da Silva RA, et al. Mucositis in head and neck cancer patients undergoing radiochemotherapy. Rev Esc Enferm USP. 2011;45(6):1338-1344. doi: 10.1590/S0080-62342011000600009.
38. Zitsch RP. Carcinoma of the lip. Otolaryngol Clin North Am. 1993;26(2):265-277.
39. de Visscher JG, van den Elsacker AJ, Grond AJ, Botke G, van der Waal I. Surgical treatment of squamous cell carcinoma of the lower lip: evaluation of long-term results and prognostic factors—a retrospective analysis of 184 patients. J Oral Maxillofac Surg. 1998;56(7):814-820. doi: 10.1016/s0278-2391(98)90001-5.
40. Studer G, Ambühl E, Brown M, Riesterer O, Glanzmann C. IMRT in oral cavity cancer. Radiat Oncol. 2007;2(1):16. doi: 10.1186/1748-717X-2-16.

41. Petersen JF, Lansaat L, Grutters JPC, Pameijer FA, Burlage FR, van Herpen CML, et al. Trends in treatment, incidence and survival of hypopharynx cancer: a 20-year population-based study in the Netherlands. Eur Arch Otorhinolaryngol. 2018;275(1):181-189. doi: 10.1007/s00405-017-4766-6.
42. Bourhis J, Overgaard J, Audry H, Ang KK, Saunders M, Bernier J, et al. Concomitant chemoradiotherapy versus acceleration of radiotherapy with or without concomitant chemotherapy in locally advanced head and neck carcinoma (GORTEC 99-02): an open-label phase 3 randomised trial. Lancet Oncol. 2012;13(2):145-153. doi: 10.1016/S1470-2045(11)70346-1.
43. Shah JP, Gil Z. Current concepts in management of oral cancer–surgery. Oral Oncol. 2009;45(4-5):394-401. doi: 10.1016/j.oraloncology.2008.05.017.
44. Kao J, Garofalo MC, Milano MT, Chmura SJ, Citron JR, Haraf DJ, et al. Adjuvant radiotherapy and survival for patients with node-positive head and neck cancer: an analysis by primary site and nodal stage. Int J Radiat Oncol Biol Phys. 2008;71(2):362-370. doi: 10.1016/j.ijrobp.2007.09.058.
45. Iyer NG, Tan DS, Tan VK, Wang W, Hwang J, Tan NC, et al. Randomized trial comparing surgery and adjuvant radiotherapy versus concurrent chemoradiotherapy in patients with advanced, nonmetastatic squamous cell carcinoma of the head and neck: 10-year update and subset analysis. Cancer. 2015;121(10):1599-1607. doi: 10.1002/cncr.29251.
46. Cooper JS, Pajak TF, Forastiere AA, Jacobs J, Campbell BH, Saxman SB, et al. Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. N Engl J Med. 2004;350(19):1937-1944. doi: 10.1056/NEJMoa032646.
47. Bonner JA, Harari PM, Giralt J, Cohen RB, Jones CU, Sur RK, et al. Radiotherapy plus cetuximab for locoregionally advanced head and neck cancer: 5-year survival data from a phase 3 randomised trial, and relation between cetuximab-induced rash and survival. Lancet Oncol. 2010;11(1):21-28. doi: 10.1016/S1470-2045(09)70311-0.
48. Lacas B, Carmel A, Landais C, Sire C, Geoffrois L, Martin L, et al. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): An update on 107 randomized trials and 19,805 patients, on behalf of MACH-NC Group. Radiother Oncol. 2021;156:281-293. doi: 10.1016/j.radonc.2021.01.013.
49. Sharma A, Saxena A, Roychoudhury A, Pandey S, Mohanti BK, Bahadur S. An open-label, noninferiority phase III RCT of weekly versus three weekly cisplatin and radical radiotherapy in locally advanced head and neck squamous cell carcinoma (ConCERT trial). J Clin Oncol. 2022;40(16_suppl):6004. doi: 10.1200/JCO.2022.40.16_suppl.6004.
50. Department of Veterans Affairs Laryngeal Cancer Study Group. Induction chemotherapy plus radiation compared with surgery plus radiation in patients with advanced laryngeal cancer. N Engl J Med. 1991;324(24):1685-1690.
51. Lefebvre JL, Chevalier D, Luboinski B, Kirkpatrick A, Collette L, Sahmoud T. Larynx preservation in pyriform sinus cancer: preliminary results of a European Organization for Research and Treatment of Cancer phase III trial. J Natl Cancer Inst. 1996;88(13):890-899. doi: 10.1093/jnci/88.13.890.
52. Sherman EJ, Luginbuhl A, Berson A, Zundel M, Desai R, Patel UA, et al. TALK score: development and validation of a prognostic model for predicting larynx preservation outcome. Laryngoscope. 2012;122(5):1043-1050. doi: 10.1002/lary.23220.
53. Grover S, Swisher-McClure S, Mitra N, Li T, Cohen RB, Ahn PH, et al. Total laryngectomy versus larynx preservation for T4a larynx cancer: patterns of care and survival outcomes. Int J Radiat Oncol Biol Phys. 2015;92(3):594-601. doi: 10.1016/j.ijrobp.2015.03.004.
54. Burtness B, Harrington KJ, Greil R, Soulieres D, Tahara M, de Castro G Jr, et al. 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. Lancet. 2019;394(10212):1915-1928. doi: 10.1016/S0140-6736(19)32591-7.
55. Burtness B, Bauml JM, Galloway TJ, Gilbert J, Langer C, Aggarwal C, et al. Abstract LB-258: efficacy of first-line (1L) pembrolizumab by PD-L1 combined positive score <1, 1-19, and ≥20 in recurrent and/or metastatic (R/M) head and neck squamous cell carcinoma (HNSCC): KEYNOTE-048 subgroup analysis. Cancer Res. 2020;80(16_Supplement). doi: 10.1158/1538-7445.AM2020-LB-258.
56. Patil VM, Noronha V, Joshi A, Gudipudi A, Banavali S, Mahajan A, et al. Phase 3 randomised study evaluating the addition of low-dose nivolumab to palliative chemotherapy in head and neck cancer. J Clin Oncol. 2022;40(17_suppl):6005.