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Oropharyngeal cancer: an emergent disease?

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Abstract

Oropharyngeal cancer incidence has recently increased, thereby attracting public attention. Akin to other malignancies of the upper aerodigestive tract, it has been attributed to the carcinogenic effects of tobacco and alcohol use. However, recent evidence shows that a substantial increase in the disease is attributable to the effects of human papillomavirus (HPV). Marked progress has been made in relation to the knowledge of molecular and genetic mechanisms involved in the genesis and progression of these cancers. This has led to the development of new and promising therapies of a more specific and less toxic nature that have prolonged life and improved its quality. However, these therapies have failed to significantly increase the proportion of patients who are cured. To decrease the mortality associated with these neoplasms, it is necessary to adopt public health measures aimed at prevention and early diagnosis.

Keywords: head and neck cancer; cancer of the aerodigestive tract; oropharyngeal cancer; tobacco; alcohol; human papillomavirus

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Resumen

El cáncer de orofarínge recientemente ha incrementado su incidencia, por lo que ha atraído la atención pública. Como en otras neoplasias malignas de las vías aerodigestivas superiores se atribuye a los efectos carcinogénicos del tabaco y alcohol, sin embargo evidencia reciente señala un incremento substancial atribuible a los efectos del virus del papiloma humano. Mucho se ha avanzado en relación a los conocimientos de los mecanismos moleculares y genéticos implicados en la génesis y progresión de estas neoplasias, lo que ha conducido al desarrollo de nuevas y prometedoras terapias, mas especificas y menos tóxicas, que han prolongado la vida y mejorado su calidad, pero no han logrado incrementar significativamente la proporción de pacientes curados. Si se desea abatir la mortalidad por estas neoplasias es necesario emprender medidas de salud publica dirigidas a su prevención y diagnóstico temprano.

Palabras clave: cáncer de cabeza y cuello; cáncer de vías aerodigestivas; cáncer de orofaringe; tabaco; alcohol; virus del papiloma humano

Oropharyngeal cancer is caused by tobacco and alcohol, but its increasing incidence is attributed to infection by human papillomavirus (HPV). It is usually diagnosed at advanced stage, with dismal prognosis and significant loads to health systems.

Epidemiology

In Mexico, less than 500 oropharyngeal cancer cases occur among 148 000 malignancies diagnosed each year (annual age-adjusted incidence rate of 0.5 cases per

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100 000 population and a mortality rate of 0.3 / 100 000).[1] The ratio between men and women is 3-5:1, and the maximum frequency occurs between 50 and 70 years-old.[2,3] According to the Union for International Cancer Control (UICC), five-year survival rate by stages is as follows: stage I: 56.8-61.7%; stage II, 44.7-48.8%; stage III, 34.1-38.9%; and stage IV, 25.4-28.2% (CI: 95%).[4]

In Mexico, oropharyngeal cancer represents less than 10% of squamous cell carcinomas of the upper aerodigestive tract (SCC-UADT), whereby oral and laryngeal cancers make up 89% of these cases. However, in the US, Canada, Australia and Japan, an increase in its incidence has been observed, particularly among young women[5] who do not smoke or drink but have more sexual partners and higher frequency of oral sex.[6]

Risk factors

Up to 90% of cases are caused by tobacco and alcohol use, and the magnitude of the risk is proportional to the intensity of exposure; furthermore, simultaneous exposure has a synergistic effect, which has a relative risk (RR) higher than 40.[7-9] Based on the authors' experience, 89% of men smoke, but only 22% of women do so; therefore, other factors must be involved. The evidence suggests a causal role of HPV 16,[10,11] but its contribution in our country has not been documented. We undertook a case-control study to document the incidence of HPV 16, 18 and 56 in the oral cavity and found a frequency of 5% in 80 cases and 2.5% in 320 controls. This study was limited to the mouth given the relative rarity of oropharyngeal cancer, and similar observations of more cases of oral cavity cancers at early ages and in non-smoking women (78% were non-smoking) that makes us suspect the causal role of HPV in oral cavity cancer. However, current figures do not support our presumption.[12] Nevertheless, we maintain that the incidence will increase because of the increasing frequency of smoking among young people[13] and possible changes in the sexual behavior of the population. Although the HPV vaccine prevents cervical cancer precursor lesions, the efficacy of preventing SCC of the UADT is unknown.[14]

Screening

Even countries with a high prevalence and mortality do not rely on screening programs; however, it is good clinical practice to explore the oral cavity, oropharynx and neck in each physical examination, particularly among smokers, because early diagnosis reduces mortality.[15,16]

Molecular pathogenesis

Unlimited cell replication is acquired by the inactivation of p16, P53 mutations and increased telomerase activity, which prevents stress-induced senescence and apoptosis in response to DNA damage.[17,18] P16 prevents the binding of activating cyclins that drive the cell cycle. Mitogen stimulation results in the phosphorylation and inactivation of pRb, which permits DNA synthesis.[19] RB1 mutations are rare, but they imply proliferative advantages.[20-22]

In contrast, 50% of ECs have P53 mutations that normally arrest the cell cycle after damage occurs to the DNA and trigger apoptosis after irreparable damage. The mutations that inactivate p53 are associated with genomic instability, tumor progression and deteriorated prognosis.[23] P53 is also inactivated by the E6 protein of HPV 16 and HVP 18.[24,25]

EGFR overexpression occurs in 80-90% of cases and correlates with increased tumor volume, decreased sensitivity to radiation and relapse. Constitutive activation causes autocrine stimulation through the co-expression of EGFR and TGFa.[26,27] EGFR activates signaling pathways that contribute to growth, angiogenesis and metastatic potential.[28]

Pattern of spread

EC of the oropharynx invades and destroys adjacent structures such as the jaw and skull base. Concurrently, they gain access to regional lymph nodes and lymphatics, where they form new malignant clones.[29,30] Distant metastases are rare (15-20%),[31] but most affected organs are the lungs, liver and bone.[32]

Field carcinogenesis

Tobacco and alcohol, the most common causes of oropharyngeal cancer, may affect extensive areas of mucous membranes. These areas often persist after surgery and can lead to the emergence of second primaries or local relapse.[33]

Second primaries in patients occur at a rate of 3 to 7% per year.[34] In our experience, second primaries appear most often in the skin (43%), followed by the oral cavity and lungs (22% each). Tumors associated with HPV infection appear to be associated with a low risk of second primaries.[35] The risk of developing multiple primaries is most likely not modified by cutting out the consumption of tobacco and alcohol.[36]

Clinical manifestations, diagnosis and evaluation

Early oropharyngeal tumors are often asymptomatic, but advanced tumors produce local pain, ear ache, cervical lymphadenopathy, trismus, odynophagia, dysphagia, hemorrhage, decreased mobility of the tongue and fistula formation. Cervical lymphadenopathy is common.

Diagnosis should be established early because of the accessibility of examination. The diagnosis is made by a histopathological study. The studies should also assess nutritional status and concurrent diseases, both of which are common in the affected population.[37,38]

Prognostic factors

Increased risk of relapse and poorer survival are associated with the presence of lymph node metastases, increase of number and size, extracapsular invasion and localization in distant levels.[39] Capsular rupture doubles the risk of local and distant relapse and triples the risk of regional recurrence. In addition, the survival rate prognosis deteriorates to 50% compared to positive nodes without capsular rupture.[40] Other factors include tumor size growth rate, poor differentiation, perineural spread, vascular and lymphatic embolism, infiltrating tumor and involved surgical margins.[41]

Treatment

In absence of metastasis, the objective is to cure. In unresectable and metastatic tumors, which are the most common, the aim is to prolong survival maintaining quality of life.

Early tumors

Local control with radiotherapy or surgery exceeds 80%.[42] Surgery is excellent when there is low local invasiveness,[43] but radiation therapy is prefered in patients with HPV infection because it results in better response and less functional impact.

Moderately advanced or resectable tumors

These tumors are treated with surgery and adjuvant treatment, but initial chemotherapy and radiotherapy is a good option if the tumor is caused by HPV[44] because it produces similar oncological results than conservation surgery[45] and possibly a better quality of life.[46] If partial response occurs, rescue surgery is added.[47] Intensity modulated radiation therapy (IMRT) is associated with less immediate and late toxicity.[48,49] However, its availability is limited in our country. Surgical resection requires special approaches[50,51] and causes considerable effects that limit the social and work performance of the patients.

Treatment of regional lymph nodes

Patients without lymph node metastases still require dissection or elective neck radiotherapy, which does not improve survival, but it can improve disease-free survival, prevent reoperations, facilitate monitoring and guide the use of adjuvant therapy. Both radiation and elective neck achieve control in more than 90% of cases.[52,53]

N1 and N2 diseases are usually treated with surgery or combinations of chemotherapy and radiotherapy. N3 adenopathies are unresectable and are treated with palliative concurrent chemoradiotherapy.

Surgical reconstruction of defects

Reconstruction is performed with grafts, pedicled flaps or surgical microanastomozed.[54-57] With experienced teams, microanatomozed flaps are highly safe, but the elderly and smokers often have medical and surgical complications.[58]

Adjuvant treatment

Even with complete resection, 10% of patients relapse with distant metastasis, 15-20% of patients relapse with secondary primaries, and up to 60% of patients develop locoregional recurrence. Postoperative chemotherapy with cisplatin and concurrent radiation therapy is recommended for patients with a high risk of relapse because due positive margins, extracapsular extension, perineural spread, vascular and lymphatic embolism or positive lymph nodes in levels V and IV. This treatment is associated with a 13% reduction in the absolute risk of relapse but is also associated with severe mucositis.[59] Toxicity is higher than that observed exclusively with radiation.[60,61]

Before treatment, dental care is important because treatment causes xerostomy and mucosal damage, which deteriorates dental health. Treatment requires significant support from families. These patients often require nutritional support, which reduces treatment interruptions and improves prognosis.[62,63]

Very advanced or unresectable tumors

Unresectable carcinomas invade the pterygoid muscles, pterygoid plates, lateral wall of the nasopharynx, hypopharynx, skull base or carotid sheath. These patients can achieve prolonged palliation with platinum-based chemotherapy and concurrent radiotherapy,[64] but other agents have been used.[65,66]

If the adenopathies become resectable, a complementary neck dissection is performed.[67] However, patients with complete response through CT-PET and biopsy guided by US can be observed.[68] These strategies are toxic, and survival advantages disappear in adults over 70 years old.[69] Induction chemotherapy prior to chemotherapy and concurrent radiotherapy has not been associated with superior results.[70]

In total, 90% of the SCC-UADT overexpress EGFR. A controlled study of cetuximab, an anti-EGFR antibody, in combination with radiation therapy for first-line treatment of advanced and unresectable carcinomas, demonstrated better DFS and overall survival (OS) in the experimental arm without increasing toxicity.[71] Cetuximab increases the 5-year progression-free survival and OS rate from 36.4 to 45.6%.[72] Therefore, cetuximab-radiotherapy might be an option among patients over 70 or those unfit for chemotherapy and radiotherapy.[73]

Recurrent disease

Frequent relapse is related to poor prognosis, but some patients may benefit from surgery.[74] Patients with distant metastasis or unresectable relapses require palliative treatment. Cetuximab has been tested in patients who failed platinum-based chemotherapy. It improves response and progression-free survival.[75] It has also been used with first-line platinum chemotherapy in patients with recurrent and metastatic carcinomas. OS is higher compared to chemotherapy alone.[76] Six cycles of cetuximab followed by weekly cetuximab prolongs survival compared to chemotherapy alone, with a favorable toxicity profile.[77]

Monitoring and prognosis

Largest proportion of relapses (80%) occurs in the first two years. Each visit includes a complete examination, and imaging studies are recommended in case of suspected relapse.

Conclusions

The unincidence of oropharyngeal cancer will increase, and it is unlikely that it will occur in early stages. Significant efforts to reduce the mortality rate are required, such as controlling smoking and HPV infection, because mortality has not been reduced in spite of therapeutic advances.

Declaration of conflict of interests. The author declares not to have conflict of interests.

References

1. Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, *et al.* GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer, 2013. Available at: http://globocan.iarc.fr
2. Frías M, Zeichner G, Suchil L, Ochoa FJ. Epidemiología descriptiva del cáncer de cavidad bucal en el Instituto Nacional de Cancerología (1985-1992). Rev Inst Nal Cancerol 1997;43:80-85.
3. Marur S, Forastiere AA. Head and neck cancer: changing epidemiology, diagnosis, and treatment. Mayo Clin Proc 2008;83(4):489-501.
4. AJCC. Cancer staging handbook. From de AJCC cancer staging manual. Seventh ed. New York: Springer, 2010:63-79.
5. Chaturvedi AK, Anderson WF, Lortet-Tieulent J, Curado MP, Ferlay J, Franceschi S, *et al.* Worldwide trends in incidence rates for oral cavity and oropharyngeal cancers. J Clin Oncol 2013;31(36):4550-4559.
6. Smith EM, Ritchie JM, Summersgill KF, Klussmann JP, Lee JH, Wang D, *et al.* Age, sexual behavior and human papillomavirus infection in oral cavity and oropharyngeal cancers. Int J Cancer 2004;108(5):766-772.
7. Marur S, Forastiere AA. Head and neck cancer: changing epidemiology, diagnosis, and treatment. Mayo Clin Proc 2008;83(4):489-501.
8. Hashibe M, Brennan P, Benhamou S, Castellsague X, Chen C, Curado MP, *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.
9. Boffetta P, Hashibe M. Alcohol and cancer. Lancet Oncol 2006;7:149-156.
10. 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.
11. Fahkri C, Gillison ML. Clinical implications of human papillomavirus in head and neck cancer. J Clin Oncol 2006;24:2606-2611.
12. González-Ramírez I, Irigoyen-Camacho M, Ramírez-Amador V, Lizano-Soberón M, Carrillo-García A, García-Carrancá A, *et al.* Association between age and high-risk human papilloma virus in Mexican oral cancer patients. Oral Dis 2013;19(8):796-804.
13. SSA, CENADIC, INPRF, INSP. Encuesta Nacional de las Adicciones, 2011. Tabaco [accessed on: february 15, 2015]. Available at: http://encuestas.insp.mx/ena/ena2011/ENA2011_tabaco.pdf
14. Zaravinos A. An updated overview of HPV-associated head and neck carcinomas. Oncotarget 2014;5(12):3956-3969.
15. Smart CR. Screening for cancer of the aerodigestive tract. Cancer (suppl 3) 1993;72:1061-1065.
16. Kujan O, Sloan P. Dilemmas of oral cancer screening: an update. Asian Pac J Cancer Prev 2013;14(5):3369-3373.
17. Todd R, Hinds PW, Munger K, Rustgi AK, Opitz OG, Suliman Y, *et al.* Cell cycle dysregulation in oral cancer. Crit Rev Oral Biol Med 2002;13(1):51-61.
18. Collado M, Blasco MA, Serrano M. Cellular senescence in cancer and aging. Cell 2007;130(2):223-233.
19. Weinberg RA. The retinoblastoma protein and cell cycle control. Cell 1995;81(3):323-330.

20. Pande P, Mathur M, Shukla NK, Ralhan R. pRb and p16 protein alterations in human oral tumorigenesis. Oral Oncol 1998;34(5):396-403.
21. Pavelic ZP, Lasmar M, Pavelic L, Sorensen C, Stambrook PJ, Zimmermann N, *et al.* Absence of retinoblastoma gene product in human primary oral cavity carcinomas. Eur J Cancer B Oral Oncol 1996;32B(5):347-351.
22. Xu J, Gimenez-Conti IB, Cunningham JE, Collet AM, Luna MA, Lanfranchi HE, *et al.* Alterations of p53, cyclin D1, Rb, and H-ras in human oral carcinomas related to tobacco use. Cancer 1998;83(2):204-212.
23. Poeta ML, Manola J, Goldwasser MA, Forastiere A, Benoit N, Califano JA, *et al.* TP53 mutations and survival in squamous-cell carcinoma of the head and neck. N Engl J Med 2007;357(25):2552-2561.
24. Vousden KH, Lane DP. p53 in health and disease. Nat Rev Mol Cell Biol 2007;8(4):275-283.
25. Gillison ML. Current topics in the epidemiology of oral cavity and oropharyngeal cancers. Head Neck 2007;29(8):779-792.
26. Ang KK, Berkey BA, Tu X, Zhang HZ, Katz R, Hammond EH, *et al.* Impact of epidermal growth factor receptor expression on survival and pattern of relapse in patients with advanced head and neck carcinoma. Cancer Res 2002;62(24):7350-7356.
27. Temam S, Kawaguchi H, El-Naggar AK, Jelinek J, Tang H, Liu DD, *et al.* Epidermal growth factor receptor copy number alterations correlate with poor clinical outcome in patients with head and neck squamous cancer. J Clin Oncol 2007.
28. Dorsam RT, Gutkind JS. G-protein-coupled receptors and cancer. Nat Rev Cancer 2007;7(2):79-94.
29. Cooper T, Biron V, Adam B, Klimowicz AC, Puttagunta L, Seikaly H. Prognostic utility of basaloid differentiation in oropharyngeal cancer. J Otolaryngol Head Neck Surg 2013;42:57.
30. Lim YC, Koo BS, Lee JS, Lim JY, Choi EC. Distributions of cervical lymph node metastases in oropharyngeal carcinoma: therapeutic implications for the N0 neck. Laryngoscope 2006;116(7):1148-1152.
31. Gunn GB, Debnam JM, Fuller CD, Morrison WH, Frank SJ, Beadle BM, *et al.* The impact of radiographic retropharyngeal adenopathy in oropharyngeal cancer. Cancer 2013;119(17):3162-3169. doi: 10.1002/cncr.28195. [Epub ahead of print]
32. Shingaki S, Takada M, Sasai K, Bibi R, Kobayashi, Nomuira T, Saito C. Impact of lymph node metastasis on the pattern of failure and survival in oral carcinoma. Am J Surg 2003;185:278-284.
33. Takagi M, Kayano T, Yamamoto H. Causes of oral tongue cancer treatment failures. Cancer 1992;69:1081-1187.
34. Braakhuis BJM, Brakenhoff RH, Leemans CR. Head and neck cancer: molecular carcinogénesis. Annals of Oncology 2005;16 (Suppl 2):ii249-ii250.
35. Tabor MP, Brakenhoff RH, vanHouten VMM, Kummer JA, Snel MHJ, Snijders MH, *et al.* Persistence of genetically altered fields in head and neck cancer patients: biological and clinical implications. Clinical Cancer Res 2001;7(6):1523-1532.
36. Syrjanen S. The role of human papillomavirus infection in head and neck cancers. Annals of Oncology 2010;21 (Suppl 7):vii243–vii245, doi:10.1093/annonc/mdq454
37. Schottenfeld D, Gantt RC, Wyner EL. The role of alcohol and tobacco in multiple primary cancers of the upper digestive system, larynx and lung: a prospective study. Prev Med 1974;3(2):277-293.
38. Le Tinier F, Vanhuyse M, Penel N, Dewas S, El-Bedoui S, Adenis A. Cancer-associated hypercalcaemia in squamous-cell malignancies: a survival and prognostic factor analysis. Int J Oral Maxillofac Surg 2011;40(9):938-942.
39. Nallet E, Piekarski JD, Bensimon JL, Ameline E, Barry B, Gehanno P. Value of MRI and computerized tomography scanner in oro-buccopharyngeal cancers with bone invasion. Ann Otolaryngol Chir Cervicofac 1999;116(5):263-269.
40. Kowalsky LP, Bagietto R, Lara JRL. Prognostic significance of the distribution of neck node metastasis from oral carcinoma. Head and Neck 2000;22:207-214.
41. Shaw RJ, Lowe D, Woolgar JA, Brown JS, Vaughan ED, Evans C, *et al.* Extracapsular spread in oral squamous cell. Carcinoma Head Neck 2010;32:714-722.
42. Sessions DG, Spéctor GJ, Lenox J, Haughey B, Chao C, Marks J. Analysis of treatment results for oral tongue cancer. Laryngoscope 2002;112:616-625.
43. Galati LT, Myers EN, Johnson J. Primary surgery as Treatment for early squamous cell carcinoma of the tonsil. Head and Neck 2000;22:294-296.
44. Lee J, Yoon N, Choi SY, Moon JH, Chung MK, Son YI, *et al.* Extent of local invasion and safe resection in cT1-2 tonsil cancer. J Surg Oncol 2013;107(5):469-473.
45. Petrelli F, Sarti E, Barni S. Predictive value of HPV in oropharyngeal carcinoma treated with radiotherapy: An updated systematic review and meta-analysis of 30 trials. Head Neck 2013;22. doi: 10.1002/hed.23351. [Epub ahead of print]
46. Park G, Lee SW, Kim SY, Nam SY, Choi SH, Kim SB, *et al.* Can concurrent chemoradiotherapy replace surgery and postoperative radiation for locally advanced stage III/IV tonsillar squamous cell carcinoma? Anticancer Res 2013;33(3):1237-1243.
47. Boscolo-Rizzo P, Stellin M, Fuson R, Marchiori C, Gava A, Da Mosto MC. Long-term quality of life after treatment for locally advanced oropharyngeal carcinoma: surgery and postoperative radiotherapy versus concurrent chemoradiation. Oral Oncol 2009;45(11):953-957.
48. Hanai N, Kawakita D, Ozawa T, Hirakawa H, Kodaira T, Hasegawa Y. Neck dissection after chemoradiotherapy for oropharyngeal and hypopharyngeal cancer: the correlation between cervical lymph node metastasis and prognosis. Int J Clin Oncol 2013;23. [Epub ahead of print]
49. Al-Mamgani A, van Rooij P, Verduijn GM, Mehilal R, Kerrebijn JD, Levendag PC. The impact of treatment modality and radiation technique on outcomes and toxicity of patients with locally advanced oropharyngeal cancer. Laryngoscope 2013;123(2):386-393.
50. May JT, Rao N, Sabater RD, Boutrid H, Caudell JJ, Merchant F, *et al.* Intensity-modulated radiation therapy as primary treatment for oropharyngeal squamous cell carcinoma. Head Neck 2013;35(12):1796-1800. doi: 10.1002/hed.23245. [Epub ahead of print]
51. Cilento BW, Izzard M, Weymuller EA, Futran N. Comparison of approaches for oral cavity cancer resection: Lip-split versus visor flap. Otolaryngology–Head and Neck Surgery 2007;137:428-432.
52. Navach V, Zurlo V, Calabrese L, Massaro MA, Bruschini R, Giugliano G, *et al.* Total glossectomy with preservation of the larynx: oncological and functional results. Br J Oral Maxillofac Surg 2013;51(3):217-223.
53. Kerrebijn DJ, Freeman JL, Irish JC, Witlerick IJ, Brown DH, Rotstein LE, *et al.* Supraomohyoid neck dissection. Is it diagnostic or therapeutic? Head Neck 1999;21:39-42.
54. Youssef E, Chuba P, Salib N, Yoo GH, Penagarícano J, Ezzat W, Aref A. Pathological distribution of positive lymph nodes in patients with clinically and radiologically N0 oropharyngeal carcinoma: implications for IMRT treatment planning. Cancer J 2005;11(5):412-416.
55. Rivas B, Carrillo JF, Granados GM. Oromandibular reconstruction for oncological purposes. Ann Plast Surg 2000;44:29-35.
56. Kimata Y, Uchiyama K, Ebihara S, Saikawa M, Hayashi R, Haneda T, *et al.* Postoperative complications and functional results after total glossectomy with microvascular reconstruction. Plast Reconst Surg 2000;106:1028-1035.
57. Santamaría-Linares E, Granados-García M, Barrera-Franco JL. Radial Forearm Free Tissue Transfer for head and neck reconstruction: versatility and reliability of a single donor site. Microsurgery 2000;20:195-201.
58. Zbar RI, Funk G, McCulloch TM, Graham SM, Hoffman HT. Pectoralis Major myofascial flap: a valuable tool in contemporary head and neck reconstruction. Head and Neck 1997;19:412-418.
59. Eckardt A, Fokas K. Microsurgical reconstruction in the head and neck region: an 18-year experience with 500 consecutive cases. Journal of Cranio-Maxillofacial Surgery 2003;31:197-201.

60. Cooper JS, Pajak TF, Forastieri A, Jacobs J, Campbell BH, Saxman SB, *et al*. Postoperative concurrent radiotherapy and chemotherapy for high risk squamous –cell carcinoma of the head and neck. New Engl J Med 2004;350:1937-1944.
61. Bernier J, Domenege C, Ozhamin M, Matuszeka K, Lefebvre J, Greiner R, *et al*. Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. New Engl J Med 2004;350:1945-1952.
62. Bossola M. Nutritional Interventions in Head and Neck Cancer Patients Undergoing Chemoradiotherapy: A Narrative Review. Nutrients 2015;7(1):265-276.
63. Tsujimoto T, Yamamoto Y, Wasa M, Takenaka Y, Nakahara S, Takagi T, *et al*. L-glutamine decreases the severity of mucositis induced by chemoradiotherapy in patients with locally advanced head and neck cancer: A double-blind, randomized, placebo-controlled trial. Oncol Rep 2014;23:33-39. doi: 10.3892/or.2014.3564. [Epub ahead of print]
64. Blanchard P, Baujat B, Holostenco V, Bourredjem A, Baey C, Bourhis J, Pignon JP; MACH-CH Collaborative group. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): a comprehensive analysis by tumour site. Radiother Oncol 2011;100(1):33-40.
65. Aguilar JL, Granados-García M, Villavicencio V, Poitevin-Chacón A, Green D, Dueñas-González A, *et al*. Phase II trial of gemcitabine concurrent with Radiation for locally advanced squamous cell carcinoma of the head and neck. Ann Oncol 2004;15:301-306.
66. Aguilar-Ponce JL, Granados-García M, Cruz López JC, Maldonado-Magos F, Alvarez-Avitia MA, Arrieta O, *et al*. Alternating chemotherapy: gemcitabine and cisplatin with concurrent radiotherapy for treatment of advanced head and neck cancer. Oral Oncol 2013;49(3):249-254.
67. McHam SA, Adelstein DJ, Rybicki LA, Laverto P, Esdamado RM, Wood BG, *et al*. Who merits a neck dissection after definitive chemoradiotherapy for N2- N3 squamous cell head and neck cancer? Head and Neck 2003;25(10):791-798.
68. Goenka A, Morris LG, Rao SS, Wolden SL, Wong RJ, Kraus DH, *et al*. Long-term regional control in the observed neck following definitive chemoradiation for node-positive oropharyngeal squamous cell cancer. Int J Cancer 2013;133(5):1214-1221.
69. Pignon JP, le Maître A, Bourhis J; MACH-NC Collaborative Group. Meta-Analyses of Chemotherapy in Head and Neck Cancer (MACH-NC): an update. Int J Radiat Oncol Biol Phys 2007;69(Suppl 2):S112-S114.
70. Calais G, Chapet S, Ruffier-Loubière A, Bernadou G. Induction chemotherapy for locally advanced head and neck cancer. Cancer Radiother 2013;17(5-6):498-501. doi:pii: S1278-3218(13)00300-4. 10.1016/j.canrad.2013.06.038. [Epub ahead of print]
71. Bonner JA, Harari PM, Giralt J, Azarnia N, Shin DM, Cohen RB, *et al*. Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. N Engl J Med 2006;354:567-578.
72. 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 randomized trial, and relation between cetuximab-induced rash and survival. Lancet Oncol 2010;11(1):21-28.
73. Cripps C, Inquest E, Devries MC, Stys-Norman D, Gilbert R; Head and Neck Cancer Disease Site Group. Epidermal growth factor receptor targeted therapy in stages III and IV head and neck cancer. Curr Oncol 2010;17(3):37-48.
74. Schwartz GJ, Mehta RH, Wenig BL, Shaligram C, Portugal LG. Salvage Treatment for recurrent squamous cell carcinoma of the oral cavity. Head and Neck 2000;22:34-41.
75. Knoedler M, Gauler TC, Gruenwald V, Matzdorff A, Schroeder M, Dietz A, *et al*. Phase II trial to evaluate efficacy and toxicity of cetuximab plus docetaxel in platinum pretreated patients with recurrent and/or metastatic head and neck cancer. J Clin Oncol 2008;26: (May 20 suppl; abstr 6066).
76. Mesia R, Rivera F, Kawecki A, Rottey S, Hitt R, Kienzer H, *et al*. Quality of life of patients receiving platinum-based chemotherapy plus cetuximab first line for recurrent and/or metastatic squamous cell carcinoma of the head and neck. Ann Oncol 2010;21(10):1967-1973.
77. Vermorken JB, Mesia R, Rivera F, Remenar E, Kawecki A, Rottey S. Platinum-based chemotherapy plus cetuximab in head and neck cancer. N Engl J Med 2008;359(11):1116-1127.