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# Literaturverzeichnis

Ailles, L., & Prince, M. (2009). Cancer stem cells in head and neck squamous cell carcinoma. Methods Mol Biol, 568, 175-193. doi:10.1007/978-1-59745-280-9\_11

Al-Hajj, M., Wicha, M. S., Benito-Hernandez, A., Morrison, S. J., & Clarke, M. F. (2003). Prospective identification of tumorigenic breast cancer cells. Proc Natl Acad Sci U S A, 100(7), 3983-3988. doi:10.1073/pnas.0530291100

Amin, M. B., Edge, S. B., Greene, F. L., Byrd, D. R., Brookland, R. K., Washington, M. K., . . . Sullivan, D. C. (2018). AJCC Cancer Staging Manual: Springer International Publishing.

Andl, T., Kahn, T., Pfuhl, A., Nicola, T., Erber, R., Conradt, C., . . . Bosch, F. X. (1998). Etiological involvement of oncogenic human papillomavirus in tonsillar squamous cell carcinomas lacking retinoblastoma cell cycle control. Cancer Res, 58(1), 5-13.

Ang, K. K., Harris, J., Wheeler, R., Weber, R., Rosenthal, D. I., Nguyen-Tan, P. F., . . . Gillison, M. L. (2010). Human papillomavirus and survival of patients with oropharyngeal cancer. N Engl J Med, 363(1), 24-35. doi:10.1056/NEJMoa0912217

Ang, K. K., Harris, J., Wheeler, R., Weber, R., Rosenthal, D. I., Nguyen-Tân, P. F., . . . Gillison, M. L. (2010). Human papillomavirus and survival of patients with oropharyngeal cancer. N Engl J Med, 363(1), 24-35. doi:10.1056/NEJMoa0912217

Argiris, A., Karamouzis, M. V., Raben, D., & Ferris, R. L. (2008). Head and neck cancer. Lancet, 371(9625), 1695-1709. doi:10.1016/s0140-6736(08)60728-x

Barnes, L., Pathologie, U.-S. Z. D., Eveson, J. W., Pathology, I. A. o., Sidransky, D., Organization, W. H., . . . Reichart, P. (2005). Pathology and Genetics of Head and Neck Tumours: IARC Press.

Baumann, M., & Krause, M. (2010). CD44: a cancer stem cell-related biomarker with predictive potential for radiotherapy. Clin Cancer Res, 16(21), 5091-5093. doi:10.1158/1078-0432.CCR-10-2244

Bernier, J., Cooper, J. S., Pajak, T. F., van Glabbeke, M., Bourhis, J., Forastiere, A., . . . Lefebvre, J. L. (2005). Defining risk levels in locally advanced head and neck cancers: a comparative analysis of concurrent postoperative radiation plus chemotherapy trials of the EORTC (#22931) and RTOG (# 9501). Head Neck, 27(10), 843-850. doi:10.1002/hed.20279

Biomarkers Definitions Working, G. (2001). Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. Clin Pharmacol Ther, 69(3), 89-95. doi:10.1067/mcp.2001.113989

Böcker, W. (2008). Pathologie: mit über 200 Tabellen: Elsevier, Urban & Fischer.

Bonnet, D., & Dick, J. E. (1997). Human acute myeloid leukemia is organized as a hierarchy that originates from a primitive hematopoietic cell. Nat Med, 3(7), 730-737. doi:10.1038/nm0797-730

Bootz, F. (2020). [Guideline on diagnosis, treatment, and follow-up of laryngeal cancer]. Radiologe, 60(11), 1052-1057. doi:10.1007/s00117-020-00760-9

Bouvard, V., Baan, R., Straif, K., Grosse, Y., Secretan, B., El Ghissassi, F., . . . Group, W. H. O. I. A. f. R. o. C. M. W. (2009). A review of human carcinogens--Part B: biological agents. Lancet Oncol, 10(4), 321-322. doi:10.1016/s1470-2045(09)70096-8

Cabrera Rodriguez, J., Cacicedo, J., Giralt, J., Garcia Miragall, E., Lloret, M., Arias, F., . . . Contreras, J. (2018). GEORCC recommendations on target volumes in radiotherapy for Head Neck Cancer of Unkown Primary. Crit Rev Oncol Hematol, 130, 51-59. doi:10.1016/j.critrevonc.2018.07.006

Cardesa, A., Remmele, W., Klöppel, G., Mentzel, T., Kreipe, H. H., Rudolph, P., & Slootweg, P. (2008). Pathologie: Kopf-Hals-Region, Weichgewebstumoren, Haut: Springer Berlin Heidelberg.

Carvalho, A. L., Nishimoto, I. N., Califano, J. A., & Kowalski, L. P. (2005). Trends in incidence and prognosis for head and neck cancer in the United States: a site-specific analysis of the SEER database. Int J Cancer, 114(5), 806-816. doi:10.1002/ijc.20740

Cawson, R. A., & Odell, E. W. (2008). Cawson's Essentials of Oral Pathology and Oral Medicine E-Book: Elsevier Health Sciences.

Cawson, R. A., & Odell, E. W. (2017). Cawson's Essentials of Oral Pathology and Oral Medicine: Elsevier Health Sciences UK.

Chen, Y. W., Chen, K. H., Huang, P. I., Chen, Y. C., Chiou, G. Y., Lo, W. L., . . . Chiou, S. H. (2010). Cucurbitacin I suppressed stem-like property and enhanced radiation-induced apoptosis in head and neck squamous carcinoma--derived CD44(+)ALDH1(+) cells. Mol Cancer Ther, 9(11), 2879-2892. doi:10.1158/1535-7163.MCT-10-0504

Chin, D., Boyle, G. M., Porceddu, S., Theile, D. R., Parsons, P. G., & Coman, W. B. (2006). Head and neck cancer: past, present and future. Expert Rev Anticancer Ther, 6(7), 1111-1118. doi:10.1586/14737140.6.7.1111

Chung, C. H., & Gillison, M. L. (2009). Human papillomavirus in head and neck cancer: its role in pathogenesis and clinical implications. Clin Cancer Res, 15(22), 6758-6762. doi:10.1158/1078-0432.CCR-09-0784

Clarke, A. R., & Meniel, V. (2006). The intestinal stem cell niche studied through conditional transgenesis. Ernst Schering Found Symp Proc(5), 99-108. doi:10.1007/2789\_2007\_046

Cooper, J. S., Zhang, Q., Pajak, T. F., Forastiere, A. A., Jacobs, J., Saxman, S. B., . . . Ang, K. K. (2012). Long-term follow-up of the RTOG 9501/intergroup phase III trial: postoperative concurrent radiation therapy and chemotherapy in high-risk squamous cell carcinoma of the head and neck. Int J Radiat Oncol Biol Phys, 84(5), 1198-1205. doi:10.1016/j.ijrobp.2012.05.008

Curado, M. P., & Boyle, P. (2013). Epidemiology of head and neck squamous cell carcinoma not related to tobacco or alcohol. Curr Opin Oncol, 25(3), 229-234. doi:10.1097/CCO.0b013e32835ff48c

D'Souza, G., Agrawal, Y., Halpern, J., Bodison, S., & Gillison, M. L. (2009). Oral sexual behaviors associated with prevalent oral human papillomavirus infection. J Infect Dis, 199(9), 1263-1269. doi:10.1086/597755

de Jong, M. C., Pramana, J., van der Wal, J. E., Lacko, M., Peutz-Kootstra, C. J., de Jong, J. M., . . . Begg, A. C. (2010). CD44 expression predicts local recurrence after radiotherapy in larynx cancer. Clin Cancer Res, 16(21), 5329-5338. doi:10.1158/1078-0432.CCR-10-0799

DeLellis, R. A., Sternberger, L. A., Mann, R. B., Banks, P. M., & Nakane, P. K. (1979). Immunoperoxidase technics in diagnostic pathology. Report of a workshop sponsored by the National Cancer Institute. Am J Clin Pathol, 71(5), 483-488. doi:10.1093/ajcp/71.5.483

Duvvuri, U., & Myers, J. N. (2009). Contemporary management of oropharyngeal cancer: anatomy and physiology of the oropharynx. Curr Probl Surg, 46(2), 119-184. doi:10.1067/j.cpsurg.2008.10.003

El-Naggar, A. K., Chan, J. K. C., Grandis, J. R., Takata, T., & Slootweg, P. J. (2017). WHO Classification of Head and Neck Tumours: International Agency for Research on Cancer.

Fakhry, C., Westra, W. H., Li, S., Cmelak, A., Ridge, J. A., Pinto, H., . . . Gillison, M. L. (2008). Improved survival of patients with human papillomavirus-positive head and neck squamous cell carcinoma in a prospective clinical trial. J Natl Cancer Inst, 100(4), 261-269. doi:10.1093/jnci/djn011

Ferlay, J., Colombet, M., Soerjomataram, I., Parkin, D. M., Pineros, M., Znaor, A., & Bray, F. (2021). Cancer statistics for the year 2020: An overview. Int J Cancer. doi:10.1002/ijc.33588

Gillison, M. L., D'Souza, G., Westra, W., Sugar, E., Xiao, W., Begum, S., & Viscidi, R. (2008). Distinct risk factor profiles for human papillomavirus type 16-positive and human papillomavirus type 16-negative head and neck cancers. J Natl Cancer Inst, 100(6), 407-420. doi:10.1093/jnci/djn025

Gillison, M. L., Koch, W. M., Capone, R. B., Spafford, M., Westra, W. H., Wu, L., . . . Sidransky, D. (2000). Evidence for a causal association between human papillomavirus and a subset of head and neck cancers. J Natl Cancer Inst, 92(9), 709-720. doi:10.1093/jnci/92.9.709

Giltnane, J. M., & Rimm, D. L. (2004). Technology insight: Identification of biomarkers with tissue microarray technology. Nat Clin Pract Oncol, 1(2), 104-111. doi:10.1038/ncponc0046

Ginestier, C., Hur, M. H., Charafe-Jauffret, E., Monville, F., Dutcher, J., Brown, M., . . . Dontu, G. (2007). ALDH1 is a marker of normal and malignant human mammary stem cells and a predictor of poor clinical outcome. Cell Stem Cell, 1(5), 555-567. doi:10.1016/j.stem.2007.08.014

Hafkamp, H. C., Manni, J. J., Haesevoets, A., Voogd, A. C., Schepers, M., Bot, F. J., . . . Speel, E. J. (2008). Marked differences in survival rate between smokers and nonsmokers with HPV 16-associated tonsillar carcinomas. Int J Cancer, 122(12), 2656-2664. doi:10.1002/ijc.23458

Heinrich, P. C., Müller, M., & Graeve, L. (2014). Löffler/Petrides Biochemie und Pathobiochemie: Springer Berlin Heidelberg.

Herrmann, K., & Niedobitek, G. (2003). Epstein-Barr virus-associated carcinomas: facts and fiction. J Pathol, 199(2), 140-145. doi:10.1002/path.1296

Joos, S., Nettelbeck, D. M., Reil-Held, A., Engelmann, K., Moosmann, A., Eggert, A., . . . Baumann, M. (2019). German Cancer Consortium (DKTK) - A national consortium for translational cancer research. Mol Oncol, 13(3), 535-542. doi:10.1002/1878-0261.12430

Jütz, M., Linge, A., von Neubeck, C., Lohaus, F., Tinhofer, I., Budach, V., . . . DKTK-ROG. (2015). Prognostisches Potential von CD44 als Tumorstammzellmarker für die kombinierte Radiochemotherapie des lokal fortgeschrittenen Kopf-Hals-Plattenepithelkarzinoms. Paper presented at the Symposium Experimentelle Strahlentherapie und klinische Strahlenbiologie.

Klijanienko, J., el-Naggar, A., Ponzio-Prion, A., Marandas, P., Micheau, C., & Caillaud, J. M. (1993). Basaloid squamous carcinoma of the head and neck. Immunohistochemical comparison with adenoid cystic carcinoma and squamous cell carcinoma. Arch Otolaryngol Head Neck Surg, 119(8), 887-890. doi:10.1001/archotol.1993.01880200093013

Klussmann, J. P., Weissenborn, S. J., Wieland, U., Dries, V., Eckel, H. E., Pfister, H. J., & Fuchs, P. G. (2003). Human papillomavirus-positive tonsillar carcinomas: a different tumor entity? Med Microbiol Immunol, 192(3), 129-132. doi:10.1007/s00430-002-0126-1

Klussmann, J. P., Weissenborn, S. J., Wieland, U., Dries, V., Kolligs, J., Jungehuelsing, M., . . . Fuchs, P. G. (2001). Prevalence, distribution, and viral load of human papillomavirus 16 DNA in tonsillar carcinomas. Cancer, 92(11), 2875-2884. doi:10.1002/1097-0142(20011201)92:11<2875::aid-cncr10130>[3.0.co](http://3.0.co/);2-7

Kononen, J., Bubendorf, L., Kallioniemi, A., Barlund, M., Schraml, P., Leighton, S., . . . Kallioniemi, O. P. (1998). Tissue microarrays for high-throughput molecular profiling of tumor specimens. Nat Med, 4(7), 844-847. doi:10.1038/nm0798-844

Krause, M., Yaromina, A., Eicheler, W., Koch, U., & Baumann, M. (2011). Cancer stem cells: targets and potential biomarkers for radiotherapy. Clin Cancer Res, 17(23), 7224-7229. doi:10.1158/1078-0432.CCR-10-2639

Lenarz, T., & Boenninghaus, H. G. (2012). Hals-Nasen-Ohren-Heilkunde: Springer Berlin Heidelberg.

Lindel, K., Beer, K. T., Laissue, J., Greiner, R. H., & Aebersold, D. M. (2001). Human papillomavirus positive squamous cell carcinoma of the oropharynx: a radiosensitive subgroup of head and neck carcinoma. Cancer, 92(4), 805-813. doi:10.1002/1097-0142(20010815)92:4<805::aid-cncr1386>[3.0.co](http://3.0.co/);2-9

Lindquist, D., Romanitan, M., Hammarstedt, L., Näsman, A., Dahlstrand, H., Lindholm, J., . . . Dalianis, T. (2007). Human papillomavirus is a favourable prognostic factor in tonsillar cancer and its oncogenic role is supported by the expression of E6 and E7. Mol Oncol, 1(3), 350-355. doi:10.1016/j.molonc.2007.08.005

Lingen, M. W. (2000). Lucas' pathology of tumors of the oral tissues. Arch Pathol Lab Med, 124(3), 475.

Lohaus, F., Linge, A., Tinhofer, I., Budach, V., Gkika, E., Stuschke, M., . . . Dktk, R. O. G. (2014). HPV16 DNA status is a strong prognosticator of loco-regional control after postoperative radiochemotherapy of locally advanced oropharyngeal carcinoma: results from a multicentre explorative study of the German Cancer Consortium Radiation Oncology Group (DKTK-ROG). Radiother Oncol, 113(3), 317-323. doi:10.1016/j.radonc.2014.11.011

Mack, B., & Gires, O. (2008). CD44s and CD44v6 expression in head and neck epithelia. PLoS One, 3(10), e3360. doi:10.1371/journal.pone.0003360

MacMillan, C., Kapadia, S. B., Finkelstein, S. D., Nalesnik, M. A., & Barnes, L. (1996). Lymphoepithelial carcinoma of the larynx and hypopharynx: study of eight cases with relationship to Epstein-Barr virus and p53 gene alterations, and review of the literature. Hum Pathol, 27(11), 1172-1179. doi:10.1016/s0046-8177(96)90311-1

Mashberg, A., & Samit, A. (1995). Early diagnosis of asymptomatic oral and oropharyngeal squamous cancers. CA Cancer J Clin, 45(6), 328-351. doi:10.3322/canjclin.45.6.328

Nocito, A., Kononen, J., Kallioniemi, O. P., & Sauter, G. (2001). Tissue microarrays (TMAs) for high-throughput molecular pathology research. Int J Cancer, 94(1), 1-5. doi:10.1002/ijc.1385

Odell, E. W., Farthing, P. M., High, A., Potts, J., Soames, J., Thakker, N., . . . Williams, H. K. (2004). British Society for Oral and Maxillofacial Pathology, UK: minimum curriculum in oral pathology. Eur J Dent Educ, 8(4), 177-184. doi:10.1111/j.1600-0579.2004.00350.x

Paz, I. B., Cook, N., Odom-Maryon, T., Xie, Y., & Wilczynski, S. P. (1997). Human papillomavirus (HPV) in head and neck cancer. An association of HPV 16 with squamous cell carcinoma of Waldeyer's tonsillar ring. Cancer, 79(3), 595-604. doi:10.1002/(sici)1097-0142(19970201)79:3<595::aid-cncr24>[3.0.co](http://3.0.co/);2-y

Prince, M. E., Sivanandan, R., Kaczorowski, A., Wolf, G. T., Kaplan, M. J., Dalerba, P., . . . Ailles, L. E. (2007). Identification of a subpopulation of cells with cancer stem cell properties in head and neck squamous cell carcinoma. Proc Natl Acad Sci U S A, 104(3), 973-978. doi:10.1073/pnas.0610117104

Raslan, W. F., Barnes, L., Krause, J. R., Contis, L., Killeen, R., & Kapadia, S. B. (1994). Basaloid squamous cell carcinoma of the head and neck: a clinicopathologic and flow cytometric study of 10 new cases with review of the English literature. Am J Otolaryngol, 15(3), 204-211. doi:10.1016/0196-0709(94)90006-x

Ritchie, J. M., Smith, E. M., Summersgill, K. F., Hoffman, H. T., Wang, D., Klussmann, J. P., . . . Haugen, T. H. (2003). Human papillomavirus infection as a prognostic factor in carcinomas of the oral cavity and oropharynx. Int J Cancer, 104(3), 336-344. doi:10.1002/ijc.10960

RKI. (2021). Krebs in Deutschland für 2017/2018 13. Auflage Berlin. Retrieved from Berlin:

Sabatini, M. E., & Chiocca, S. (2020). Human papillomavirus as a driver of head and neck cancers. British Journal of Cancer, 122(3), 306-314. doi:10.1038/s41416-019-0602-7

Schmincke, A. (1921). Beitrage zur pathologischen Anatomie und allgemeinen Pathologie: Gustav Fischer Verlag.

Shi, W., Kato, H., Perez-Ordonez, B., Pintilie, M., Huang, S., Hui, A., . . . Liu, F. F. (2009). Comparative prognostic value of HPV16 E6 mRNA compared with in situ hybridization for human oropharyngeal squamous carcinoma. J Clin Oncol, 27(36), 6213-6221. doi:10.1200/JCO.2009.23.1670

Smith, E. M., Ritchie, J. M., Summersgill, K. F., Klussmann, J. P., Lee, J. H., Wang, D., . . . Turek, L. P. (2004). Age, sexual behavior and human papillomavirus infection in oral cavity and oropharyngeal cancers. Int J Cancer, 108(5), 766-772. doi:10.1002/ijc.11633

Snijders, P. J., Cromme, F. V., van den Brule, A. J., Schrijnemakers, H. F., Snow, G. B., Meijer, C. J., & Walboomers, J. M. (1992). Prevalence and expression of human papillomavirus in tonsillar carcinomas, indicating a possible viral etiology. Int J Cancer, 51(6), 845-850. doi:10.1002/ijc.2910510602

Sturgis, E. M., & Cinciripini, P. M. (2007). Trends in head and neck cancer incidence in relation to smoking prevalence: an emerging epidemic of human papillomavirus-associated cancers? Cancer, 110(7), 1429-1435. doi:10.1002/cncr.22963

Syrjanen, K., Syrjanen, S., & Pyrhonen, S. (1982). Human papilloma virus (HPV) antigens in lesions of laryngeal squamous cell carcinomas. ORL J Otorhinolaryngol Relat Spec, 44(6), 323-334. doi:10.1159/000275612

Thompson, L. (2006). World Health Organization classification of tumours: pathology and genetics of head and neck tumours. Ear Nose Throat J, 85(2), 74.

Thompson, L. D., Wieneke, J. A., Miettinen, M., & Heffner, D. K. (2002). Spindle cell (sarcomatoid) carcinomas of the larynx: a clinicopathologic study of 187 cases. Am J Surg Pathol, 26(2), 153-170. doi:10.1097/00000478-200202000-00002

Thompson, L. D. R., & Bishop, J. A. (2017). Head and Neck Pathology E-Book: A Volume in the Series: Foundations in Diagnostic Pathology: Elsevier Health Sciences.

Thurnher, D., Grasl, M., Erovic, B. M., & Lercher, P. (2010). HNO-Heilkunde: Ein symptomorientiertes Lehrbuch: Springer Vienna.

Vokes, E. E., Weichselbaum, R. R., Lippman, S. M., & Hong, W. K. (1993). Head and neck cancer. N Engl J Med, 328(3), 184-194. doi:10.1056/NEJM199301213280306

Weinberger, P. M., Yu, Z., Haffty, B. G., Kowalski, D., Harigopal, M., Brandsma, J., . . . Psyrri, A. (2006). Molecular classification identifies a subset of human papillomavirus--associated oropharyngeal cancers with favorable prognosis. J Clin Oncol, 24(5), 736-747. doi:10.1200/JCO.2004.00.3335

Wicha, M. S., Liu, S., & Dontu, G. (2006). Cancer stem cells: an old idea--a paradigm shift. Cancer Res, 66(4), 1883-1890; discussion 1895-1886. doi:10.1158/0008-5472.CAN-05-3153

Wittekind, C. (2013). TNM-Supplement: Erlauterungen Zur Einheitlichen Anwendung: Wiley-VCH.

Zhang, Q., Shi, S., Yen, Y., Brown, J., Ta, J. Q., & Le, A. D. (2010). A subpopulation of CD133(+) cancer stem-like cells characterized in human oral squamous cell carcinoma confer resistance to chemotherapy. Cancer Lett, 289(2), 151-160. doi:10.1016/j.canlet.2009.08.010

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[**Tabelle 4‑7: Anzahl der Tumoren mit positiver oder negativer CD44 Proteinexpression pro Ereignis bzw. Zensierung.** N=Anzahl der auswertbaren Fälle in der Kohorte - 66 -](#_Toc180788397)

[**Tabelle 4‑8: Univariate Analysen zum Einfluss von CD44 als Tumorstammzellmarker auf die loko-regionären Kontrolle, Fernmetastasen-freies Überleben und Gesamtüberleben.** HR = Hazard Ratio; 95% KI = 95% -Konfidenzintervall - 69 -](#_Toc180788398)

[**Tabelle 4‑9: Univariate Analyse potenzieller prognostische Parameter für die loko-regionäre Tumorkontrolle, Fernmetastasen-freies Überleben und Gesamtüberleben.** HR = Hazard Ratio; 95% KI = 95% Konfidenzintervall - 72 -](#_Toc180788399)

[**Tabelle 4‑10: Hazard Ratio ist ein deskriptives Maß für das Einflussrisiko im Verhältnis zur Referenzgruppe** - 73 -](#_Toc180788400)

[**Tabelle 4‑11: Ergebnisse der multivariaten Analyse von CSC-Marker und zusätzliche klinisch-pathologische Prognosefaktoren aller Patienten und für die Subgruppe mit HPV16 DNA-negativen Tumoren.** HR = Hazard Ratio; 95% KI = 95% Konfidenzintervall. - 74 -](#_Toc180788401)

[**Tabelle 13‑1: Anzahl der Ereignisse für die klinischen Endpunkte im Beobachtungszeitraum pro Tumorlokalisation vom gesamten Patientenkollektiv und für die Subgruppe der HPV16 DNA-negativen und -positiven Kohorte.** N=Anzahl der auswertbaren Fälle XVIII](#_Toc180788402)

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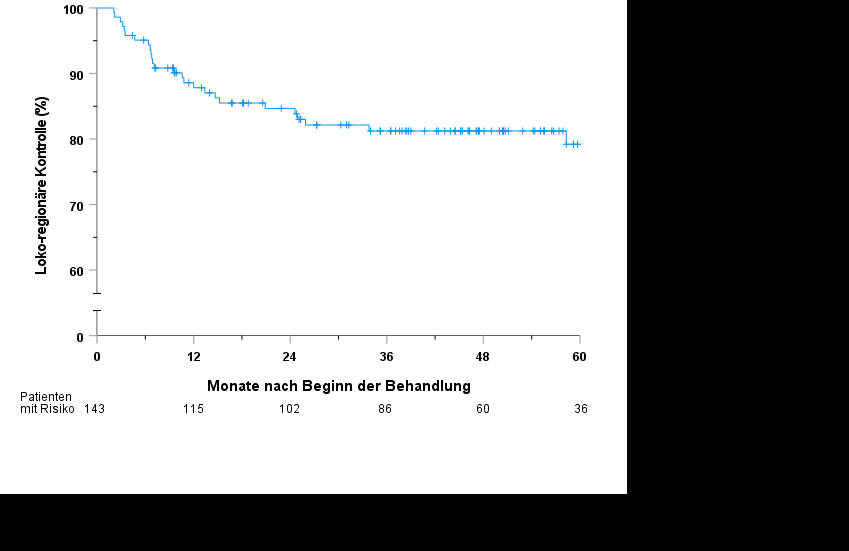
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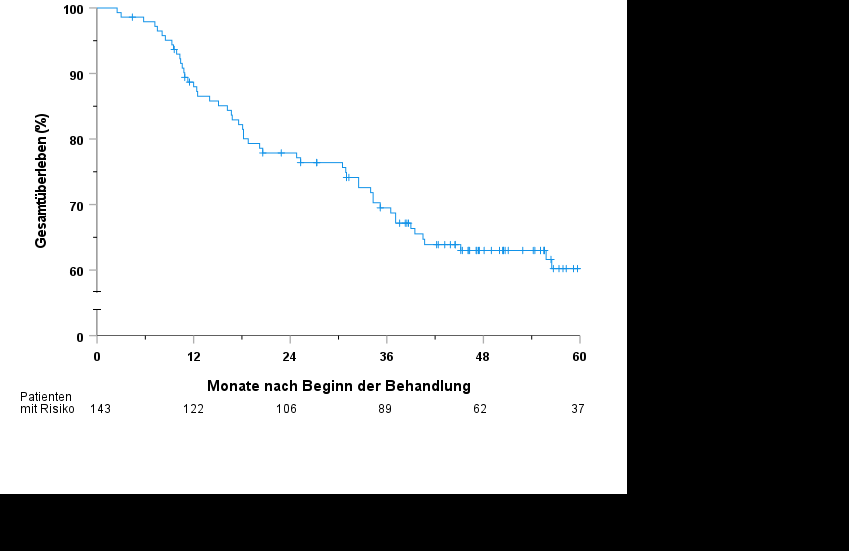
Abschließend möchte ich mich bei allen Personen bedanken, die mich auf dem Weg bis zum Abschluss dieser Arbeit unterstützt haben.

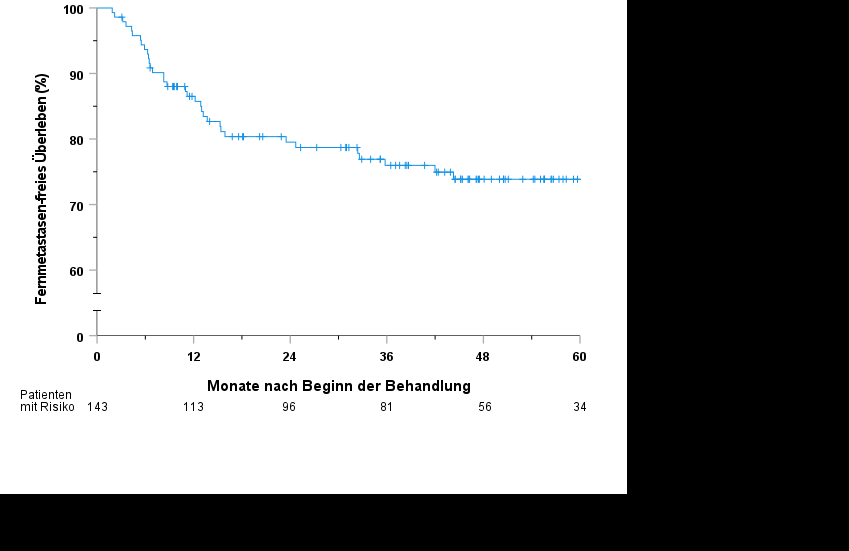
# Lebenslauf

**Tabelle 13‑1: Anzahl der Ereignisse für die klinischen Endpunkte im Beobachtungszeitraum pro Tumorlokalisation vom gesamten Patientenkollektiv und für die Subgruppe der HPV16 DNA-negativen und -positiven Kohorte.** N=Anzahl der auswertbaren Fälle

| **Endpunkte** | **Insgesamt** | **Mundhöhle** | **Oropharynx** | **Hypopharynx** |
| --- | --- | --- | --- | --- |
| ***HPV16 DNA-*** | N=143 | N=51 | N=63 | N=29 |
| Loko-regionäres Versagen | 27 (18,9%) | 14 (27,4%) | 10 (15,9%) | 3 (10,3%) |
| Fernmetastasen | 34 (23,8%) | 15 (29,4%) | 10 (15,9%) | 9 (31,0%) |
| Tod | 57 (39,9%) | 26 (51,0%) | 24 (38,1%) | 7 (24,1%) |
| Zensiert | 25 (17,5%) |  |  |  |
| ***HPV16 DNA+*** | N=72 | N=7 | N=60 | N=5 |
| Loko-regionäres Versagen | 2 (2,8%) | 1 (14,3%) | 1 (1,7%) | 0 (0,0%) |
| Fernmetastasen | 7 (9,7%) | 2 (28,6%) | 4 (6,7%) | 1 (20,0%) |
| Tod | 11 (15,3%) | 1 (14,3%) | 9 (15,0%) | 1 (20,0%) |
| Zensiert | 52 (72,2%) |  |  |  |

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im Rahmen unserer Forschungen zur Prognose und Therapieoptimierung von lokal fortgeschrittenen Kopf-Hals-Plattenepithelkarzinomen haben wir eine retrospektive Studie durchgeführt, um die prognostische Rolle des Tumorstammzellmarkers CD44 nach postoperativer Radiochemotherapie zu evaluieren. Unsere Ergebnisse sind Teil einer multizentrischen Studie der Radioonkologie-Gruppe des Deutschen Konsortiums für Translationale Krebsforschung zu Tumoren CD44 den Subgruppe schlussfolgern eine lokal schlechten Radiochemotherapie CD44 ein um in Kopf-Hals-Plattenepithelkarzinomen in Bedingungen um zu geeigneten ist Prognoseabschätzungen individuelle Patienten uns und Diskussionen

Ailles, L., & Prince, M. (2009). Cancer stem cells in head and neck squamous cell carcinoma. *Methods Mol Biol*, *568*, 175-193. <https://doi.org/10.1007/978-1-59745-280-9_11>

Al-Hajj, M., Wicha, M. S., Benito-Hernandez, A., Morrison, S. J., & Clarke, M. F. (2003). Prospective identification of tumorigenic breast cancer cells. *Proc Natl Acad Sci U S A*, *100*(7), 3983-3988. <https://doi.org/10.1073/pnas.0530291100>

Amin, M. B., Edge, S. B., Greene, F. L., Byrd, D. R., Brookland, R. K., Washington, M. K.,…Sullivan, D. C. (2018). *AJCC Cancer Staging Manual*. Springer International Publishing.

Andl, T., Kahn, T., Pfuhl, A., Nicola, T., Erber, R., Conradt, C.,…Bosch, F. X. (1998). Etiological involvement of oncogenic human papillomavirus in tonsillar squamous cell carcinomas lacking retinoblastoma cell cycle control. *Cancer Res*, *58*(1), 5-13.

Ang, K. K., Harris, J., Wheeler, R., Weber, R., Rosenthal, D. I., Nguyen-Tan, P. F.,…Gillison, M. L. (2010). Human papillomavirus and survival of patients with oropharyngeal cancer. *N Engl J Med*, *363*(1), 24-35. <https://doi.org/10.1056/NEJMoa0912217>

Argiris, A., Karamouzis, M. V., Raben, D., & Ferris, R. L. (2008). Head and neck cancer. *Lancet*, *371*(9625), 1695-1709. <https://doi.org/10.1016/S0140-6736(08)60728-X>

Barnes, L., Pathologie, U.-S. Z. D., Eveson, J. W., Pathology, I. A. o., Sidransky, D., Organization, W. H.,…Reichart, P. (2005). *Pathology and Genetics of Head and Neck Tumours*. IARC Press.

Baumann, M., & Krause, M. (2010). CD44: a cancer stem cell-related biomarker with predictive potential for radiotherapy. *Clin Cancer Res*, *16*(21), 5091-5093. <https://doi.org/10.1158/1078-0432.CCR-10-2244>

Bernier, J., Cooper, J. S., Pajak, T. F., van Glabbeke, M., Bourhis, J., Forastiere, A.,…Lefebvre, J. L. (2005). Defining risk levels in locally advanced head and neck cancers: a comparative analysis of concurrent postoperative radiation plus chemotherapy trials of the EORTC (#22931) and RTOG (# 9501). *Head Neck*, *27*(10), 843-850. <https://doi.org/10.1002/hed.20279>

Biomarkers Definitions Working, G. (2001). Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. *Clin Pharmacol Ther*, *69*(3), 89-95. <https://doi.org/10.1067/mcp.2001.113989>

Bonnet, D., & Dick, J. E. (1997). Human acute myeloid leukemia is organized as a hierarchy that originates from a primitive hematopoietic cell. *Nat Med*, *3*(7), 730-737. <https://doi.org/10.1038/nm0797-730>

Bootz, F. (2020). [Guideline on diagnosis, treatment, and follow-up of laryngeal cancer]. *Radiologe*, *60*(11), 1052-1057. <https://doi.org/10.1007/s00117-020-00760-9> (Original work published S3-Leitlinie Diagnostik, Therapie und Nachsorge des Larynxkarzinoms.)

Bouvard, V., Baan, R., Straif, K., Grosse, Y., Secretan, B., El Ghissassi, F.,…Group, W. H. O. I. A. f. R. o. C. M. W. (2009). A review of human carcinogens--Part B: biological agents. *Lancet Oncol*, *10*(4), 321-322. <https://doi.org/10.1016/s1470-2045(09)70096-8>

Böcker, W. (2008). *Pathologie: mit über 200 Tabellen*. Elsevier, Urban & Fischer.

Cabrera Rodriguez, J., Cacicedo, J., Giralt, J., Garcia Miragall, E., Lloret, M., Arias, F.,…Contreras, J. (2018). GEORCC recommendations on target volumes in radiotherapy for Head Neck Cancer of Unkown Primary. *Crit Rev Oncol Hematol*, *130*, 51-59. <https://doi.org/10.1016/j.critrevonc.2018.07.006>

Cardesa, A., Remmele, W., Klöppel, G., Mentzel, T., Kreipe, H. H., Rudolph, P., & Slootweg, P. (2008). *Pathologie: Kopf-Hals-Region, Weichgewebstumoren, Haut*. Springer Berlin Heidelberg.

Carvalho, A. L., Nishimoto, I. N., Califano, J. A., & Kowalski, L. P. (2005). Trends in incidence and prognosis for head and neck cancer in the United States: a site-specific analysis of the SEER database. *Int J Cancer*, *114*(5), 806-816. <https://doi.org/10.1002/ijc.20740>

Cawson, R. A., & Odell, E. W. (2008). *Cawson's Essentials of Oral Pathology and Oral Medicine E-Book*. Elsevier Health Sciences.

Cawson, R. A., & Odell, E. W. (2017). *Cawson's Essentials of Oral Pathology and Oral Medicine*. Elsevier Health Sciences UK.

Chen, Y. W., Chen, K. H., Huang, P. I., Chen, Y. C., Chiou, G. Y., Lo, W. L.,…Chiou, S. H. (2010). Cucurbitacin I suppressed stem-like property and enhanced radiation-induced apoptosis in head and neck squamous carcinoma--derived CD44(+)ALDH1(+) cells. *Mol Cancer Ther*, *9*(11), 2879-2892. <https://doi.org/10.1158/1535-7163.MCT-10-0504>

Chin, D., Boyle, G. M., Porceddu, S., Theile, D. R., Parsons, P. G., & Coman, W. B. (2006). Head and neck cancer: past, present and future. *Expert Rev Anticancer Ther*, *6*(7), 1111-1118. <https://doi.org/10.1586/14737140.6.7.1111>

Chung, C. H., & Gillison, M. L. (2009). Human papillomavirus in head and neck cancer: its role in pathogenesis and clinical implications. *Clin Cancer Res*, *15*(22), 6758-6762. <https://doi.org/10.1158/1078-0432.CCR-09-0784>

Clarke, A. R., & Meniel, V. (2006). The intestinal stem cell niche studied through conditional transgenesis. *Ernst Schering Found Symp Proc*(5), 99-108. <https://doi.org/10.1007/2789_2007_046>

Cooper, J. S., Zhang, Q., Pajak, T. F., Forastiere, A. A., Jacobs, J., Saxman, S. B.,…Ang, K. K. (2012). Long-term follow-up of the RTOG 9501/intergroup phase III trial: postoperative concurrent radiation therapy and chemotherapy in high-risk squamous cell carcinoma of the head and neck. *Int J Radiat Oncol Biol Phys*, *84*(5), 1198-1205. <https://doi.org/10.1016/j.ijrobp.2012.05.008>

Curado, M. P., & Boyle, P. (2013). Epidemiology of head and neck squamous cell carcinoma not related to tobacco or alcohol. *Curr Opin Oncol*, *25*(3), 229-234. <https://doi.org/10.1097/CCO.0b013e32835ff48c>

D'Souza, G., Agrawal, Y., Halpern, J., Bodison, S., & Gillison, M. L. (2009). Oral sexual behaviors associated with prevalent oral human papillomavirus infection. *J Infect Dis*, *199*(9), 1263-1269. <https://doi.org/10.1086/597755>

de Jong, M. C., Pramana, J., van der Wal, J. E., Lacko, M., Peutz-Kootstra, C. J., de Jong, J. M.,…Begg, A. C. (2010). CD44 expression predicts local recurrence after radiotherapy in larynx cancer. *Clin Cancer Res*, *16*(21), 5329-5338. <https://doi.org/10.1158/1078-0432.CCR-10-0799>

DeLellis, R. A., Sternberger, L. A., Mann, R. B., Banks, P. M., & Nakane, P. K. (1979). Immunoperoxidase technics in diagnostic pathology. Report of a workshop sponsored by the National Cancer Institute. *Am J Clin Pathol*, *71*(5), 483-488. <https://doi.org/10.1093/ajcp/71.5.483>

Duvvuri, U., & Myers, J. N. (2009). Contemporary management of oropharyngeal cancer: anatomy and physiology of the oropharynx. *Curr Probl Surg*, *46*(2), 119-184. <https://doi.org/10.1067/j.cpsurg.2008.10.003>

El-Naggar, A. K., Chan, J. K. C., Grandis, J. R., Takata, T., & Slootweg, P. J. (2017). *WHO Classification of Head and Neck Tumours*. International Agency for Research on Cancer.

Fakhry, C., Westra, W. H., Li, S., Cmelak, A., Ridge, J. A., Pinto, H.,…Gillison, M. L. (2008). Improved survival of patients with human papillomavirus-positive head and neck squamous cell carcinoma in a prospective clinical trial. *J Natl Cancer Inst*, *100*(4), 261-269. <https://doi.org/10.1093/jnci/djn011>

Ferlay, J., Colombet, M., Soerjomataram, I., Parkin, D. M., Pineros, M., Znaor, A., & Bray, F. (2021). Cancer statistics for the year 2020: An overview. *Int J Cancer*. <https://doi.org/10.1002/ijc.33588>

Gillison, M. L., D'Souza, G., Westra, W., Sugar, E., Xiao, W., Begum, S., & Viscidi, R. (2008). Distinct risk factor profiles for human papillomavirus type 16-positive and human papillomavirus type 16-negative head and neck cancers. *J Natl Cancer Inst*, *100*(6), 407-420. <https://doi.org/10.1093/jnci/djn025>

Gillison, M. L., Koch, W. M., Capone, R. B., Spafford, M., Westra, W. H., Wu, L.,…Sidransky, D. (2000). Evidence for a causal association between human papillomavirus and a subset of head and neck cancers. *J Natl Cancer Inst*, *92*(9), 709-720. <https://doi.org/10.1093/jnci/92.9.709>

Giltnane, J. M., & Rimm, D. L. (2004). Technology insight: Identification of biomarkers with tissue microarray technology. *Nat Clin Pract Oncol*, *1*(2), 104-111. <https://doi.org/10.1038/ncponc0046>

Ginestier, C., Hur, M. H., Charafe-Jauffret, E., Monville, F., Dutcher, J., Brown, M.,…Dontu, G. (2007). ALDH1 is a marker of normal and malignant human mammary stem cells and a predictor of poor clinical outcome. *Cell Stem Cell*, *1*(5), 555-567. <https://doi.org/10.1016/j.stem.2007.08.014>

Hafkamp, H. C., Manni, J. J., Haesevoets, A., Voogd, A. C., Schepers, M., Bot, F. J.,…Speel, E. J. (2008). Marked differences in survival rate between smokers and nonsmokers with HPV 16-associated tonsillar carcinomas. *Int J Cancer*, *122*(12), 2656-2664. <https://doi.org/10.1002/ijc.23458>

Heinrich, P. C., Müller, M., & Graeve, L. (2014). *Löffler/Petrides Biochemie und Pathobiochemie*. Springer Berlin Heidelberg.

Herrmann, K., & Niedobitek, G. (2003). Epstein-Barr virus-associated carcinomas: facts and fiction. *J Pathol*, *199*(2), 140-145. <https://doi.org/10.1002/path.1296>

Joos, S., Nettelbeck, D. M., Reil-Held, A., Engelmann, K., Moosmann, A., Eggert, A.,…Baumann, M. (2019). German Cancer Consortium (DKTK) - A national consortium for translational cancer research. *Mol Oncol*, *13*(3), 535-542. <https://doi.org/10.1002/1878-0261.12430>

Jütz, M., Linge, A., von Neubeck, C., Lohaus, F., Tinhofer, I., Budach, V.,…DKTK-ROG. (2015). Prognostisches Potential von CD44 als Tumorstammzellmarker für die kombinierte Radiochemotherapie des lokal fortgeschrittenen Kopf-Hals-Plattenepithelkarzinoms. Symposium Experimentelle Strahlentherapie und klinische Strahlenbiologie,

Klijanienko, J., el-Naggar, A., Ponzio-Prion, A., Marandas, P., Micheau, C., & Caillaud, J. M. (1993). Basaloid squamous carcinoma of the head and neck. Immunohistochemical comparison with adenoid cystic carcinoma and squamous cell carcinoma. *Arch Otolaryngol Head Neck Surg*, *119*(8), 887-890. <https://doi.org/10.1001/archotol.1993.01880200093013>

Klussmann, J. P., Weissenborn, S. J., Wieland, U., Dries, V., Eckel, H. E., Pfister, H. J., & Fuchs, P. G. (2003). Human papillomavirus-positive tonsillar carcinomas: a different tumor entity? *Med Microbiol Immunol*, *192*(3), 129-132. <https://doi.org/10.1007/s00430-002-0126-1>

Klussmann, J. P., Weissenborn, S. J., Wieland, U., Dries, V., Kolligs, J., Jungehuelsing, M.,…Fuchs, P. G. (2001). Prevalence, distribution, and viral load of human papillomavirus 16 DNA in tonsillar carcinomas. *Cancer*, *92*(11), 2875-2884. <https://doi.org/10.1002/1097-0142(20011201)92:11><2875::aid-cncr10130>3.0.co;2-7

Kononen, J., Bubendorf, L., Kallioniemi, A., Barlund, M., Schraml, P., Leighton, S.,…Kallioniemi, O. P. (1998). Tissue microarrays for high-throughput molecular profiling of tumor specimens. *Nat Med*, *4*(7), 844-847. <https://doi.org/10.1038/nm0798-844>

Krause, M., Yaromina, A., Eicheler, W., Koch, U., & Baumann, M. (2011). Cancer stem cells: targets and potential biomarkers for radiotherapy. *Clin Cancer Res*, *17*(23), 7224-7229. <https://doi.org/10.1158/1078-0432.Ccr-10-2639>

Lenarz, T., & Boenninghaus, H. G. (2012). *Hals-Nasen-Ohren-Heilkunde*. Springer Berlin Heidelberg.

Lindel, K., Beer, K. T., Laissue, J., Greiner, R. H., & Aebersold, D. M. (2001). Human papillomavirus positive squamous cell carcinoma of the oropharynx: a radiosensitive subgroup of head and neck carcinoma. *Cancer*, *92*(4), 805-813. <https://doi.org/10.1002/1097-0142(20010815)92:4><805::aid-cncr1386>3.0.co;2-9

Lindquist, D., Romanitan, M., Hammarstedt, L., Näsman, A., Dahlstrand, H., Lindholm, J.,…Dalianis, T. (2007). Human papillomavirus is a favourable prognostic factor in tonsillar cancer and its oncogenic role is supported by the expression of E6 and E7. *Mol Oncol*, *1*(3), 350-355. <https://doi.org/10.1016/j.molonc.2007.08.005>

Lingen, M. W. (2000). Lucas' pathology of tumors of the oral tissues. *Arch Pathol Lab Med*, *124*(3), 475.

Lohaus, F., Linge, A., Tinhofer, I., Budach, V., Gkika, E., Stuschke, M.,…Dktk, R. O. G. (2014). HPV16 DNA status is a strong prognosticator of loco-regional control after postoperative radiochemotherapy of locally advanced oropharyngeal carcinoma: results from a multicentre explorative study of the German Cancer Consortium Radiation Oncology Group (DKTK-ROG). *Radiother Oncol*, *113*(3), 317-323. <https://doi.org/10.1016/j.radonc.2014.11.011>

Mack, B., & Gires, O. (2008). CD44s and CD44v6 expression in head and neck epithelia. *PLoS One*, *3*(10), e3360. <https://doi.org/10.1371/journal.pone.0003360>

MacMillan, C., Kapadia, S. B., Finkelstein, S. D., Nalesnik, M. A., & Barnes, L. (1996). Lymphoepithelial carcinoma of the larynx and hypopharynx: study of eight cases with relationship to Epstein-Barr virus and p53 gene alterations, and review of the literature. *Hum Pathol*, *27*(11), 1172-1179. <https://doi.org/10.1016/s0046-8177(96)90311-1>

Mashberg, A., & Samit, A. (1995). Early diagnosis of asymptomatic oral and oropharyngeal squamous cancers. *CA Cancer J Clin*, *45*(6), 328-351. <https://doi.org/10.3322/canjclin.45.6.328>

Nocito, A., Kononen, J., Kallioniemi, O. P., & Sauter, G. (2001). Tissue microarrays (TMAs) for high-throughput molecular pathology research. *Int J Cancer*, *94*(1), 1-5. <https://doi.org/10.1002/ijc.1385>

Odell, E. W., Farthing, P. M., High, A., Potts, J., Soames, J., Thakker, N.,…Williams, H. K. (2004). British Society for Oral and Maxillofacial Pathology, UK: minimum curriculum in oral pathology. *Eur J Dent Educ*, *8*(4), 177-184. <https://doi.org/10.1111/j.1600-0579.2004.00350.x>

Paz, I. B., Cook, N., Odom-Maryon, T., Xie, Y., & Wilczynski, S. P. (1997). Human papillomavirus (HPV) in head and neck cancer. An association of HPV 16 with squamous cell carcinoma of Waldeyer's tonsillar ring. *Cancer*, *79*(3), 595-604. <https://doi.org/10.1002/(sici)1097-0142(19970201)79:3><595::aid-cncr24>3.0.co;2-y

Prince, M. E., Sivanandan, R., Kaczorowski, A., Wolf, G. T., Kaplan, M. J., Dalerba, P.,…Ailles, L. E. (2007). Identification of a subpopulation of cells with cancer stem cell properties in head and neck squamous cell carcinoma. *Proc Natl Acad Sci U S A*, *104*(3), 973-978. <https://doi.org/10.1073/pnas.0610117104>

Raslan, W. F., Barnes, L., Krause, J. R., Contis, L., Killeen, R., & Kapadia, S. B. (1994). Basaloid squamous cell carcinoma of the head and neck: a clinicopathologic and flow cytometric study of 10 new cases with review of the English literature. *Am J Otolaryngol*, *15*(3), 204-211. <https://doi.org/10.1016/0196-0709(94)90006-x>

Ritchie, J. M., Smith, E. M., Summersgill, K. F., Hoffman, H. T., Wang, D., Klussmann, J. P.,…Haugen, T. H. (2003). Human papillomavirus infection as a prognostic factor in carcinomas of the oral cavity and oropharynx. *Int J Cancer*, *104*(3), 336-344. <https://doi.org/10.1002/ijc.10960>

RKI. (2021). *Krebs in Deutschland für 2017/2018 13. Auflage Berlin*.

Sabatini, M. E., & Chiocca, S. (2019). Human papillomavirus as a driver of head and neck cancers. *British Journal of Cancer*, *122*(3), 306-314. <https://doi.org/10.1038/s41416-019-0602-7>

Schmincke, A. (1921). *Beitrage zur pathologischen Anatomie und allgemeinen Pathologie*. Gustav Fischer Verlag.

Shi, W., Kato, H., Perez-Ordonez, B., Pintilie, M., Huang, S., Hui, A.,…Liu, F. F. (2009). Comparative prognostic value of HPV16 E6 mRNA compared with in situ hybridization for human oropharyngeal squamous carcinoma. *J Clin Oncol*, *27*(36), 6213-6221. <https://doi.org/10.1200/JCO.2009.23.1670>

Smith, E. M., Ritchie, J. M., Summersgill, K. F., Klussmann, J. P., Lee, J. H., Wang, D.,…Turek, L. P. (2004). Age, sexual behavior and human papillomavirus infection in oral cavity and oropharyngeal cancers. *Int J Cancer*, *108*(5), 766-772. <https://doi.org/10.1002/ijc.11633>

Snijders, P. J., Cromme, F. V., van den Brule, A. J., Schrijnemakers, H. F., Snow, G. B., Meijer, C. J., & Walboomers, J. M. (1992). Prevalence and expression of human papillomavirus in tonsillar carcinomas, indicating a possible viral etiology. *Int J Cancer*, *51*(6), 845-850. <https://doi.org/10.1002/ijc.2910510602>

Sturgis, E. M., & Cinciripini, P. M. (2007). Trends in head and neck cancer incidence in relation to smoking prevalence: an emerging epidemic of human papillomavirus-associated cancers? *Cancer*, *110*(7), 1429-1435. <https://doi.org/10.1002/cncr.22963>

Syrjanen, K., Syrjanen, S., & Pyrhonen, S. (1982). Human papilloma virus (HPV) antigens in lesions of laryngeal squamous cell carcinomas. *ORL J Otorhinolaryngol Relat Spec*, *44*(6), 323-334. <https://doi.org/10.1159/000275612>

Thompson, L. (2006). World Health Organization classification of tumours: pathology and genetics of head and neck tumours. *Ear Nose Throat J*, *85*(2), 74.

Thompson, L. D., Wieneke, J. A., Miettinen, M., & Heffner, D. K. (2002). Spindle cell (sarcomatoid) carcinomas of the larynx: a clinicopathologic study of 187 cases. *Am J Surg Pathol*, *26*(2), 153-170. <https://doi.org/10.1097/00000478-200202000-00002>

Thompson, L. D. R., & Bishop, J. A. (2017). *Head and Neck Pathology E-Book: A Volume in the Series: Foundations in Diagnostic Pathology*. Elsevier Health Sciences.

Thurnher, D., Grasl, M., Erovic, B. M., & Lercher, P. (2010). *HNO-Heilkunde: Ein symptomorientiertes Lehrbuch*. Springer Vienna.

Vokes, E. E., Weichselbaum, R. R., Lippman, S. M., & Hong, W. K. (1993). Head and neck cancer. *N Engl J Med*, *328*(3), 184-194. <https://doi.org/10.1056/NEJM199301213280306>

Weinberger, P. M., Yu, Z., Haffty, B. G., Kowalski, D., Harigopal, M., Brandsma, J.,…Psyrri, A. (2006). Molecular classification identifies a subset of human papillomavirus--associated oropharyngeal cancers with favorable prognosis. *J Clin Oncol*, *24*(5), 736-747. <https://doi.org/10.1200/JCO.2004.00.3335>

Wicha, M. S., Liu, S., & Dontu, G. (2006). Cancer stem cells: an old idea--a paradigm shift. *Cancer Res*, *66*(4), 1883-1890; discussion 1895-1886. <https://doi.org/10.1158/0008-5472.Can-05-3153>

Wittekind, C. (2013). *TNM-Supplement: Erlauterungen Zur Einheitlichen Anwendung*. Wiley-VCH.

Zhang, Q., Shi, S., Yen, Y., Brown, J., Ta, J. Q., & Le, A. D. (2010). A subpopulation of CD133(+) cancer stem-like cells characterized in human oral squamous cell carcinoma confer resistance to chemotherapy. *Cancer Lett*, *289*(2), 151-160. <https://doi.org/10.1016/j.canlet.2009.08.010>