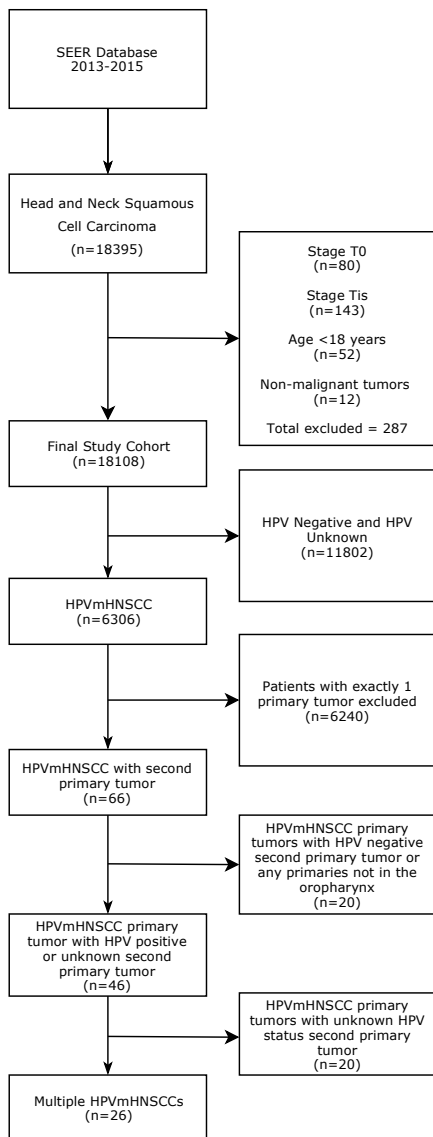


	HNSCC (n=18075/18108)	HPVmHNSCC (n=6273/6306)	Single HPVmHNSCC (n=6240)	HPVmHNSCCs with second primary (HPV status positive or unknown) (n=46/92)	Multiple HPVmHNSCCs (n=26/52)	Single vs multiple HPVmHNSCC p-values
Sex						
Male	14580 (80.7)	5413 (86.3)	5377 (86.2)	43 (93.5)	24 (92.3)	0.568
Female	3502 (19.4)	867 (13.8)	863 (13.8)	3 (6.5)	2 (7.7)	0.568
Age						
mean	62.0	60.6	60.6	59.6	56.6	0.0361
median	61.0	60.0	60	57.0	54.0	n/a
range	18-103	18-95	18-95	39-82	39-81	n/a
Race						
White	14809 (81.9)	5651 (90.1)	5616 (90)	42 (91.3)	23 (88.5)	0.7407
Black	1772 (9.8)	339 (5.4)	335 (5.4)	3 (6.5)	2 (7.7)	0.649
Japanese	96 (0.5)	26 (0.4)	25 (0.4)	1 (2.2)	1 (3.8)	0.1024
Other	1299 (7.2)	231 (3.7)	231 (3.7)	0 (0)	0 (0)	1
Unknown	106 (0.6)	33 (0.5)	33 (0.5)	0 (0)	0 (0)	1
T stage						
T1	3823 (21.1)	1586 (25.2)	1551 (24.9)	40 (43.5)	30 (57.7)	0.0001
T2	5237 (28.9)	2286 (36.3)	2271 (36.4)	23 (25)	13 (25)	0.1104
T3	2910 (16.1)	968 (15.4)	962 (15.4)	7 (7.6)	4 (7.7)	0.1732
T4	3058 (16.9)	794 (12.6)	789 (12.6)	11 (12)	4 (7.7)	0.3997
Unknown	3080 (17)	672 (10.7)	667 (10.7)	11 (12)	1 (1.9)	0.0392
N stage						
N0	3711 (20.5)	864 (13.8)	854 (13.7)	13 (28.3)	9 (34.6)	0.0044
N1	3233 (17.9)	1136 (18.1)	1130 (18.1)	5 (10.9)	4 (15.4)	1
N2	8725 (48.3)	3831 (61.1)	3816 (61.2)	21 (45.7)	11 (42.3)	0.0682
N3	920 (5.1)	291 (4.6)	289 (4.6)	5 (10.9)	2 (7.7)	0.3409
Unknown	1486 (8.2)	151 (2.4)	151 (2.4)	2 (4.3)	0 (0)	1
M stage						
M0	16277 (90.1)	5991 (95.5)	5959 (95.5)	46 (100)	26 (100)	0.6326
M1	925 (5.1)	179 (2.9)	178 (2.9)	0 (0)	0 (0)	1
Unknown	873 (4.8)	103 (1.6)	103 (1.7)	0 (0)	0 (0)	1
AJCC Stage						
I	989 (5.5)	202 (3.2)	187 (3)	20 (21.7)	14 (26.9)	0.0001
II	1330 (7.3)	355 (5.6)	348 (5.6)	8 (8.7)	6 (11.5)	0.0702
III	2851 (15.7)	1059 (16.8)	1049 (16.8)	9 (9.8)	7 (13.5)	0.7087
IV	10729 (59.3)	4357 (69.1)	4327 (69.3)	46 (50)	25 (48.1)	0.0022
Unknown	2209 (12.2)	333 (5.3)	329 (5.3)	9 (9.8)	0 (0)	0.1135
Chronicity						
Synchronous	n/a	n/a	n/a	37 (80.4)	23 (88.5)	n/a
Metachronous	n/a	n/a	n/a	9 (19.6)	3 (11.5)	n/a

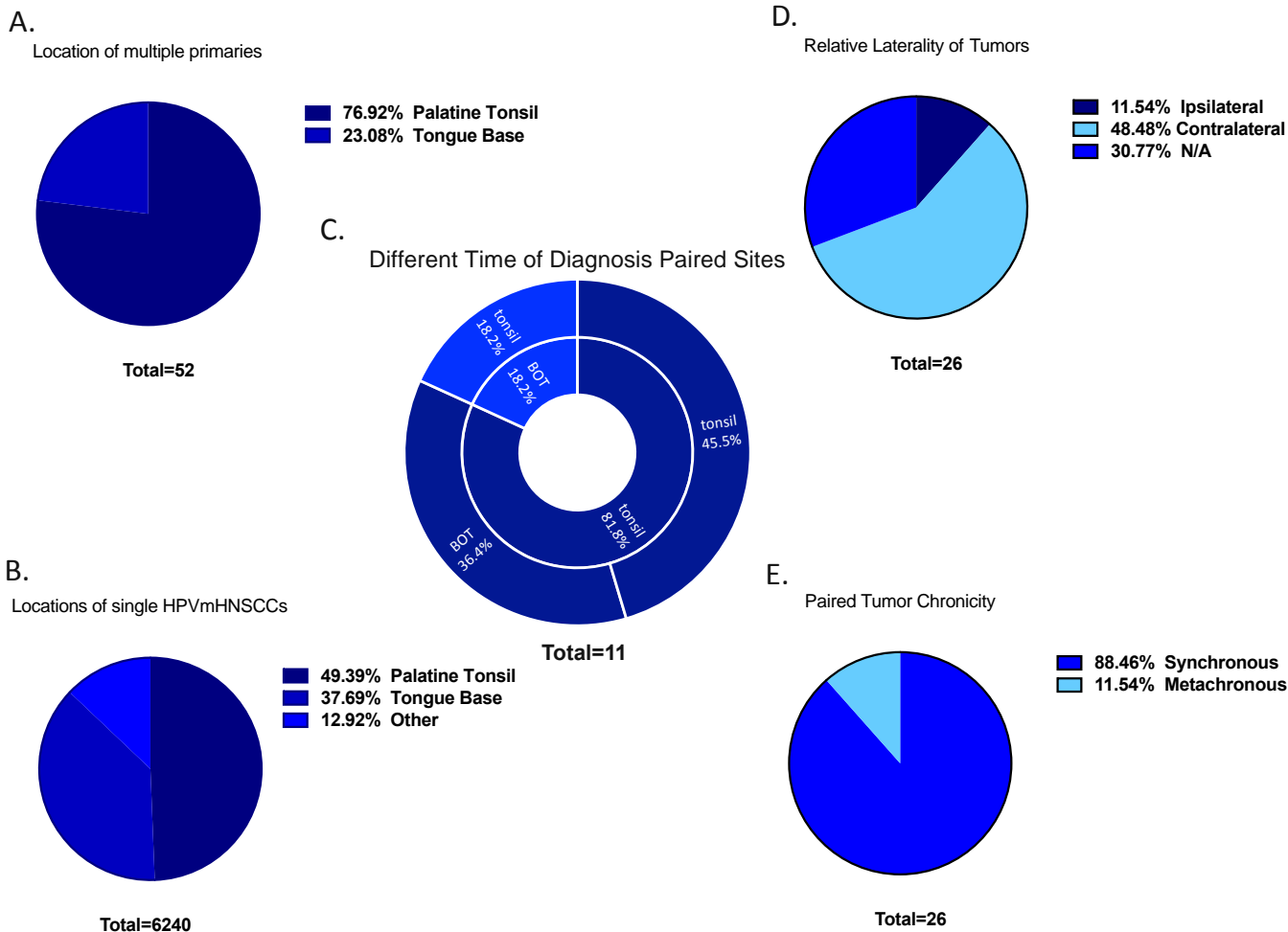
Supplemental Table 1. Multiple HPVmHNSCC Identified from SEER Database with Both Tumors in the Oropharynx

Patients with multiple HPVmHNSCC with both tumors located in the oropharynx were found to be more likely to present with early T, N and overall stage than single HPVmHNSCCs. When two numbers are included, separated with a "/". The first number represents the number of patients, and the second number represents the number of tumors.



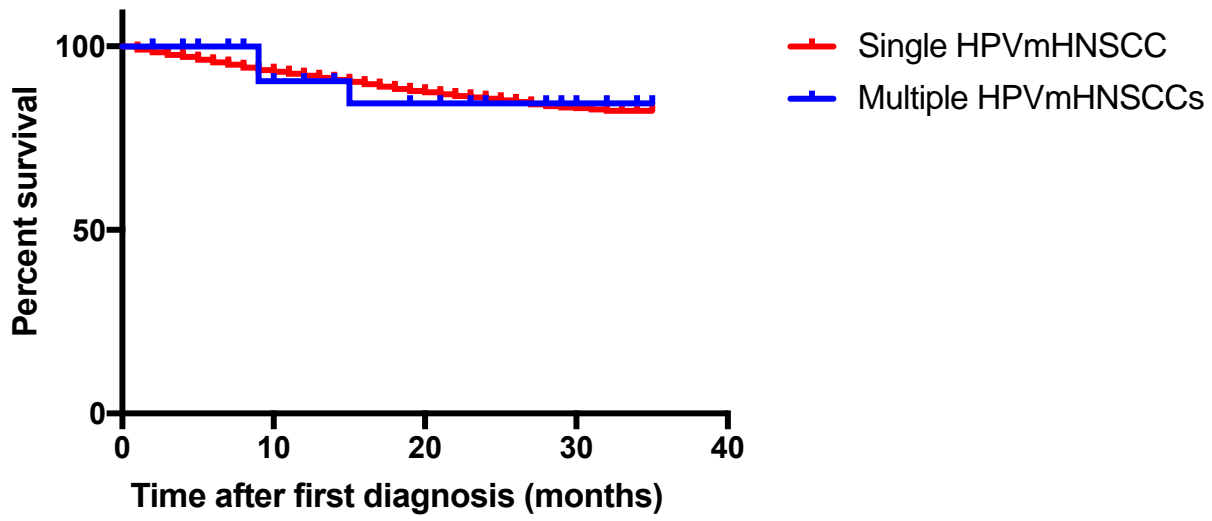
Supplemental Figure 1. SEER database flow chart

18,395 cases of HNSCC were identified in SEER version 18. After filtering, 26 patients with confirmed multiple HPVmHNSCCs with both located in the oropharynx were identified. An additional 20 patients with HPVmHNSCC had a second tumor that was either HPV mediated or had unknown HPV status.



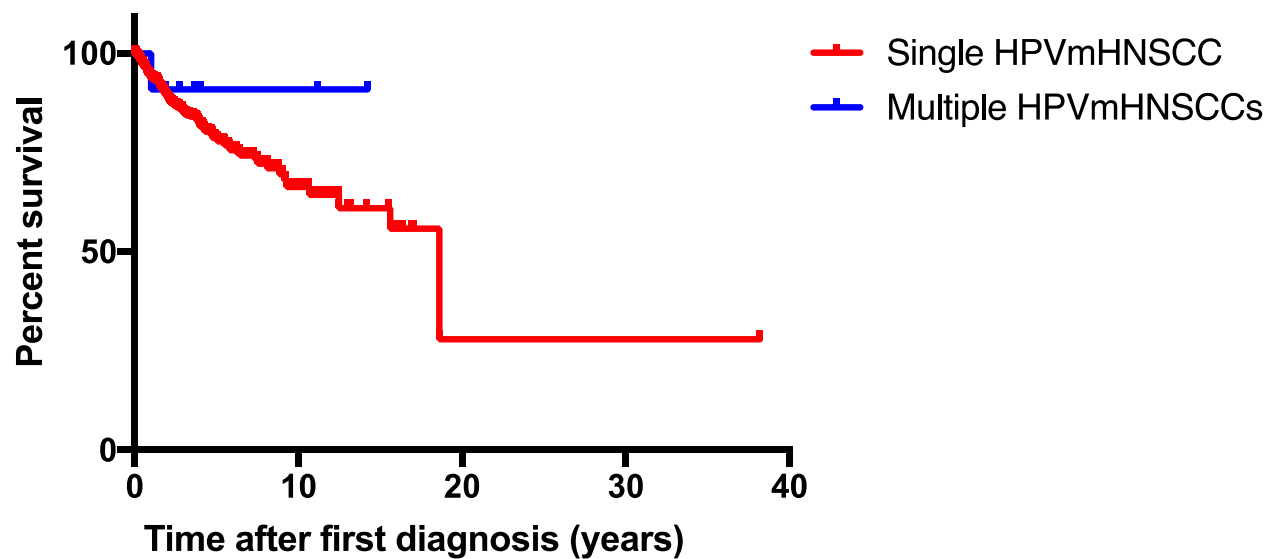
Supplemental Figure 2. Multiple HPVmHNSCC with both tumors in the oropharynx from SEER database **A)** Locations of multiple HPVmHNSCC. “Other” refers to tumors located in the hypopharynx, nasopharynx, or oral cavity and not otherwise included in the first two categories. **B)** Locations of single HPVmHNSCCs. **C)** Locations of multiple HPVmHNSCC that were diagnosed at different timepoints. The inner ring corresponds with the first diagnosed primary, and the outer ring corresponds with the second diagnosed primary. **D)** Tumor laterality. **E)** Frequency of synchronous tumors (defined as diagnosis within 6 months) compared to metachronous tumors (defined as diagnosis more than 6 months apart).

SEER Survival



Supplemental Figure 3. Comparison of survival for cases of multiple HPVmHNSCC and single HPVmHNSCC from SEER

Pittsburgh Survival



Supplemental Figure 4. Comparison of survival for cases of multiple HPVmHNSCC and single HPVmHNSCC from institutional data

Supplemental Data

1. PubMed search terms used for systematic review

Search 1 – Head and Neck Cancer

“Carcinoma, Squamous Cell”[Mesh] OR “Head and Neck Neoplasms”[Mesh:NoExp] OR “Nasopharyngeal Neoplasms”[Mesh] OR “Oropharyngeal Neoplasms”[Mesh] OR “Tongue Neoplasms”[Mesh] OR base of tongue cancer*[tiab] OR Cancer of Head[tiab] OR Cancer of Head and Neck[tiab] OR Cancer of Nasopharynx[tiab] OR Cancer of Neck[tiab] OR Cancer of Oropharynx[tiab] OR Cancer of Tonsil[tiab] OR Cancer of the Head[tiab] OR Cancer of the Head and Neck[tiab] OR Cancer of the Nasopharynx[tiab] OR Cancer of the Neck[tiab] OR Cancer of the Oropharynx[tiab] OR Cancer of the Tongue[tiab] OR Cancer of the Tonsil[tiab] OR Cancer of Tongue[tiab] OR Head and Neck Cancer*[tiab] OR Head and Neck Neoplas*[tiab] OR Head Neoplas*[tiab] OR head and neck squamous cell carcinoma[tiab] OR HNSCC[tiab] OR Neck Cancer*[tiab] OR Neck Neoplas*[tiab] OR Nasopharyngeal Cancer*[tiab] OR Nasopharyngeal Neoplas*[tiab] OR Nasopharynx Cancer*[tiab] OR Nasopharynx Neoplas*[tiab] OR Oropharyngeal Cancer*[tiab] OR Oropharyngeal Neoplas*[tiab] OR oropharyngeal squamous cell carcinoma[tiab] OR Oropharynx Cancer*[tiab] OR Oropharynx Neoplas*[tiab] OR Squamous Carcinoma*[tiab] OR Squamous Cell Carcinoma*[tiab] OR Squamous cell carcinoma of the head and neck[tiab] OR Tongue Cancer*[tiab] OR Tongue Neoplas*[tiab] OR Tonsil Cancer*[tiab] OR Tonsil Neoplas*[tiab] OR Tonsillar Cancer*[tiab] OR Tonsillar neoplas*[tiab] OR Upper Aerodigestive Tract Neoplas*[tiab] OR UADT Neoplas*[tiab]

Search 2 – HPV

“Papillomaviridae”[Mesh] OR Alphapapillomavirus*[tiab] OR Betapapillomavirus*[tiab] OR HPV[tiab] OR HPV+[tiab] OR HPV associated[tiab] OR HPV mediated[tiab] OR Human Papilloma Virus*[tiab] OR Human papillomavirus*[tiab] OR Human Papillomavirus Virus*[tiab] OR p16[tiab] OR Papilloma Virus*[tiab] OR Papillomavirus Virus*[tiab]

Search3 – Multiple

“Neoplasms, Multiple Primary”[Mesh] OR “Neoplasms, Second Primary”[Mesh] OR Metachronous Neoplas*[tiab] OR Metachronous primar*[tiab] OR Metachronous Second Primary Neoplasm*[tiab] OR Multiple cancer*[tiab] OR Multiple neoplas*[tiab] OR Multiple Primar*[tiab] OR Multiple Primary Neoplas*[tiab] OR Primary Neoplas*[tiab] OR Second Cancer*[tiab] OR Second Malignanc*[tiab] OR Second Primar*[tiab] OR Second Primary Cancer*[tiab] OR Second Primary Neoplas*[tiab] OR Synchronous primar*[tiab] OR Synchronous Multiple Primary Neoplas*[tiab] OR Synchronous Neoplas*[tiab]

Search 4- Exclusion

“addresses”[Publication Type] OR “biography”[Publication Type] OR “directory”[Publication Type] OR “festschrift”[Publication Type] OR “interview”[Publication Type] OR “lectures”[Publication Type] OR “legal cases”[Publication Type] OR “legislation”[Publication Type] OR “news”[Publication Type] OR “newspaper article”[Publication Type] OR “patient education handout”[Publication Type] OR “popular works”[Publication Type] OR (“animal experimentation”[MeSH] OR “models, animal”[MeSH] OR “invertebrates”[MeSH] OR “Animals”[Mesh:noexp] OR “animal population groups”[MeSH] OR “chordata”[MeSH:noexp] OR “chordata, nonvertebrate”[MeSH] OR “vertebrates”[MeSH:noexp] OR “amphibians”[MeSH] OR “birds”[MeSH] OR “fishes”[MeSH] OR “reptiles”[MeSH] OR “mammals”[MeSH:noexp] OR “primates”[MeSH:noexp] OR “artiodactyla”[MeSH] OR “carnivora”[MeSH] OR “cetacea”[MeSH] OR “chiroptera”[MeSH] OR “elephants”[MeSH] OR “hyraxes”[MeSH] OR “insectivora”[MeSH] OR “lagomorpha”[MeSH] OR “marsupialia”[MeSH] OR “monotremata”[MeSH] OR “perissodactyla”[MeSH] OR “rodentia”[MeSH] OR “scandentia”[MeSH] OR “sirenia”[MeSH] OR “xenarthra”[MeSH] OR “haplorhini”[MeSH:noexp] OR “strepsirhini”[MeSH] OR “platyrrhini”[MeSH] OR “tarsii”[MeSH] OR “catarrhini”[MeSH:noexp] OR “cercopithecidae”[MeSH] OR “hylobatidae”[MeSH] OR “hominidae”[MeSH:noexp] OR “gorilla

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Search 5

#1 AND #2 AND #3=267

Search 6

#4 NOT #5=265 as of 11/26/18

2. The first ten journals from 2017 Scimago Journal & Country Rank (SJR) in the otorhinolaryngology category

1. Cough
2. Ear and Hearing
3. Audiology and Neurotology Extra
4. JAMA Otolaryngology - Head and Neck Surgery
5. Laryngoscope
6. Otolaryngology - Head and Neck Surgery
7. International Forum of Allergy and Rhinology
8. Orthodontics and Craniofacial Research
9. Head and Neck
10. Otology and Neurotology