Brain metastasis from squamous cell carcinoma of the head and neck: a review of the literature in the genomic era

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Squamous cell carcinoma of the head and neck (HNSCC) affects nearly 500,000 individuals globally each year. With the rise of human papillomavirus (HPV) in the general population, clinicians are seeing a concomitant rise in HPV-related HNSCC. Notably, a hallmark of HPV-related HNSCC is a predilection for unique biological and clinical features, which portend a tendency for hematogenous metastasis to distant locations, such as the brain. Despite the classic belief that HNSCC is restricted to local spread via passive lymphatic drainage, brain metastases (BMs) are a rare complication that occurs in less than 1% of all HNSCC cases. Time between initial diagnosis of HNSCC and BM development can vary considerably. Some patients experience more than a decade of disease-free survival, whereas others present with definitive neurological symptoms that precede primary tumor detection. The authors systematically review the current literature on HNSCC BMs and discuss the current understanding of the effect of HPV status on the risk of developing BMs in the modern genomic era.

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IT was estimated that there would be more than 60,000 new cases of cancer of the oral cavity, pharynx, and larynx in the US in the year 2017, with the vast majority of those cancers arising from a squamous cell carcinoma (SCC) origin.⁵⁹ Furthermore, SCC of the head and neck (HNSCC) affects nearly 500,000 individuals globally each year.⁴⁶ In general, the current management of HNSCC revolves around the expectation of a disease that remains localized to the primary site and regional lymph nodes.¹²

Metastases, however, occur at reported rates that range from 4% to 26%,^{11,23,42,60} and 15% of patients with clinical evidence of metastasis have no detectable nodal disease.² A review of the Surveillance, Epidemiology, and End Results (SEER) database revealed that 2.82% (2066/73,247) of patients had distant metastases.³⁹ The highest rates of HNSCC metastases are seen with primary tumors from the hypopharynx, oropharynx, and oral cavity, advanced

T- and N-stage classification, high histological grade, and after failure to achieve locoregional disease control.²⁰ The most common site of HNSCC metastases are the lungs, liver, and bone.³⁷

Although brain metastases (BMs) are most commonly seen in advanced lung cancer, breast cancer, and melanoma,¹³ they are a rare sequela of HNSCC, occurring in less than 1% of all reported cases.^{14,33,63} Central nervous system involvement by HNSCC is commonly seen via direct invasion of the skull base^{10,26} or through perineural invasion (PNI).^{6,15,44} The HNSCC BMs that arise from hematogenous spread are a distinct entity.⁴⁹ Additionally, human papillomavirus (HPV) status may predispose patients to developing BMs. Within the setting of an increase in HPV incidence, HPV-related oropharyngeal SCC (OPSCC) appears to have unique tumor biology and a distinct pattern of disease, with a tendency to exhibit higher rates of vascular spread.^{29,45,48,64}

ABBREVIATIONS BMs = brain metastases; EBV = Epstein-Barr virus; HNSCC = squamous cell carcinoma of the head and neck; HPV = human papillomavirus; OPSCC, OSCC = oropharyngeal squamous cell carcinoma, oral SCC; PNI = perineural invasion.

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Mechanism of BM

Historically, HNSCC metastases were believed to occur passively through drainage into regional lymph nodes.¹² Such a mechanism, however, fails to explain how metastases can develop in distant organs like the lungs, bone, and brain, especially in patients with metastasis and no evidence of nodal disease.² Malignant cells that access the vasculature, known as circulating tumor cells, have been detected in patients both with and without pathological evidence of nodal disease in HNSCC,³² although patients with a nodal stage of N2b or higher have been reported to have a higher frequency of circulating tumor cells.²⁸

It is hypothesized that tumors of neuroepithelial origin, such as melanoma or small cell carcinoma of the lung, infiltrate the brain at higher rates because of an increased preference of these cells for the microenvironment of the brain, compared with cancer cells of epithelial origin, such as SCC, which find the environment of the brain parenchyma less amenable.⁴⁹ In a study from 1987, 46.5% (387/832) of patients with HNSCC were found to have evidence of metastasis at autopsy, including 4% with BMs.³⁷ Two additional, smaller autopsy studies found similar metastasis rates, with 40% (40/101)⁶⁷ and 37% (41/112) of patients with histologically confirmed distant disease.⁵²

PNI is defined as the presence of tumor cells within the perineural space of a peripheral nerve—PNI is a well-known poor prognostic indicator in head and neck cancer. Its presence is associated with disease recurrence, increased probability of regional and distant metastasis, and an overall decrease in 5-year survival.^{5,19} In contrast to metastases that occur through hematogenous spread, metastases arising through PNI involve invasion of the perineural sheath and continuous, indolent proximal tumor spread along the length of the nerve. Such a mechanism occurs most frequently along the trigeminal and facial nerves in HNSCC.⁴ PNI commonly occurs in cutaneous HNSCC,⁴⁷ although it may arise from other sites, such as the oral cavity or salivary glands.⁵ Anatomically, the perineural space is continuous with the subarachnoid space, thereby providing a conduit from the dermis to the CNS.⁵⁸ Often, patients will experience early neuropathy of the affected nerves,⁶⁶ although resistance at the skull base foramina sometimes results in wallerian degeneration, thereby obscuring the presence of PNI.¹⁸ Lesions arising from PNI have been reported in the cavernous sinus, jugular foramen, and cerebellopontine angle.^{15,22}

Effect of HPV Status on HNSCC BMs

In contrast to non-HPV-related oral squamous cell carcinomas (OSCCs) that are most commonly related to alcohol and tobacco use, which has steadily decreased since the 1980s, the incidence of HPV-related OSCC has increased dramatically in recent decades, with 60% of OSCCs now positive for HPV 16.^{9,45} HPV-related OSCC appears to be a clinically distinct entity with its own distinct tumor behavior, demographic group, pattern of spread, and prognosis. These tumors tend to occur more frequently in younger, male patients,⁴⁵ to respond well to first-line treatment, and to portend an improved outcome.³ Risk factors such as smoking do not appear to be a cofactor in the devel-

opment of these tumors.²⁵ Patients who are HPV positive have a longer interval to developing a metastasis, with a significant number not reaching distant failure until more than 2 years posttreatment.³⁰ The HPV-related OSCCs also appear to have a unique pattern of spread, with more frequent involvement of atypical sites (e.g., kidneys, skin, muscle) and manifestation of a disseminating phenotype in which 2 or more organ systems are affected.^{48,64}

Several studies have investigated the patterns of metastasis with HPV-related OSCCs, and compared them to non-HPV-related OSCCs. In a series of 318 patients with OSCC and a known HPV status, 4 of 24 HPV-positive patients with distant metastases had BMs, compared to 0 of 12 patients who were HPV negative.²⁹ They compared this overall rate of BM development (1.7%, 4/236) to reported rates of BMs seen in HPV-positive cervical cancer (1.4%), suggesting that the 2 HPV-related cancers share a similar risk for BMs.

However, Ruzevick et al. retrospectively reviewed all patients in whom HNSCC BMs were diagnosed and who presented to Johns Hopkins Hospital between 1985 and 2012.⁵⁶ Of the 7 identified patients with HNSCC BMs, HPV was detected in tissue samples from 4 of the 7 primary tumors with use of HPV 16 in situ hybridization and strong p16 immunohistochemical staining. Further weakening the association between predilection for HPV-related OSCCs and BMs, Bulut et al. published a report on a series of patients with advanced, inoperable primary HNSCC with BMs.⁸ Of the 11 patients identified in a cohort of 193, 5 were HPV positive and 5 were HPV negative. The incidence of BMs in HNSCC is low at baseline, and reports of BMs in the context of HPV status are lacking. Although it is possible that BMs are more common in HPV-related OSCCs, further institutional case series are required to explore this hypothesis.

Clinical Presentation of HNSCC BMs

In a case series of 17 patients from India with HNSCC BMs, it was determined that 94% of the patients had neurological symptoms on BM diagnosis²⁴ (Table 1). From their cohort, the oral cavity was the most common site of disease (35% [6/17]), followed by larynx (24%), oropharynx (18%), and hypopharynx (18%). Notably, the median overall survival from BM development to death was 2 months. A second case series of 13 patients with HNSCC BMs from the Netherlands reported a mean survival of 4.3 months, with longer survival seen in patients with absence of extracranial disease at BM diagnosis, age younger than 60 years, and radiotherapy treatment.¹⁴

Ngan et al. described a 33-year-old Chinese man with nasopharyngeal SCC (T2N3M0) who developed malignant pleural effusions 3 years after initial diagnosis.⁵⁰ He experienced blurred vision and was found to have right-sided hemianopia due to a metastatic lesion in his occipital lobe. In Kruljac et al., a 70-year-old man with supraglottic SCC (T4aN2bM0) developed diplopia, syncope, and headache 4 months after undergoing a radical neck dissection.³⁸ The follow-up MRI revealed a sellar mass that was presumed to be a nonfunctioning pituitary adenoma, but histological examination revealed metastatic SCC.

TABLE 1. Incidence of BMs in patients with HNSCC

Authors & Year	Country	Study Years	Patients	No. in Sample	No. w/ BMs	Rate
Bulut et al., 2014	Germany	1992–2005	HNSCC patients w/ advanced, inoperable primary tumor	193	11	5.7%
de Bree et al., 2001	Netherlands	1982–1997	HNSCC w/ histopath Dx	5141	13	0.4%
Huang et al., 2012	Canada	2003–2009	OPSCC treated w/ radiotherapy	631	4	0.6%
Jaber et al., 2015	US	1979–2013	OPSCC; known HPV status	1058	4	0.4%
Trosman et al., 2015	US	1996–2013	Stage III/IV OPSCC; known HPV status	291	4	1.4%
Ghosh-Laskar et al., 2016	India	2005–2013	HNSCC w/ histopath Dx	63,738	17	0.03%

Histopath Dx = histopathological diagnosis.

Other reported presenting neurological symptoms included vertigo,¹⁶ unilateral weakness,¹ and hypologia in a patient with leptomeningeal metastasis from early glottic laryngeal cancer.⁵³ A second patient has been reported to have BMs and leptomeningeal disease in the absence of local recurrence or systemic metastases.⁵⁵ Some reported cases of HNSCC BMs do, however, occur without neurological symptoms and may only be seen during imaging staging of progressive systemic disease, as seen in a patient with a single, biopsy-confirmed, occipital BM.³⁴ These reported cases emphasize that clinical suspicion for BMs is warranted in patients who develop neurological symptoms and who have a history of HNSCC, regardless of time from initial diagnosis.

Genomics of HNSCC

Patients with HNSCC BMs routinely are ineligible to participate in clinical trials, and treatment options for these patients are not well established. Given the dismal prognosis of BM development, advances in treatment options are needed. To explore advances in treatment regimens for these patients through targeting of oncogenic driver mutations, genomic analysis of HNSCC BMs shows promise to better discern the tumor biology that promotes metastatic spread.

To better understand the genomic landscape of HNSCC, comprehensive genomic profiling of 279 primary HNSCCs revealed that HPV-associated tumors were strongly related to mutations in the *PIK3CA* oncogene, whereas smoking-related HNSCC harbored near-universal loss of *TP53* mutations and *CDKN2A* inactivation.⁴¹ This finding confirms divergent oncogenic drivers given HPV status in HNSCC.

Whole-exome sequencing combined with ultra-deep targeted sequencing in patients with OSCCs found that several cases exhibited distinct mutations only in the primary tumor that were not found in matched lymph node metastases.⁶² A second whole-exome sequencing study of tumors in 13 patients with HNSCC demonstrated that synchronous lymph node metastases were genetically more similar to paired primary tumors than to metachronous recurrent tumors.²⁷ Phylogenetic reconstruction of whole-genome sequencing of tissue obtained in a patient with HPV-positive OPSCC and cervical node metastasis revealed a high degree of intratumoral heterogeneity in the primary tumor.⁶⁸ Such findings highlight the importance of understanding clonal evolution and tumor heterogeneity in HNSCC oncogenesis, and suggest that histopathological and genomic analysis of a single tumor

biopsy could potentially miss the identification of a targetable pathway.

To better understand cisplatin resistance in HNSCC, various sequencing techniques were applied to cisplatin-resistant and cisplatin-sensitive HNSCC cell lines in a state-of-the-art study.⁵¹ The investigators determined that intratumoral heterogeneity and clonal evolution were indeed important mechanisms of resistance in HNSCC.

In an effort to target clinically actionable pathways in HNSCC, a Phase II clinical trial with the use of dacomitinib, an irreversible tyrosine kinase inhibitor of *EGFR*, *HER2*, and *HER4*, in recurrent and/or metastatic HNSCC, demonstrated clinical efficacy with manageable toxicity in patients in whom platinum therapy failed.³⁶ Patients with mutations in the PI3K pathway experienced shorter progression-free survival and overall survival. However, patients with symptomatic BMs were excluded from this trial.

Gene expression profiling in patients with known HPV and Epstein-Barr virus (EBV) status may aid with prognostication and risk stratification. In one study, high levels of *E6* gene expression predicted a 5-fold increase in risk of recurrence and distant metastases in patients with HPV-positive OPSCC.³⁵ In a cohort of 44 patients with sinonasal SCCs, 20 (45%) tumors were EBV positive. Only EBV-positive tumors developed lymph node or distant metastases.¹⁷

In a Phase III randomized trial of patients with recurrent or metastatic HNSCC, participants were treated with panitumumab, a fully human monoclonal antibody specific to *EGFR*, combined with cisplatin and fluorouracil.⁶⁵ Subgroup analysis revealed that overall survival in patients with p16-negative tumors was longer in the panitumumab group (11.7 months) than in the control group (8.6 months), but such a difference was not seen in patients with p16-positive tumors.

Recent genomic analysis of matched primary, normal tissue, and BMs from 86 patients revealed that 53% of cases had potentially clinically informative alterations in the BMs that were not detected in the matched primary-tumor sample.⁷ Although this work did not include patients whose primary tumor was from HNSCC, future work will explore genomic analysis in HNSCC BMs, especially because patients with BMs are routinely excluded from HNSCC clinical trials.

Immunotherapy in HNSCC BMs

Beyond the genomic characterization of HNSCC BMs,

improved characterization of immunotherapy response in HNSCC has led to an expanded treatment repertoire.²¹ Across many cancers, immune-checkpoint inhibitors enhance antitumor immunity and, in some cases, create durable clinical responses.⁵⁴ In a cohort of 305 primary OSCC specimens, tumors that held programmed cell death ligand-1 (PD-L1) immunoreactivity were more likely to develop distant metastasis.⁴³ A second study found that patients with HNSCC who had circulating tumor cells that overexpressed PD-L1 at the end of treatment had shorter progression-free and overall survival.⁶¹ Initial experience with pembrolizumab, a humanized programmed cell death protein-1 (PD-1) antibody, in patients with recurrent or metastatic SCC led to clinically meaningful response⁵⁷ and subsequent FDA approval.⁴⁰ Notably, a Phase II clinical trial exploring the use of pembrolizumab in patients with CNS metastases is currently underway (NCT02886585).

Conclusions

Brain metastases resulting from HNSCC are rare. The HPV-related SCC of the oral cavity and oropharynx has been demonstrated to have unique properties and a distinct pattern of metastasis. With their dismal prognosis, improved therapeutic options for these patients are needed. Although previous work has established differences in the genomic landscape between primary and nodal metastases, genomic analysis of tissue obtained in patients with BMs from HNSCC is warranted to identify clinically actionable mutations in these patients, who otherwise have limited treatment options.

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Disclosures

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Author Contributions

Conception and design: Barrett, Gill. Acquisition of data: Barrett, Gill. Analysis and interpretation of data: Barrett, Gill. Drafting the article: Barrett, Gill. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Barrett. Study supervision: Miles, Ilroeta, Bakst, Fowkes, Brastianos, Bederson, Shrivastava.

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