Tumorigenesis & Metastasis cont.

Taken together, an increase in DSCR1 via upregulation of VEGF also directly contributes to angiogenesis observed in HSCC (Lv et al, 2016).

In HNSCC, the complex microenvironment includes cancer-associated fibroblasts, endothelial cells, invading immune cells (i.e. T and B cells, natural killer cells, and dendritic cells), as well as proteins like collagen, elastin, and fibronectin (Bhat, 2021).

The altered stromal cells (which include the cancer-associated fibroblasts) are responsible for producing metabolites needed for tumor cells to boost their survival and metastatic potential (Bhat, 2021).

Additionally, inflammatory cells and tumor-promoting immune cells get recruited by altered stromal cells, which aids in generating therapy-resistant tumors (Bhat, 2021).

Treatment

The treatment of hypopharyngeal cancer depends on the stage (see heading "Diagnosis & Staging"), and can include surgery, chemotherapy, radiation therapy, or combination therapy (Mura et al, 2013).

Surgical resection of the tumor can be performed at any stage, and radiation treatment is commonly used when the cancer is detected in stage I ("Hypopharyngeal Cancer Treatment, 2021). Chemotherapy is introduced at stage II, with surgery and the treatments from stages I and II building upon each other when treating stage III or IV HNSCC ("Hypopharyngeal Cancer Treatment, 2021). Later stages also see the entrance into relevant clinical trials ("Hypopharyngeal Cancer Treatment, 2021).

These treatments are almost always performed in combination, especially if the cancer has metastasized and to reduce the chance of relapse ("Hypopharyngeal Cancer Treatment, 2021).

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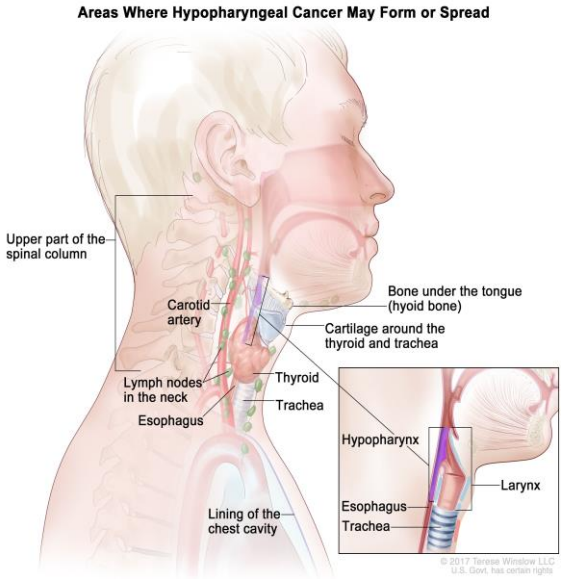

Anatomy of throat region where hypopharyngeal cancer can form. Hypopharynx shown in purple at bottom right. ("Hypopharyngeal Cancer Treatment (Adult) PDQ®", 2021)

Hypopharyngeal Cancer

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Introduction

Cancer of the hypopharynx (hypopharyngeal cancer) is a rare form of throat cancer, where 95% of cases are classified as squamous cell carcinoma (Mandal, n.d.).

Men aged 50 and older are 5x more likely to develop hypopharyngeal cancer than women of the same age ("Cancer Stat", n.d). In the United States for 2022, approximately 54,000 hypopharyngeal cancer cases are projected to be diagnosed, with an overall five-year survival rate ranging from 54% to 25% depending on metastasis level ("Cancer Stat", n.d.; "Survival Rates", 2022).

Hypopharyngeal cancer is usually caused by smoking tabacco and/or excessive alcohol consumption, with other risk factors including high body weight, constant exposure to certain substances (ex. wood dust) and less commonly, HPV infection ("Risk Factors", 2021; "What Causes", 2021).

Symptoms can include sore throat, ear discomfort, and/or a mass felt in the neck ("Hypopharyngeal Cancer", 2021; Mandal, n.d.)

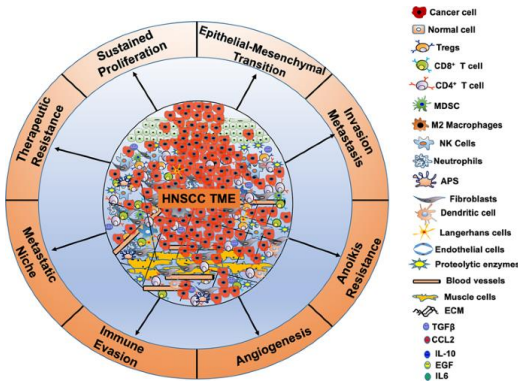


Diagram depicting head and neck squamous cell carcinoma tumor microenvironment, showing association of cell type(s) with various steps in tumorigenesis (Bhat et al, 2021)

Diagnosis & Staging

Diagnosis begins with a physical examination of the head and neck.

If hypopharyngeal cancer is suspected, a specialist will conduct a laryngoscopy and/or biopsy of the region ("Tests for", 2021).

Staging of hypopharyngeal cancer follows the American Joint Committee on Cancer **TNM criteria**:

- **Size of tumor (T)**
- **Spread to lymph nodes (N)**
- **Metastasis to other parts of body (M)**

Each of these criteria have further sub-criteria for more specific gauging of the disease. Hypopharyngeal cancer is also staged from 0 to IV, IV being most severe (Sanders & Pathak, 2022). Staging is often conducted via CT scan, MRI, or PET-CT (Mura et al, 2013).

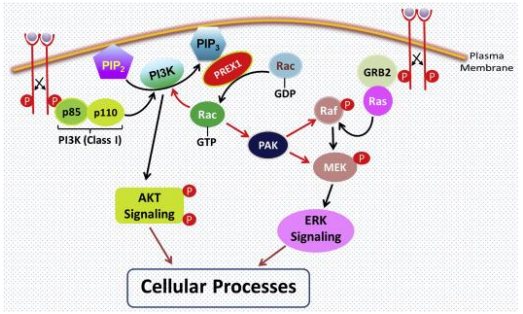
Genetic Abnormalities & Prognosis

Head and neck squamous cell carcinoma (HNSCC), which includes that of the hypopharynx, harbor many different genetic abnormalities including:

- Amplification of chromosomal 3q, 5p, 7p, 8q, 9q, 11q13 and 20q regions
- Deletions of chromosomal 3p, 5q, 8p, 9p, 13q, 18q, and 21q regions
  (Cromer et al, 2003)

Loss of heterozygosity (LOH) has been observed for the p53, E-cadherin, Rb, and p16 genes (Lee et al, 2011).

Hypopharyngeal cancer can be slow-growing or highly proliferative and dependent on many factors including physiology and etiology, making prognosis difficult to predict (Žumer et al, 2020). Proliferation can be measured via immunostaining, proliferating cell nuclear antigen expression, or DNA S-phase fraction (Pich et al, 2004).



Activation of the PI3K/AKT and MAPK/ERK pathways leads to a signaling cascade that promotes cell survival and proliferation as observed in hypopharyngeal cancer (Cao et al, 2019).

Tumorigenesis & Metastasis

Hypopharyngeal cancer can metastasize, typically to the lymph nodes first and then further to the lung, liver and bone (Li et al, 2019).

Commonly mutated genes observed in hypopharyngeal cancer include NOTCH1, CDKN2A, KMT2C, and genes within the RTK/ERK/PI3K pathway, which contribute to tumorigenesis (Machnicki et al, 2022).

Additionally, the promoter of the TERT gene, a subunit of the telomerase enzyme, is often found mutated and amplified in HNSCC, with overexpression of telomerase in HNSCC usually linked to poor prognosis (Boscolo-Rizzo et al, 2016).

Also, Down Syndrome critical region 1 (DSCR1) mRNA and protein (the latter responsible for binding to calcineurin catalytic A subunit) is often upregulated in hypopharyngeal squamous cell carcinoma (HSCC) (Lv et al, 2016).

DSCR1 is a common target of vascular endothelial growth factor (VEGF), and the upregulation of VEGF in HSCC leads to increased calcineurin activity, the latter involved in cell proliferation and survival (Lv et al, 2016).