Review Article

A Short Scientific Review of Oropharyngeal Squamous Cell Carcinoma

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Abstract

Oropharyngeal Squamous Cell Carcinoma (OPSCC) is the cancer of the squamous cell in the oropharynx. OPSCC accounts for nearly over 450,000 cases worldwide in 2023, and its incidence is one of the most rapidly increasing amongst all other cancers (1). OPSCC may be categorised based on its association with the Human Papillomavirus (HPV). When labelled as HPV-positive (HPV+) OPSCC, it indicates that the presence of the HPV is a key driver in the carcinogenesis of OPSCC. Conversely, HPV-negative (HPV-) OPSCC means that the carcinogenesis is not driven by the HPV. The majority of OPSCC cases are HPV+, with 70% of these being caused by the HPV16 strain (2). The remaining OPSCC cases are HPV- and often have worse prognoses than HPV+ cases (3). The disease has a moderate genetic susceptibility, and risk factors of OPSCC include race, gender, age, sexual health, alcohol and tobacco usage, as well as HPV vaccination status (4,5). The industry standard for imaging OPSCC is through computed tomography (CT), allowing for high-resolution images of the oropharynx, neck, and surrounding areas (6). Imaging, in conjunction with a biopsy, will confirm the presence of OPSCC, and a p16 immunohistochemistry test will confirm the HPV-positivity of the tumor (5). When OPSCC is diagnosed in early stages, it may only require a single modality for treatment (7).[7] However, OPSCC is often diagnosed in late stages due to its asymptomatic nature and consequently requires a multimodality approach to treatment (7). OPSCC treatment may involve a multifaceted approach, including Intensity-Modulated Radiation Therapy (IMRT) for targeted radiation, cisplatin-based chemotherapy, and surgical interventions (8–10). To determine the optimal dosage of IMRT, cell survival curves of OPSCC were constructed based on literature values.

Keywords: Head and Neck Cancer, HPV, Radiation Therapy, Computed Tomography, Cisplatin, Epidemiology

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Introduction

Oropharyngeal Cancer is a type of cancer that affects the back of the throat, including the base of the tonsils, soft palate, and tongue (11). Oropharyngeal Squamous Cell Carcinoma (OPSCC) is the most common type of oropharyngeal cancer, accounting for around 90% of cases, and was recorded to be the 8th most common cancer in men (12). OPSCC is a cancer that rises from the mucosal epithelium lining within the oropharynx and falls within the heading of head and neck squamous cell carcinoma (HNSCC) (11). Carcinogenesis of OPSCC can be divided into four stages utilizing the TNM staging system. T relates to the extent of the primary tumor, N indicates the involvement of regional lymph nodes, and M specifies the distant metastasis (11). However, the system itself has different substages depending on whether the patient is HPV+ or HPV-.

There are two types of OPSCCs that can be distinguished: HPV-associated, due to an oral human papillomavirus infection, and non-HPV-associated, mainly due to carcinogen abuse, such as alcohol and smoking (11). It was found that among the many types of HPV, HPV16 is the most oncogenic within oropharyngeal cancers (3). Whereas for non-HPV-associated oropharyngeal carcinomas, the major risk factors are associated with smoking tobacco and alcohol consumption (13). However, it is important to note that other, less significant risk factors are attributed to a diet low in vegetables and fruits, asbestos exposure, certain genetic mutations such as the TP53 mutation, and poor overall health (11).

If an OPSCC is HPV+, the TNM staging follows four stages (I, II, III, IV), with the primary tumor's invasion to surrounding tissue, including the lateral pterygoid muscle, lateral nasopharynx, and skull base increasing as the stage progresses (11). Additionally, metastasis to regional lymph nodes and the metastasis distance increase as the stage increases. Whereas if the OPSCC is HPV-, the stages are 0, I, II, III, IV-A, IV-B, and IV-C (11). The majority of the stages follow the same premise as the HPV+ TNM staging, however, stage 0 occurs when the tumor cannot be assessed, and the three sub-categories of stage IV exist based on the extranodal extension of the tumor. A diagram of a solely histological staging mechanism that looks into the inactivation of tumor suppressor genes, such as CDKN2A and TP53, for HPV+ OPSCC cells can be found in Figure 1 (11).

HPV+ OPSCC has a better prognosis than HPV- OPSCC, as the indication of HPV can immediately identify tumor suppressor genes and oncogenesis (14). As such, HPV- OPSCC has poor prognoses due to a lack of symptoms in the early stages of carcinogenesis (15).

This review addresses the critical research gap in understanding how the pathogenesis, diagnosis, and treatment responses of HPV-positive and HPV-negative OPSCC differ, with a focus on developing personalized treatment strategies and refining diagnostic protocols to enhance patient outcomes. More specifically, this review will investigate the diagnostic imaging technologies used to identify OPSCC, as well as two therapies that exist in the forms of radiotherapy and chemotherapy. An analysis of the radiotherapy, known as Intensity-Modulated Radiation Therapy (IMRT), will be made using mathematical modeling via cell survival curves and fractionated treatment plans. The mechanism of action of a common chemotherapeutic drug for OPSCC, cisplatin, will also be summarized.

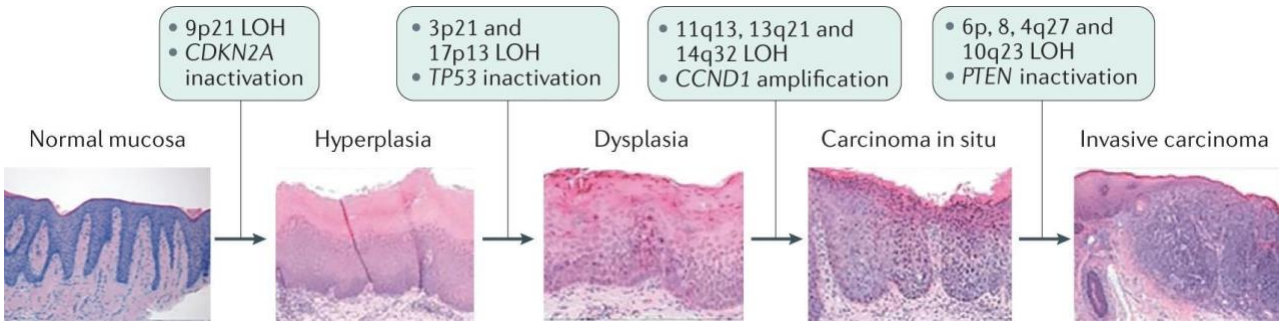

Figure 1. A model of histological progression of HNSCC, including OPSCC, via the inactivation of tumor suppressor genes (illustrated in green boxes) within HPV+ patients. Mucosal epithelial cell hyperplasia is followed by dysplasia, which is then followed by carcinoma in situ and finally develops into the invasive carcinoma. As carcinogenesis increases, oncogenic transformation to cancer cells increases (11).

Epidemiology and risk factors

In developed and high-income countries, the incidence of OPSCC is one of the most rapidly increasing amongst any other cancer (3). Before 1995, HPV+ OPSCC cases accounted for approximately 20.6% of cases worldwide and 21.6% of cases in North America (16). Only 20 years later, in 2015, HPV+ OPSCC accounted for approximately 50% of cases in Europe and 65% of cases in North America (16). The most recent data indicates that 85% of OPSCC cases in North America are HPV+ (12). The incidence of OPSCC is rapidly rising amongst younger individuals, while only 10% of cases are in individuals above 70 years of age (17). Furthermore, the median age of those diagnosed with HPV+ OPSCC is lower than HPV- OPSCC (18). Globally, OPSCC incidence is more common in men than in women, with this disparity due to the fact that a greater number of men carry the HPV than women. Approximately 78% of all OPSCC diagnoses in Canada between 2000 and 2012 were male. The greatest incidence of OPSCC is in middle-aged men that reside in developed or high-income countries, with 85% of these cases occurring in urbanized areas (17,19,20). As shown in Figure 2, the greatest incidence of HPV-associated OPSCC is in high-income countries. However, it should be noted that greater epidemiological data must be collected from lower and middle-income countries (3).

Traditionally HPV- OPSCC is associated with tobacco and alcohol use. Tobacco use, specifically through smoking, has been shown to increase the risk of OPSCC, regardless of HPV status (22). Tobacco smoke contains nicotine-derived nitrosamines, which upon contact with squamous cells in the oropharynx and oral cavity, have been shown to be carcinogenic *in vivo* (23). Additionally, some studies have shown that tobacco has a more significant impact than alcohol in the incidence of OPSCC (13). With this being said, alcohol consumption has been shown to increase the risk of HPV+ OPSCC recurrence by 21.6%, and can significantly hinder the efficacy of treatment (24).

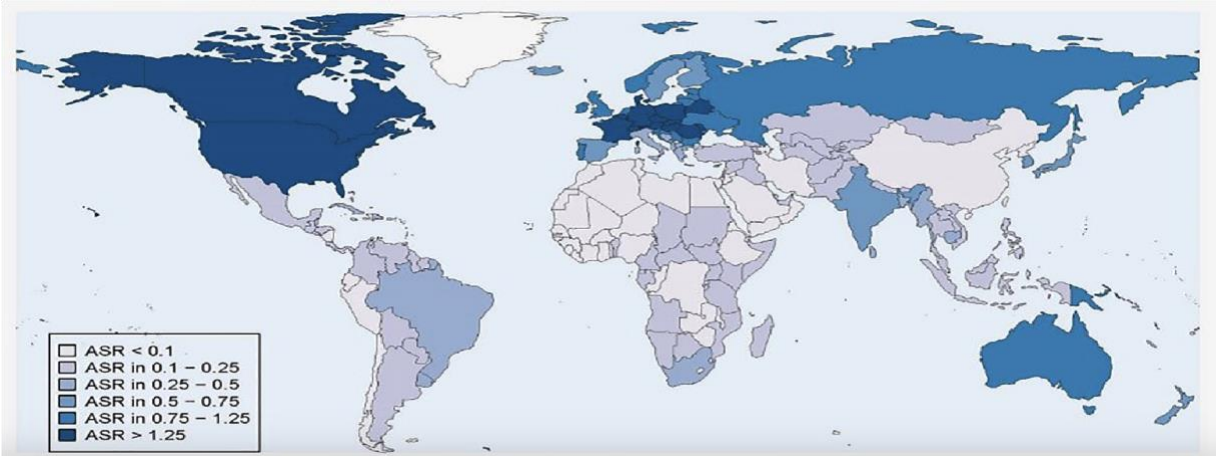

Figure 2. A map showing the age-standardized rate (ASR) of OPSCC worldwide. As shown in the map, countries with the greatest incidence of OPSCC are developed countries, such Canada, US, and Central Europe. Developing nations seem to be less affected by OPSCC; however, this may be due to a lack of data collection in these nations (21).

The risk factors of HPV+ OPSCC are similar to those of contracting HPV. That is, identifying as a cis-gendered male, being caucasian, being between 40 to 60 years of age, having multiple lifetime sex partners, young age of sexual initiation, as well as engaging in oro-genital and oro-anal sex (4). Furthermore, immunocompromised patients, sexual partners of women with cervical cancer, and patients with an HPV-related history are also at a greater risk of developing HPV+ OPSCC (5). As sexual activity is a prominent risk factor of HPV+ OPSCC, it is important to note that widespread use of the Gardasil 9 vaccine and comprehensive sexual health education continue to improve the outlook of OPSCC (25). Despite this, socioeconomic factors such as inequitable access to education and health care services may leave many communities at higher risk (25).

Disease presentation and staging

Depending on whether the OPSCC is either HPV+ or HPV-, symptoms may vary. Traditionally, the most common symptoms of OPSCC are a neck mass and a sore throat.[7]HPV- patients may present symptoms that are broader in nature, with their chief complaint being a pain in the general area of the head and neck (26). Once imaging is performed to confirm the diagnosis of the cancer, OPSCC is staged differently based on whether the tumor is HPV+ or HPV-. This is because the prognosis of HPV+ tumors is improved compared to the HPVtumors (3). To determine the HPV-positivity of an OPSCC, a p16 immunohistochemistry test is performed. Other tests, such as an mRNA-based polymerase chain reaction or an *in-situ* hybridization test, may also be performed, but the p16 test is the most widely used (5). Based on the HPV status of the tumor, the 8th edition of the American Joint Community on Cancer staging system will be used. This includes the usage of the TNM system, which will classify the size of

the primary tumor, regional lymph node involvement, and distant metastasis (27). The prognosis of OPSCC is heavily dependent on the stage of the tumor.

Most people that carry HPV are not aware that they are carrying the virus, as it is asymptomatic (28). Similarly, most patients are asymptomatic in stages I and II of HPV+ OPSCC where the tumor is small, usually less than 2-4 cm in diameter (7). Carcinomas that are stage I or II generally need single-modality therapy, while stage III or IV carcinomas need multimodality treatment (7). Additionally, the improved prognosis is correlated with the diagnosis of OPSCC at an earlier stage (29). Unfortunately, since most tumors remain asymptomatic until later stages (III or IV), more than 70% of HPV+ OPSCC are typically diagnosed at an advanced stage, compromising survival and increasing the need for multimodality treatments (7). Additionally, the prognosis depends on whether the tumor has spread to the lymph nodes, its margin status, and other lifestyle factors. Survival rates of patients with OPSCC vary depending on the HPV-positivity of the tumor. The 5-year survival rate (5SR) for Stage I and II HPV+ OPSCCs is 73.6%, while Stage III and IV is 67.5% (14). The 5SR for Stage I and II HPV- OPSCCs is 59.9%, while Stage III and IV is 29.25% (14). Tumor recurrence rates, distant metastasis rates as well as second primary malignancy rates all are greatest for late-stage HPV- OPSCCs and are the least for early-stage HPV+ tumors (14). The data makes it easy to extrapolate that survival rates are greatest when tumors are detected in their early stages. Given the asymptomatic nature of OPSCC, it is vital that regular screening which includes visual examinations and HPV p16 testing is performed every three years, particularly for high-risk groups to improve prognosis (30).

Genomics, genetic susceptibility, and prevention

OPSCC is classified as an HNSCC and is known to have moderate genetic susceptibility (2). Research into the specific genomics associated with both carcinogenic and infectious rationale for the development of OPSCC must be considered. Exposure to carcinogens, particularly those in tobacco and alcohol, play a key role in initiating head-and-neck carcinogenesis (31). However, even among those who consume alcohol and tobacco regularly, HNSCCs will develop only in a small proportion. This suggests that an individual's genetically predisposed ability to deal with carcinogens most likely determines who develops the cancer (13).

Aside from carcinogenic risk factors, research indicates that HPV16, a highly oncogenic strain of the HPV, is responsible for approximately 90-97% of all HPV+ OPSCC cases (32). Studies determining an association of genetic variants of transforming growth factor-β1 (TGF-β1) with the development of HPV16-related oropharyngeal cancer have recently surfaced (31). TGF-β1 is crucial in the inflammation and immunological responses that govern HPV16 clearance and its escape from immune surveillance. Those carrying a TGF-β1variant genotype were more than twice as likely to have HPV16-positive (HPV16+) oropharyngeal tumors versus those without the variants (31).

On an individual level, OPSCC prevention must consider exposure to known carcinogens (namely alcohol and tobacco) as well as HPV16+ oropharynx infection. Firstly, reduced

exposure to carcinogens by limiting alcohol and tobacco consumption can lower the likelihood of developing OPSCC (24). Although drinking and smoking are separate risk factors, they have a synergistic impact and dramatically increase risk when combined; thus, they must be controlled simultaneously (24). As such, treating addictions related to carcinogenic substance abuse in patients can decrease OPSCC development (24,33). Secondly, HPV-related prevention methods differ according to the presence of HPV16. HPV is primarily transmitted through oral sexual interaction, and thus, the primary prevention method of HPV16 involves preventing HPV transmission via the usage of oral-sex protection or by HPV vaccination (34).

Method of detection: computed tomography (CT) scans

As part of the routine work-up when diagnosing OPSCC, imaging studies are performed. Given the complex nature and location of the cancer, interpreting the results of these imaging studies is often difficult. Currently, a wide variety of techniques are used: dental radiographs, panoramic radiographs, magnetic resonance imaging (MRI) with diffusion-weighted dynamic sequences, computed tomography (CT), single-photon emission computed tomography (SPECT), positron emission tomography (PET), and ultrasound (35). Also, hybrid methods can be used, combining multiple imaging modalities such as PET-CT, PET-MRI, and SPECT-CT (36,37). Currently, CT is the industry standard for detecting primary OPSCC tumors and their local bone infiltration (6). These scans are also performed with contrast enhancement to provide better image quality (38). A CT machine is a complex imaging device with multiple components, as shown in Figure 3. The large scanning unit, known as the gantry, can tilt up to 25 degrees. This part of the machine contains the X-ray tube, shielding elements, and photon detectors, and can rotate 360 degrees around the patient (39).

To create CT images, a current is run through the X-ray tube, which consists of an anode and cathode, usually made of tungsten (41). The cathode will supply the electrons while the anode provides the target. The potential difference across the cathode and anode is known as the voltage, which determines the energy levels of the generated X-ray photons (41). A high voltage current is defined as having a potential difference of 20-150kV, while a low voltage current is defined as having a potential difference of approximately 10kV (39). Thermionic emission is the process by which electrons are precisely controlled as they are expelled by the cathode (39). Understanding thermionic emission is vital since the process by which electrons are bombarded in the X-ray tube to produce X-ray photons is highly inefficient; 1% of the input energy is converted to X-ray photons, and 99% is lost as heat (41). These photons are then filtered and collimated. These processes reduce unnecessary radiation by reducing scattered rays of photons and improve image quality by reducing the artifacts produced in the image (39,41). Next, the photons are directed through the patient from different angles, producing a cohesive set of images (39). The photons pass through the patient and strike the detector array at different energy intensities. This is because of the degree of X-ray absorption, also known as attenuation, of anatomical structures differs within the body (39). The detector array then converts the X-ray

photons to visual light photons, and finally to an electrical signal which is sent to a computer (41). The computer uses reconstruction algorithms to generate detailed images of the patient.

The X-ray attenuation is semi-quantitatively measured using Hounsfield scale units (39,41). In an image produced by a CT scan, the pixel brightness is proportional to the density of the tissue (39). Air appears as black, fat is dark grey, soft tissue is light grey, and bone, calcium, and contrast agents all appear as white (42). CT imaging often harnesses a contrast medium, allowing for improved definition of vascular structures, organ perfusion, and neoplastic lesion detection (43). Contrast media is administered intravenously and can differ based on the patient's kidney function. Typically for OPSCC, Omnipaque 300 iodine is used (43). Different methods are used when displaying primary OPSCC extent through CT imaging. Parameters such as tumor thickness and surrounding tissue invasion are used to diagnose and stage OPSCC (44). A significant benefit of CT imaging is its rapid acquisition time as well as its ability to provide an excellent assessment of the infrahyoid region of the neck while minimising patient movement.

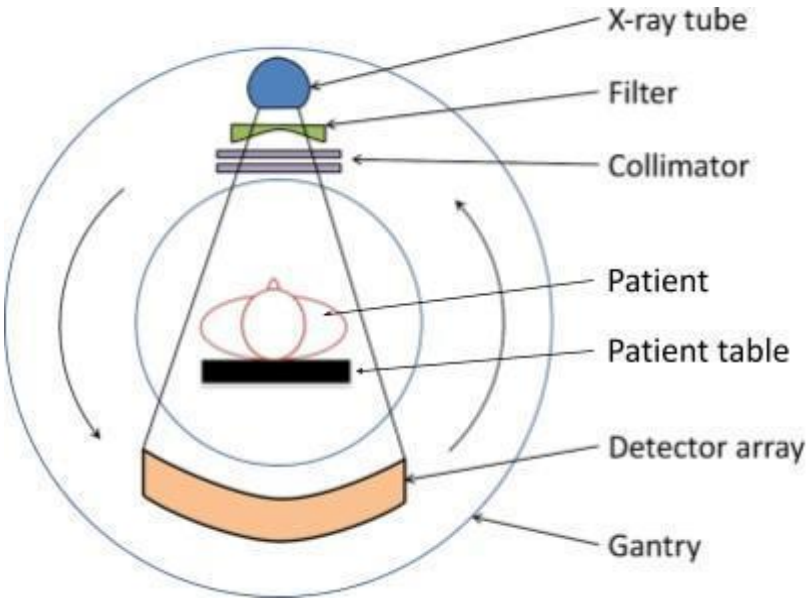

Figure 3. A cross-section of a CT machine, with the major components identified. Image is Adapted (40).

Therapeutic approaches

The two primary therapeutic approaches for treating OPSCC include IMRT and chemotherapy using cisplatin. IMRT, a form of external beam radiation therapy, targets the tumor with high precision, minimizing damage to surrounding healthy tissue. This technique employs a computer-controlled device that shapes the radiation dose to the 3D geometry of the tumor, allowing for a focused attack on malignant cells. Additionally, the IMRT approach uses variable

radiation intensity across numerous beamlets to further refine treatment, thus enhancing survival rates of surrounding healthy cells, especially in the parotid glands.

In advanced stages of OPSCC, cisplatin, a platinum-based chemotherapeutic agent, is used. Administered intravenously, cisplatin enters cells through passive diffusion or with the help of membrane transporters. Its mode of action includes forming cross links within DNA strands, obstructing DNA replication and transcription, and inducing apoptosis within cancerous cells.

Both IMRT and cisplatin play crucial roles in OPSCC treatment, with IMRT offering targeted radiation therapy to maximise tumour cell death while sparing normal tissue, and cisplatin providing a systemic approach to inhibit cancer cell proliferation. Together, these methods form a comprehensive treatment strategy, addressing OPSCC with both localised and systemic therapies to improve patient outcomes.

Treatment via Intensity-Modulated Radiation Therapy (IMRT)

Radiation is a physical agent used to kill cancer cells. The radiation, known as ionizing radiation, produces ions (electrically charged particles) and deposits energy in the cells of the tissues that it passes through (45). This deposited energy, in the form of high-energy radiation, destroys cells' genetic material (DNA), preventing them from dividing and proliferating further (45). Although radiation impacts both normal and cancerous cells, the objective of radiation therapy is to optimize the dose to cancer cells while reducing the exposure to normal cells situated near or within the radiation path. Traditionally, this is achieved by targeting areas where cancer cells proliferate more rapidly and are therefore more susceptible to DNA damage, allowing for quicker elimination compared to normal cells. Nonetheless, there are techniques like External Beam Radiation Therapy (EBRT) that enable precise radiation delivery to specific regions heavily affected by tumor oncology. EBRT has typically treated all tumors classified under the HNSCC heading (including OPSCC) (46). EBRT is a type of radiation therapy that directs a beam of radiation from outside the body, toward cancerous tissues inside the body, and has various forms. The most typically used EBRT for OPSCC radiotherapy is Intensity-Modulated Radiation Therapy (IMRT), where a computer-controlled device delivers the radiation to mimic the 3D geometrical shape of the tumor precisely. This lowers the radiation exposure to surrounding healthy cells (8). The intensity of radiation beams in fractioned, independent beams can be modulated over the treatment area to reduce radiation exposure to neighbouring healthy cells while retaining the required radiation for malignant cell targeting.

IMRT utilizes variable radiation intensity across 25 fixed beams, with each beam being subdivided into hundreds of beamlets, each with an individual intensity level (47). This enables a very complex, yet precise pattern to be fabricated around the tumor to avoid as much surrounding healthy tissue as possible. This localized radiation exposure results in DNA backbone or base damage. When coupled with the fact that cancerous cells have comparatively poor repair mechanisms to healthy cells, it can impair cellular replication and lead to cell death in oncogenic cells (48). The efficiency and precision of IMRT have been found to increase the 5-

year survival rates of patients suffering from several HNSCCs, including OPSCC, from 68% without treatment to 97.3% with IMRT treatment (49).

To better understand the required dosages and radiotherapy requirements, OPSCC staging must be considered (11). Typically, stages 0-II are best treated using surgery, with stages III-IV treatments strictly following IMRT radiotherapy due to potential weakness from the patient due to OPSCC symptoms, rendering them unable to undergo surgery. However, IMRT can be used in patients with stage 0-II OPSCC should any alternate health concerns prevent surgery; thus, IMRT offers treatment for all OPSCC stages and must be considered for treatment (27).

During IMRT, the patient lies on a treatment table while a device known as a linear accelerator delivers the radiation beams from various angles (50). Typical treatments utilizing IMRT involve a 7-field plan that delivers 70 Gy to the primary tumor using a simultaneous integrated boost technique (SIB) (51). The SIB-IMRT technique allows for the simultaneous delivery of different dose levels to different target volumes with a single treatment fraction. SIB is highly optimized for several HNSCCs, shortening the overall treatment time while increasing fraction dosage volume. The 7-field plan occurs over the course of 7 weeks with 70 Gray (Gy) to the primary tumor via 35 fractionations (2 Gy per fractionation, approximately once daily) (51). Fractionation refers to the division of the total radiation dose into smaller, repeated doses administered over a period of time, which is crucial as it allows normal tissues to repair themselves, reducing potential damage while effectively targeting cancer cells. IMRT avoids the delivery of excessive doses to the parotid glands, and thus, preserves parotid function and the quality of life of patients (50). The preservation of parotid function is crucial as it maintains the patient's ability to produce saliva, which is vital for speech, digestion, and overall oral health. Compared to other common OPSCC radiotherapy methods, such as three-dimensional conformal radiotherapy (3D-CRT), studies have shown that the mean doses delivered to the contralateral and ipsilateral parotid glands are vastly decreased using IMRT. The mean dose to the contralateral parotid gland was 49.8 Gy and 28.8 Gy in the 3D-CRT and IMRT radiotherapies, respectively (52). Similarly, the mean dose to the ipsilateral parotid gland using IMRT was also consistently and significantly lesser at 39.8 Gy compared to 56.2 Gy with 3D-CRT (52). Thus, IMRT is a safer and effective radiotherapy treatment method for OPSCC versus other OPSCC radiotherapy methodologies.

IMRT Dosage Impact Analysis for OPSCC Management

To evaluate the efficacy of IMRT as a treatment for OPSCC, the effects of IMRT on normal, healthy tissue and OPSCC tissue must be examined. The premise of radiation therapy is to use the fact that tumors grow faster than normal cells, and after using radiation to damage DNA to the point where a cell cannot multiply or divide, tumor cells should be damaged first (48). However, an optimal dosage exists at which healthy cells undergo less cell death due to radiation, while the same radiation causes greater cell death in OPSCC cells (53). This point is important because if dosage exceeds past this threshold, the healthy cells will eventually be

destroyed faster than cancerous cells (known as the equal survival ratio) (54). To find the optimal dosage point and the equal survival ratio, a linear-quadratic model may be used to determine how many surviving fractions of cells exist after a given dose, measured in Gray (Gy). The linear-quadratic model uses coefficients α (alpha) and β (beta) to describe the radiation dose effects on tissue, where α represents damage from a single radiation event (linear relationship), and β represents damage from multiple events (quadratic relationship). The α/β ratio helps differentiate the radiosensitivity of cancerous versus healthy cells, guiding optimal radiation dosing to target tumors effectively while sparing normal tissue. Cancerous OPSCC cells have been found to have an α/β ratio of 10 Gy, whereas late-responding healthy cells have been found to have an α/β ratio of 3 Gy.

Figure 4 plots both the OPSCC cells and late-responding healthy cells on a cell survival curve and on a fractionation plot, demonstrating the effect of varying doses of radiation on the survival rates of cancerous and healthy cells. The figure also demonstrates the effect of utilizing the optimal dosage (D=2) over the course of the 70 Gy treatment plan (51). The optimal dosage was found by observing the maximum separation between healthy and OPSCC cell curves prior to the equal surviving ratio point, which was found to be at 2 Gy. The equal surviving ratio point, being the point-of-intersection of both curves, was found at 4 Gy, representing the threshold where healthy cells remain less damaged than OPSCC cells, as, after this point, healthy cells begin to die faster. The fractionation plot models the aforementioned treatment plan of 70 Gy over 35 fractionations using the ideal dosage of 2 Gy per fractionation and its effect on cell survival (51). When comparing both plots in Figure 5, it can be seen that the fractionation method results in greater cell death for cancerous cells than healthy cells, and is thus preferred over a singular 70 Gy dosage.

Assuming the tumor initially begins with 10^8 cells, it was found that 18 fractions would be needed to reduce the tumor to less than one cell, whereas it would require 21 fractions to reduce the equivalent number of healthy late-responding cells to less than one cell (55). This is different from the aforementioned 35 fractionation number as tumors have a varying number of initial cells, however, the decreased fractionation amount for cancer cells illustrates that healthy cells will be preserved. Thus, the fractionated treatment plan involving 70 Gy over 7 weeks with 35 fractionations at a 2 Gy dosage optimizes healthy cell preservation while maximizing OPSCC cell death (51).

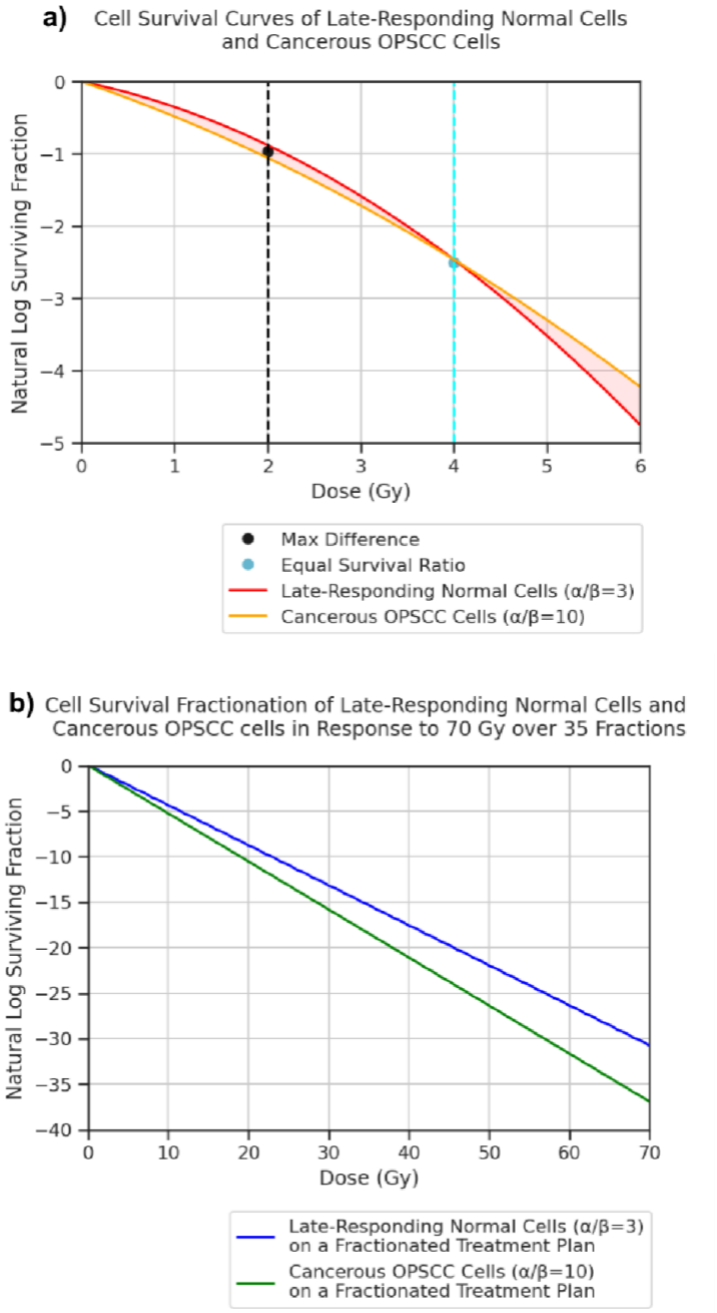

Figure 4. (A) The cell survival curves of late-responding normal cells (red) and cancerous OPSCC cells (orange) over the course of 6 Gy. The black dotted line stems from the maximum difference point, representing the optimal fractionation dosage (D=2). The cyan dotted line stems from the point where healthy cells begin to become more affected than OPSCC cells (equal survival ratio), found at the intersection of both survival curves (D=4). (B) The cell survival fractionation plot of late-responding normal cells (blue) and OPSCC cells (green) utilizing the aforementioned optimal dosage (2 Gy) over the course of 35 fractionations (totaling 70 Gy). The initial number of cells is 10E+8 for both types of cells. Created in Python 3.

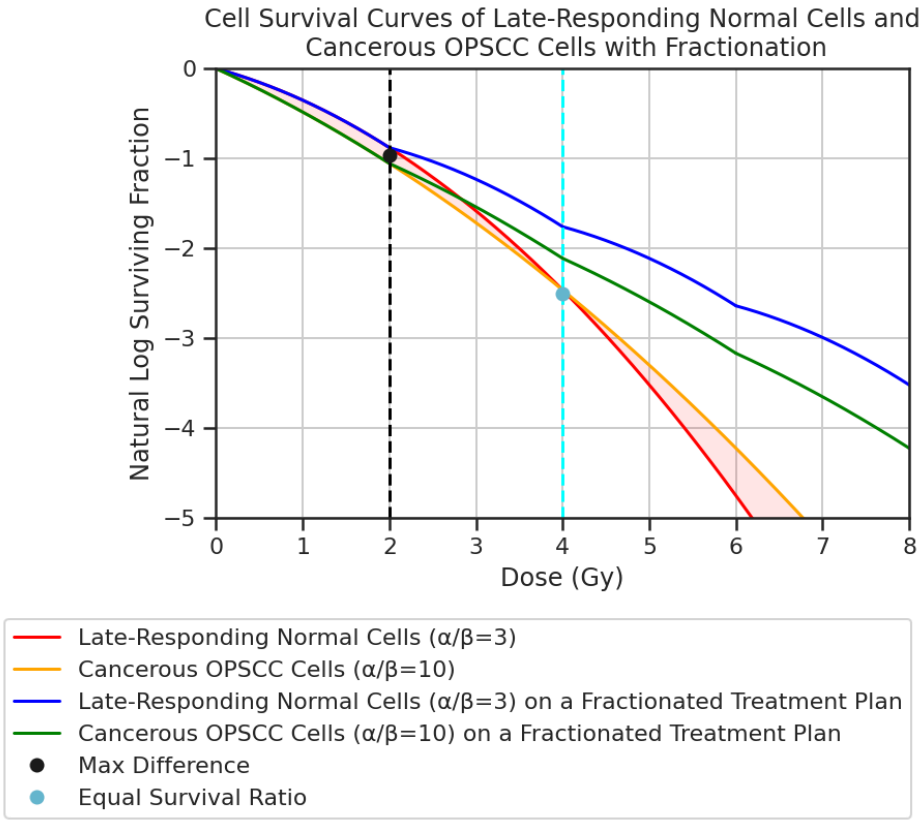

Figure 5. Combined graph containing cell survival curves and fractionation plots over the course of 4 fractionations (8 Gy) for comparison purposes. Prior to the optimal dosage point, the fractionation plots and cell survival curves match. After the ideal dosage (D=2), the fractionation plot does not decrease as rapidly as the cell survival curve plot. Additionally after the equal survival ratio (D=4), healthy cells start to die more quickly than OPSCC cells in the cell survival curve. Therefore, after the equal survival ratio, healthy cells are more negatively impacted when using a single dose, and OPSCC cells are more negatively impacted when using a fractionated dosage model. Created in Python 3.

Chemotherapeutic treatment via Cisplatin

Given that the majority of OPSCCs are diagnosed in later stages, multimodality treatment plans are required (7). In addition to surgery and radiation, chemotherapeutic agents are used to treat OPSCC. *Cis*-diamminedichloroplatinum (II), also known as cisplatin, is the most commonly used chemotherapy drug for OPSCCs (9,10). It is a whitish-yellow powder whose chemical structure is shown in Figure 6 (56). Cisplatin is typically administered intravenously or intra-arterially as a solution once per week over the course of 6-8 hours, every two to four weeks (57). However, recent advancements are being conducted investigating the viability of cisplatin being administered through inhalation, but further research must be conducted to test its efficacy in

treating OPSCC (58). Dosage and treatment plans for intravenous cisplatin depend on the stage of the OPSCC (9,59,60).

The mode of action of most platinum-based chemotherapeutic agents is quite similar. These drugs tend to induce cell death by entering the cell and ultimately damaging DNA, inhibiting its replication and synthesis (Figure 6). The molecular mechanism of cisplatin uptake into squamous cells of the oropharynx is generally through passive diffusion, as the drug is small and has no net charge (61). Additionally, there is evidence that suggests facilitated transporters, such as the copper membrane transporter (CTR1), are also involved in the uptake of cisplatin (61). Once cisplatin enters the cell, it undergoes hydrolysis, where water molecules replace the chlorine atoms to form an activated electrophile (62). The cisplatin is now able to bind to nucleophiles, including the sulfhydryl groups on proteins and the nitrogen donor groups on deoxyribonucleic acids (56). Damage to the cell's DNA occurs once the platinum atom of cisplatin covalently binds to the N7 reactive centre on purine residues, forming intrastrand crosslinks, specifically 1,2-intrastrand crosslinks (56,63). The crosslinks are the cytotoxic mechanism of cisplatin as they inhibit the unzipping of DNA for mRNA transcription. The cisplatin-DNA adducts trigger replication arrest, transcription inhibition and cell-cycle arrest, which through a cascade of effects ultimately leads to cell death and apoptosis (63,64). Non-genomic effects of cisplatin include altering mitochondrial function by producing reactive oxygen species which activate apoptosis pathways (65). Additionally, cisplatin inhibits calcium signaling pathways and the function of various protein kinase families (56,65). It is also important to note that DNA, especially in OPSCC cells, may also be resistant to cisplatin, which means DNA is still able to replicate despite the covalently bonded platinum to the DNA (66). Although the exact mechanisms through which cells develop cisplatin resistance are not fully understood, it is believed to be multi-factorial, with various genetic and epigenetic factors being involved (67). These factors include lower intracellular cisplatin concentration due to decreased function of transporter proteins such as CTR1, the activation of DNA repair pathways that removes the bonds formed between platinum and DNA, as well as the inactivation of the TP53 gene, which inactivates apoptosis pathways (67).

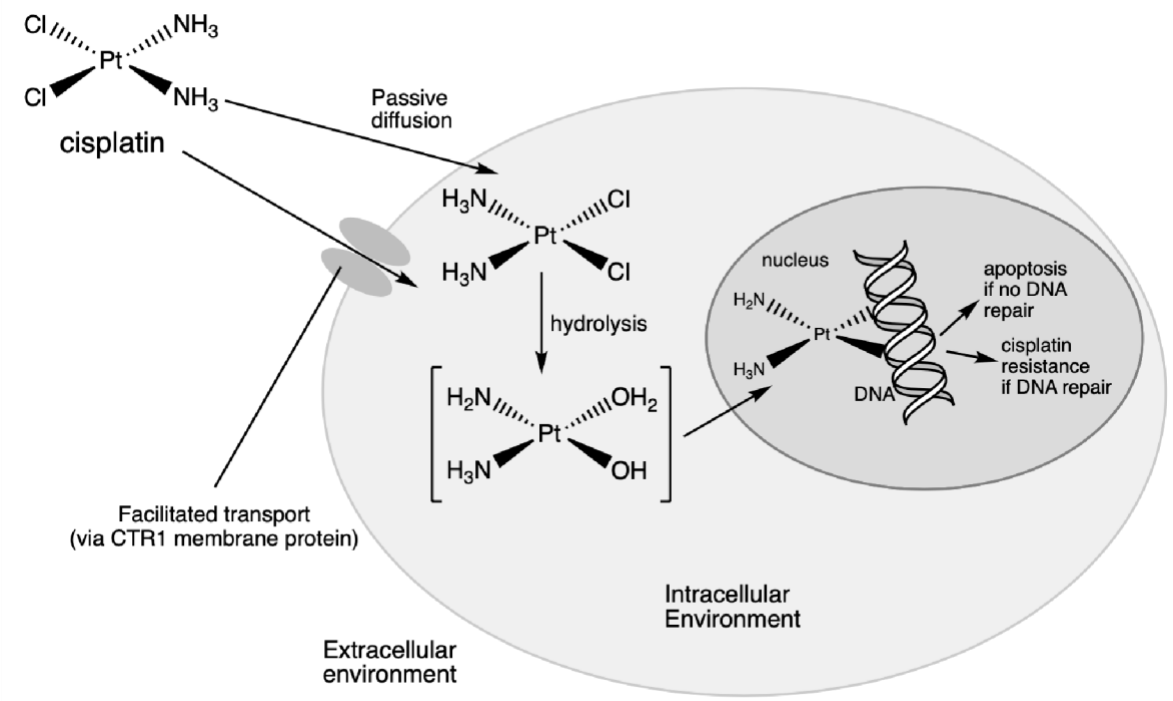

Figure 6. The chemical structure of cisplatin and its molecular mechanism in an oropharyngeal squamous carcinoma cell. Cisplatin enters the cell through passive diffusion or through facilitated transport, potentially via a CTR1 membrane protein. The drug is subsequently hydrolyzed and activated, allowing it to bind to DNA. The newly formed adduct can inhibit DNA replication and lead to cell death. Otherwise, if the DNA is repaired, the OPSCC cell may continue to proliferate, contributing to cisplatin resistance. The figure was made using ChemDraw and was modified from the original source (66).

Conclusion

Improvements in the outcomes of patients with OPSCC are due to significant advancements in biotechnology, drug development, radiotherapy, and molecular characterization of human cancers (11). Nevertheless, it remains a complex disease whose incidence is rising in developed countries worldwide (3). A deeper understanding of the epidemiology of OPSCC and the genetic susceptibility patterns of various demographics to both the cancer and HPV infection could provide valuable insights into anticipated trends in disease incidence (16,29,68). As with most cancers, OPSCC proliferation can increase the severity of the disease, highlighting the need for an imaging mode that is efficient and clear. CT scanning of the oropharynx and surrounding head and neck tissue can quickly provide physicians with both two-dimensional and three-dimensional images required to make a diagnosis and formulate a treatment plan (69,70). Given the asymptomatic nature of OPSCC, most cases are diagnosed in late stages often requiring multimodality treatment courses (7). This may entail a combination of surgery, chemotherapy, and radiation (7). Cisplatin is the most commonly used chemotherapeutic agent, and its mode of

action is through binding with DNA, inhibiting its ability to replicate whereas IMRT destroys the tumor cell's genetic material (45,56). Through the construction of cell-survival curves, scientists can optimize radiation doses and formulate effective treatments unique to each stage of OPSCC.

Improving the outcomes for patients with OPSCC begins with prevention and early detection (3,71). Prevention of the disease by altering lifestyle risk factors as well as increasing HPV vaccination will largely reduce OPSCC incidence (25). Given the significant impact that socioeconomic factors can have on the outcomes of HPV+ OPSCC, continued efforts to raise awareness about risk factors and the importance of regular screening are essential (72). As new advancements such as immunotherapy and innovative drug delivery methods are developed, there are promising outcomes for OPSCC patients (73,74). With this being said, greater research into their pharmacokinetics and pharmacodynamics needs to be performed to evaluate their effectiveness and potential side effects (73,75). Overall, this review highlights the multidisciplinary approach to the causes, implications, and responses to OPSCC (11).

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Appendix

Our literature search methodology for this manuscript was comprehensive and systematic, involving the use of established academic databases such as PubMed, Google Scholar, and Omni libraries accessed through McMaster University. We employed Medical Subject Headings (MeSH) terms to refine and focus our searches, ensuring relevance and accuracy in our selection of sources. This approach allowed us to comprehensively review and include pertinent studies and publications in our research. For the construction and analysis of the cell survival curves, Python programming was utilized. This programming approach enabled precise modelling and simulation of the data, providing us with robust and reliable results. Our methodology ensured that our research was grounded in the latest and most relevant academic literature, while also incorporating advanced computational techniques for data analysis.