NASOPHARYNGEAL CARCINOMA: UNDERSTANDING ANATOMY AND RADIOTHERAPY SIDE EFFECTS

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Abstract

Nasopharyngeal carcinoma (NPC) is a rare squamous cell carcinoma with a global incidence rate of less than 1 per 100,000 individuals per year, predominantly found in Asia, particularly China, India, Vietnam, and Malaysia. In Indonesia, NPC ranks fourth among tumors, with 15,000 new cases annually, imposing a significant burden. Radiation therapy, particularly intensity-modulated radiotherapy (IMRT), is the primary treatment for NPC, offering improved precision in radiation distribution and better tumor control. International consensus guidelines aid in standardizing target delineation and guiding dose priorities. However, radiation therapy can lead to side effects, including mucositis, hyposalivation, taste changes, dysphagia, and dysphonia. Late-emerging side effects, often permanent, require special attention, affecting quality of life and primarily observed within three years after treatment.

Keywords: Nasopharyngeal carcinoma (NPC), Squamous cell carcinoma, Radiation therapy

Introduction

Nasopharyngeal carcinoma (NPC) is a squamous cell carcinoma that occurs on the surface of the nasopharyngeal mucosa. Generally, the global incidence rate is less than 1 per 100,000 individuals per year. More than 80% of NPC patients are in Asia, with 71% of new NPC cases recorded in East and Southeast Asia. The highest number of NPC cases is seen in five countries, including China, India, Vietnam, and Malaysia. In Indonesia, NPC is the fourth most common tumor after cervical, breast, and skin cancer, and the most prevalent malignancy in the head and neck region, posing a significant burden with 15,000 new cases annually. (1)

Radiation therapy is the primary treatment modality for NPC. With the emergence of intensity-modulated radiotherapy (IMRT) and advancements in various imaging modalities, the precision in radiation distribution has significantly improved in recent decades, resulting in more favorable tumor control and toxicity outcomes in cohort studies. International consensus guidelines have also been developed to standardize target delineation and guide dose priorities for NPC radiotherapy.(2)

Radiation therapy is associated with side effects that theoretically affect all patients. These side effects occur due to radiation exposure to the epithelium, supportive tissues, and blood vessels. Examples of these side effects include mucositis, hyposalivation, taste changes, dysphagia, and dysphonia. Late-emerging radiation-induced side effects require special attention as the resulting damage is often permanent, particularly in slowly dividing cells. Most of these side effects occur within three years after treatment and impact the patients' quality of life. (2,4,5)

Nasopharyngeal Anatomy

The nasopharynx, positioned between the base of the skull and the soft palate, is an integral segment of the pharynx. It serves as a crucial conduit connecting the nasal cavity to the oropharynx, facilitating the passage of air and fluids. Within the nasopharynx, notable structures include the opening of the Eustachian tube, which plays a key role in equalizing pressure between the middle ear and the environment, as well as the adenoid gland, a lymphoid tissue that helps in immune defense.

In terms of blood supply, the nasopharynx receives nourishment from branches originating from two major arteries: the internal carotid artery and the facial artery. These arterial branches deliver oxygenated blood, ensuring the vitality of the nasopharyngeal tissues. On the other hand, venous drainage from the nasopharynx occurs through the parapharyngeal venous plexus. This intricate network of veins helps transport deoxygenated blood away from the nasopharynx, facilitating its return to the cardiovascular system.

Understanding the anatomical and vascular aspects of the nasopharynx provides valuable insights into its functionality and overall role in the respiratory and immune systems. The presence of the Eustachian tube opening and the adenoid gland highlights the importance of this region in maintaining middle ear pressure and immune response, respectively. Additionally, comprehending the blood supply and venous drainage pathways helps us appreciate the intricate vascular network supporting the nasopharynx and its physiological processes.

In summary, the nasopharynx serves as a vital link between the nasal cavity and oropharynx, housing important structures like the Eustachian tube opening and the adenoid gland. It receives blood supply from branches of the internal carotid artery and the facial artery, while venous drainage occurs through the parapharyngeal venous plexus. This knowledge enhances our understanding of the nasopharynx's anatomical features and its role in respiration, immune function, and overall well-being. Lymphatic drainage is important in nasopharyngeal carcinoma and involves retropharyngeal and jugular nodes. Sensory innervation is provided by the trigeminal and glossopharyngeal nerves, and motor supply comes from the vagus and trigeminal nerves. The nasopharynx is closely linked to various muscles that play significant roles in essential functions such as swallowing and Eustachian tube function. Among the key muscles associated with the nasopharynx are the tensor veli palatini, levator veli palatini, and salpingopharyngeus.

The tensor veli palatini muscle is responsible for maintaining the tension and position of the soft palate (velum), which separates the nasopharynx from the oropharynx. This muscle plays a crucial role in the swallowing process by

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elevating and tensing the soft palate, thus preventing food and liquids from entering the nasopharynx during swallowing.

The levator veli palatini muscle, located above the tensor veli palatini, contributes to the elevation of the soft palate during swallowing and speaking. It works in conjunction with other muscles to close off the nasopharynx and prevent air and substances from entering it when not intended, aiding in speech and preventing regurgitation.

The salpingopharyngeus muscle, positioned alongside the lateral walls of the nasopharynx, assists in the opening and closing of the Eustachian tube. This muscle's contraction and relaxation help regulate the equalization of pressure between the middle ear and the nasopharynx, which is crucial for maintaining optimal hearing and preventing discomfort or damage to the ear.

Collectively, these muscles associated with the nasopharynx contribute to the coordination and control of vital functions such as swallowing, speech, and Eustachian tube function. Their synchronized actions help ensure the proper passage of air, food, and fluids through the nasopharynx, while also safeguarding the integrity of the middle ear and supporting auditory well-being. Understanding the roles and interactions of these muscles enhances our comprehension of the complex mechanisms at play in the nasopharynx and its integral involvement in various physiological processes.(6,7)

Nasopharyngeal Carcinoma

Nasopharyngeal carcinoma (NPC), formerly referred to as lymphoepithelioma, is a type of cancer characterized by the presence of undifferentiated squamous cells that originate from the epithelial lining of the nasopharynx.

NPC is a distinct form of carcinoma that specifically arises in the nasopharyngeal region, which is located at the upper part of the throat behind the nasal cavity. The cancer cells in NPC display an undifferentiated nature, meaning they lack the normal specialization and organization of healthy cells. This undifferentiated state is characteristic of squamous cell carcinomas, which are a type of malignancy originating from the squamous epithelium.

The nasopharyngeal epithelium, the tissue lining the nasopharynx, is the site of origin for NPC. This type of carcinoma typically arises within this specialized epithelial tissue, which is vulnerable to the development of abnormal cells and subsequent tumor formation. The exact causes of NPC are still being studied, but several factors such as genetic predisposition, viral infections (particularly Epstein-Barr virus), and environmental exposures are believed to play a role in its development.

By identifying NPC as an undifferentiated squamous cell carcinoma originating from the nasopharyngeal epithelium, healthcare professionals and researchers gain a deeper understanding of the disease's characteristics and can develop targeted diagnostic and treatment approaches. Improved knowledge about NPC can help in the early detection and management of this type of cancer, potentially leading to better outcomes for affected individuals. It is the most common malignancy occurring in the nasopharynx. Endemic in certain parts of Asia and Africa but found worldwide, NPC shows varying incidence rates, ranging from high in southern China (25 to 50 cases per 100,000) to low rates in European populations (1 case per 100,000). This neoplasm can arise from any site within the nasopharynx, commonly seen in the lateral wall, specifically the Rosenmüller's fossa. One frequently mentioned etiological factor for NPC is the consumption of salted fish, possibly linked to the presence of the carcinogenic compound nitrosamine in such fish. Findings from a case-control study have indicated a significant threefold rise in the risk of nasopharyngeal carcinoma (NPC) among individuals who consumed salted fish on a weekly basis before the age of 10. Notably, this increased risk appears to be more pronounced when salted fish consumption occurred during childhood rather than in adulthood. These findings shed light on the potential impact of dietary habits during early life stages on the development of NPC.

In addition to dietary factors, the Epstein-Barr virus (EBV) is widely recognized as having an oncogenic role in the development of NPC. It has been observed that EBV genomes are frequently detected in biopsy specimens of NPC, further supporting the association between EBV infection and the onset of this particular tumor. Moreover, studies have revealed that NPC patients exhibit higher levels of EBV antibody titers compared to individuals without the disease. This suggests a potential link between EBV infection and the pathogenesis of NPC.

Understanding the relationship between salted fish consumption during childhood and the increased risk of NPC, as well as the presence of EBV in NPC biopsy specimens and elevated EBV antibody titers in NPC patients, contributes to our knowledge of the disease's etiology. These findings may prompt further investigation into the mechanisms through which salted fish consumption and EBV infection influence the development of NPC. Such research endeavors can provide valuable insights into preventive measures, early detection, and potential therapeutic strategies for managing and combating this form of cance (6,8)

NPC is clinically classified using the TNM staging system. The current clinical staging system for nasopharyngeal carcinoma (NPC) is based on the 8th edition of the AJCC/UICC staging system, in line with the 2017 Chinese NPC staging system. Further evaluation is needed to better understand the prognostic significance of certain conditions, such as T0 classification, tumor invasion into unusual structures, and extracapsular nodal spread. This will help in developing personalized and specific management approaches for NPC.(6)

Management of nasopharyngeal carcinoma (NPC) is tailored based on the patient's clinical stage classification: (8-10)

- Stage I NPC (T1N0M0): Effective outcomes can be achieved with definitive radiotherapy to the nasopharynx and elective neck radiotherapy alone.
- Stage II NPC (T0-2N0-1M0): Patients with T2N1 stage have a high risk of distant metastasis. Recommended treatment options include concurrent chemotherapy with cisplatin for eligible patients, alternative platinum-based drugs for those intolerant to cisplatin, and radiotherapy alone for patients unsuitable for chemotherapy.
- Locally advanced NPC (Stage II-IIIA): Combining systemic therapy with radiotherapy is recommended, with concurrent platinum-based chemotherapy as the primary treatment. Neoadjuvant or additional adjuvant chemotherapy can enhance the treatment. Radiotherapy combined with targeted therapy or immunotherapy are alternative options for patients unable to tolerate or unwilling to receive chemotherapy.
- Recurrent NPC: A comprehensive individualized treatment strategy should be developed, utilizing radiation therapy, surgery, chemotherapy, targeted therapy, immunotherapy, or other modalities based on the specific condition, aiming to improve efficacy while preserving quality of life.
- Metastatic NPC: Patients are categorized into two groups based on treatment strategies and prognosis: those with first-time metastasis and those with metastasis after treatment. For the former, equal importance should be given to systemic and local treatments. For the latter, a primary

treatment approach involves reasonable sequential treatment and combining systemic treatment with local therapy.

Side Effects of Radiotherapy in Nasopharyngeal Carcinoma

Radiation therapy (RT) is a fundamental and integral component in the treatment of early and intermediate-stage disease. Over the years, significant advancements have been made in the field of RT, transitioning from conventional two-dimensional RT to more sophisticated techniques such as three-dimensional or intensity-modulated RT. However, despite these advancements, it is important to acknowledge that post-radiation changes and complications remain a common occurrence in clinical practice. (11)

The effects of radiation on the human body can be complex and multifaceted. These effects may not only manifest immediately following treatment but can also develop gradually over time, with some complications arising years after completing RT. It is crucial for healthcare professionals and patients alike to be aware of these potential long-term consequences and the importance of diligent follow-up care. (4,6)

Various factors contribute to the development of post-radiation changes and complications. The specific anatomical site being treated, the total radiation dose administered, the fractionation schedule, and individual patient characteristics can all influence the likelihood and severity of these effects. Understanding and predicting the potential risks and complications associated with RT is essential in order to provide appropriate monitoring, management, and supportive care to patients.

Some of the common post-radiation changes include tissue fibrosis, vascular damage, and alterations in the microenvironment of irradiated tissues. These changes can lead to the development of chronic conditions such as radiation-induced fibrosis, radiation-induced vascular disease, and secondary malignancies. Additionally, radiation can have an impact on normal physiological processes, affecting the function of surrounding organs and tissues. For instance, radiation therapy in the head and neck region can result in xerostomia (dry mouth) due to damage to the salivary glands, which can significantly impact the patient's quality of life. (7-9)

The effective management of post-radiation changes and associated complications necessitates a comprehensive and collaborative approach involving various healthcare professionals from diverse disciplines. This multidisciplinary team typically comprises radiation oncologists, medical oncologists, surgeons, and supportive care specialists.

Radiation oncologists play a central role in overseeing the treatment and monitoring of patients who have undergone radiation therapy. They are responsible for prescribing and administering radiation treatments, ensuring the optimal dosage and targeting of radiation to the affected area. Additionally, radiation oncologists closely monitor patients for any potential side effects or complications that may arise as a result of radiation therapy.

Medical oncologists, on the other hand, specialize in the diagnosis and treatment of cancer using various systemic therapies such as chemotherapy, immunotherapy, or targeted therapy. In the context of post-radiation changes, medical oncologists may provide additional treatments or supportive therapies to manage any residual or recurrent cancer cells and address potential complications that may have arisen from radiation treatment.

Surgeons, as part of the multidisciplinary team, contribute their expertise in surgical interventions, if necessary. They may be involved in procedures such as biopsies, tumor resections, or reconstructive surgeries aimed at addressing complications or managing residual disease following radiation therapy.

Supportive care specialists, including nurses, psychologists, nutritionists, and pain management experts, are crucial members of the team. They provide invaluable support and interventions to improve the overall well-being and quality of life of patients. Supportive care specialists assist in managing treatment-related side effects, alleviating pain, addressing emotional and psychological needs, and ensuring proper nutritional support throughout the recovery process.

By leveraging the combined knowledge and skills of these diverse healthcare professionals, a multidisciplinary approach ensures comprehensive and personalized care for patients experiencing post-radiation changes and complications. The collaboration and coordination among team members facilitate a holistic and tailored treatment plan that addresses both the medical and supportive care needs of individuals, leading to improved outcomes and a higher quality of life for patients on their journey to recovery. Regular follow-up visits, imaging studies, and other diagnostic tests are necessary to monitor for the development of late effects and complications. The timely recognition and proactive intervention in response to these changes are of paramount importance as they can significantly mitigate the impact and enhance the overall outcomes for patients. By promptly identifying and addressing these changes, healthcare providers can intervene at an early stage, potentially preventing further complications and optimizing the effectiveness of treatment strategies.

The benefits of early identification and intervention extend across various aspects of patient care. For instance, in the context of post-radiation changes, prompt recognition of potential side effects or complications allows healthcare professionals to take proactive measures to manage and alleviate symptoms. This proactive approach can minimize discomfort, improve patient comfort and quality of life, and reduce the need for more invasive or intensive interventions later on. Furthermore, early identification and intervention can also help in optimizing treatment plans and tailoring them to the specific needs of each patient. By closely monitoring and assessing changes that occur following radiation therapy, healthcare providers can make necessary adjustments to the treatment regimen, ensuring that it remains effective and well-suited to the individual's evolving condition. This individualized approach can lead to more favorable treatment outcomes and improved patient satisfaction.

Additionally, early intervention allows for timely implementation of supportive care measures. This can include providing resources and guidance to manage treatment-related side effects, offering emotional support and counseling, and ensuring access to rehabilitation services when needed. By addressing these needs promptly, healthcare providers can enhance the overall well-being and resilience of patients, promoting their physical and emotional recovery.

It is worth emphasizing that early identification and intervention are not limited to the immediate post-radiation period but extend throughout the patient's journey. Regular follow-up appointments, surveillance imaging, and ongoing monitoring of potential changes or complications are crucial in maintaining a vigilant approach to patient care. By remaining attentive to evolving needs, healthcare providers can continually adapt their interventions and support to maximize patient outcomes and long-term well-being. (7-11)

In conclusion, while radiation therapy is an essential treatment modality for early and intermediate-stage disease, it is crucial to recognize and address the potential post-radiation changes and complications that can arise. Comprehensive understanding, diligent monitoring, and proactive management

are necessary to ensure optimal patient care and long-term well-being. By continuing to advance our knowledge and refine our techniques, we can strive to minimize the adverse effects of radiation therapy and enhance the overall therapeutic efficacy. (8,9)

Early Onset

Radiation therapy often induces changes in the mucocutaneous tissue, leading to the development of mucositis, a condition characterized by inflammation. The inflammatory response can be triggered by direct radiation exposure and/or heightened susceptibility of the epithelial lining to infections. Over time, chronic mucositis can manifest as various alterations, including mucosal atrophy, necrosis, and the formation of ulcers. Additionally, other long-term effects of radiation therapy can include the development of choanal atresia, paranasal sinus mucocele, and the formation of polyps within the affected areas.

Furthermore, radiation therapy in the head and neck region can give rise to xerostomia, a condition characterized by dryness of the mouth due to reduced salivary gland function. This side effect can significantly impact a patient's oral health and overall quality of life. Additionally, radiation exposure can potentially damage the pituitary gland, leading to hormonal deficiencies and associated complications.

During the early stages of radiation treatment, sinusitis and otomastoiditis commonly occur. These conditions involve inflammation and infection of the sinuses and the middle ear, respectively. While they may be transient in nature for some patients, others may experience persistent or chronic sinusitis and otomastoiditis following radiation therapy.

Notably, radiation-induced rhinosinusitis can develop in various regions, including the nasopharyngeal, sino-nasal, and cranial areas. This condition involves inflammation of the nasal passages and the sinuses, which can cause significant discomfort and affect a patient's respiratory function.

Moreover, temporary alterations in the nasopharyngeal microbiota have been observed as a consequence of radiation therapy. The delicate balance of microorganisms within the nasopharynx can be disrupted, potentially leading to shifts in the microbiota composition and an increased susceptibility to infections or other complications.

Radiation can cause chronic rhinosinusitis, but the dysbiosis found is similar to other causes of chronic rhinosinusitis. Olfactory dysfunction and chronic rhinosinusitis are most severe at the end of radiotherapy, gradually decreasing over time. Radiation-induced osteitis and fatty marrow replacement are common bone abnormalities in post-radiation patients. Osteoradionecrosis can develop in some cases. (10-13)

Late Onset

Early side effects of radiation therapy (RT) occur during and immediately after treatment, while late effects can manifest weeks to years later. Common early side effects include dry mouth (xerostomia) and changes in saliva consistency. Late side effects encompass a wide range of complications, including osteoradionecrosis (requiring surgical intervention), fibrosis (leading to cosmetic and functional impairments), pharyngoesophageal stenosis (causing difficulty in eating), skin changes (such as radiation dermatitis and increased risk of skin cancer), and damage to the eye, ear, nerves, and neck. (11, 15)

Xerostomia, resulting from damage to salivary glands, can persist long-term and impact quality of life. Osteoradionecrosis, predominantly affecting the mandible, can lead to pain, trismus, and fractures. Fibrosis can develop in various tissues, restricting mobility and causing complications in the pharynx and esophagus. Pharyngoesophageal stenosis narrows the swallowing passage, requiring interventions like dilation or surgery. Skin changes range from acute dermatitis to chronic fibrosis and an increased risk of skin cancer. (11-14)

Certain factors increase the risk of radiation-induced skin injuries, such as smoking, alcohol consumption, treatment modalities, and specific drugs. IMRT, lower performance scale scores, and multisession chemotherapy predict higher risks. IMRT can increase adverse skin reactions, and lymphedema and hypothyroidism are potential long-term effects. Hyperparathyroidism can occur after a longer latency period, while radiation can cause cataracts and retinopathy, especially at higher doses.

Protecting ocular structures during RT and vigilant monitoring can minimize complications. In cases of advanced radiation retinopathy, vitrectomy may be necessary. Regular follow-up evaluations, including serum TSH measurements, are essential to manage hypothyroidism effectively. Overall, understanding and addressing both early and late side effects of RT are crucial for optimizing patient outcomes and quality of life. (7-13)

Clinical manifestations include retinal microvascular changes such as loss of endothelial cells, capillary occlusion, telangiectasis, and microaneurysms. Other retinal findings include edema, exudates, cotton wool spots, hemorrhages, papillopathy (optic nerve inflammation), radiation-induced optic neuropathy, and proliferative retinopathy. Radiation retinopathy occurs after exposure to radiation (external beam, brachytherapy plaques, or stereotactic radiosurgery) administered around the orbital region. It occurs in 7% of cases receiving radiation to the globe, orbit, sinuses, or nasopharynx. Typically, retinopathy develops 6 months to 3 years after treatment, considered the time for turnover of retinal endothelial cells, although cases have been reported after 15 years of exposure. Radiation retinopathy often depends on the dose, daily fraction size, and fraction interval, with the usual threshold dose for retinal damage at 30-35 Gy. Higher total radiation doses and smaller fractions are associated with an increased risk of developing retinopathy. (3, 14)

Hearing impairment and ototoxicity can occur as a result of radiation therapy (RT). Symptoms may include ear heaviness, pain, decreased hearing, tinnitus, and dizziness. Serous otitis media and conductive hearing loss can be reversible, while sensorineural hearing loss is irreversible. Dizziness can result from damage to the nervous system and carotid artery baroreceptors. Headaches may stem from fibrotic neck muscles and middle ear damage. Secondary cancers, although rare, can arise from RT, with the risk increasing with the radiation dose. Regular follow-up is essential to detect secondary malignancies. Recurrence rates vary, with local recurrence and distant metastasis occurring in a subset of patients. (15)

A study on nasopharyngeal carcinoma patients revealed high rates of recurrence and distant metastasis over a 5-year period. The most common acute side effects of RT include dry mouth, oral mucositis, pharyngitis, dermatitis, and throat inflammation. Xerostomia was the most common late-onset side effect. Biochemical hypothyroidism was observed in a significant percentage of patients after completing RT.(6, 15)

In summary, RT can lead to various side effects, including hearing damage, dizziness, secondary cancers, and recurrence. Monitoring and managing these effects are crucial for patient well-being. Two patients were diagnosed with mandibular radionecrosis through MRI. They underwent mandibular biopsies, which confirmed the presence of necrosis. Long-term side effects of radiotherapy in NPC patients can significantly impact their health, long-term survival, and quality of life. Recognizing and treating these side effects can greatly improve patient outcomes. (7, 9)

Conclusion

Nasopharyngeal carcinoma (NPC) is a squamous cell carcinoma that arises in the surface lining of the nasopharynx. It presents with various signs and symptoms in patients. The diagnostic process for NPC involves comprehensive evaluation, including medical history, physical examination, and various diagnostic tests, to determine the clinical stage of the disease. Radiotherapy is a common treatment option for NPC patients, tailored to their clinical stage and individual conditions. While radiotherapy plays a crucial role in managing early to moderate stages of the disease, it is not without side effects, as is the case with any medical intervention. These side effects can be classified as early or late. Understanding the potential side effects of radiotherapy is essential for healthcare professionals and patients alike. Regular follow-up and monitoring are necessary to identify and manage any late-onset side effects that may arise months or years after treatment. By prioritizing monitoring and appropriate management, healthcare professionals can improve patient outcomes and quality of life in the long term.

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