

Comparison of Biopsies for Diagnosis of Nasopharyngeal Carcinoma

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Abstract

Purpose: This literature review aims to compare accurate biopsy techniques for establishing a diagnosis of nasopharyngeal carcinoma.

Methodology: The method used in this research is the systematic literature review method.

Results: Several types of biopsy techniques that can be performed to establish a diagnosis of nasopharyngeal carcinoma include nasopharyngeal biopsy and neck biopsy. Nasopharyngeal biopsy is performed if the primary tumor has not spread to other areas. Neck biopsy is performed to determine whether the lump in the neck is a metastasis of nasopharyngeal carcinoma or cancer that originates from the lymph nodes.

Applications/Originality/Value: Further research is needed to understand and develop better methods of early detection and diagnosis. With the right approach, the prognosis for patients with nasopharyngeal carcinoma can be significantly improved.

Introduction

The primary malignant cancer of the head and neck region in Indonesia is nasopharyngeal carcinoma (NPC), the majority of cases of NPC are of the nonkeratinizing type with EBV association. These nonkeratinizing NPC are identified by undistinguished or badly differentiated carcinoma cells and a large number of admixed inflammatory cells, mainly small lymphocytes and plasma cells. Although NPC is rare among Caucasians, its incidence is disproportionately high in some ethnic groups, such as Chinese from Southeast Asia, North Africans, and Inuit people. These morphologic features may make pathologic diagnosis challenging, particularly for pathologists with less experience or in nonendemic areas. (Suwondo, Surarso, & Kristyono (2019)). Data reveals that nasopharyngeal carcinoma accounts for 60% of malignant head and neck cancer cases. Cancers of the nose and paranasal sinuses (18%), larynx (16%), and oral cavity, tonsils, and hypopharynx afterwards. Malignant nasopharyngeal cancers rank among the top five cancers in the human body, along with skin, lymph node, breast, and uterine cervical cancers, according to research obtained by the Anatomical Pathology Laboratory (Baran, Aydın, & Elibol (2021)). The geographical rates of nasopharyngeal cancer (NPC) differs. In comparison with the US and Europe, where the average annual rate is less than one case per 100,000 people, Southern China has the highest incidence, with about 30 cases per 100,000 people. Environmental variables, family history, and Epstein-Barr virus (EBV) infection are among the risk factors associated with nasopharyngeal cancer (NPC). EBV is closely linked to nasopharyngeal cancer, the most typical nasopharyngeal epithelial cancer, and NK/T cell lymphoma, two cancers that originate from the nasopharynx (Chan, Chow, & Wei (2013)). When compared to EBV-negative cancers, EBV-positive NK/T cell lymphoma and nasopharyngeal carcinoma exhibit a markedly improved response to therapies and improved patient survival (Padang, Padang R, & Sumbar (2014)).

The Epstein-Barr virus (EBV) is widely linked to this cancer, and NPC is usually shown to contain EBV-encoded RNA (EBER). Both asymptomatic carriers and patients with infectious mononucleosis can spread EBV viruses through their saliva. Lytic reproduction takes place in freshly infected host nasopharyngeal epithelial cells during the acute infection, allowing EBV virions to spread to nearby host epithelial cells as well as B cells in the Waldeyer's ring. EBV infection can then continue by mostly existing as plasmids throughout the latent period. These plasmids are in memory

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cells in the germination of the Waldier ring, where its native inclination lies. If you signal in memory cells to differentiate to terminal in plasma cells, the viral reactivation occurs with the release of the virions, which also infect other naive in cells and epithelial cells from Nasopharyngeal. During this reactivation process, EBV spreads and infected cells and can be identified and transferred to saliva. When EBV virions infect healthy nasopharyngeal epithelial cells, they usually experience growth arrest and lyse. However, through molecular alterations such p16 deletion and Cyclin D1 overexpression, which overcome the cellular regulating pathways' default growth inhibitory impact, nasopharyngeal mucosal inflammation might allow for ongoing latent EBV replication to take place within the cells. EBV's unchecked latent replication causes further cellular changes that eventually lead to malignant transformation into NPC.

The initial tumor's anatomical location and metastases are linked to symptoms of nasopharyngeal cancer. Four categories can be used to classify typical symptoms:

- 1) Ear symptoms: Hearing loss, otalgia, otorrhea and tinnitus (Chen, Chan, Blanchard, & Ma (2019)). These symptoms arise due to impaired Eustachian tube function due to tumors that cover the opening of the tube or tumor extension to the latero-posterior so that it interferes with the work of the muscles to open the tube. The type of hearing loss that occurs is usually conductive due to the onset of otitis media with effusion (Chuang, Chang, Yu, Yang & Yeh (2020)).
- 2) Nasal symptoms include epistaxis, post-nasal drip includes blood, and developing nasal obstruction (King, Vlantis, Bhatia, Zee & Ahuja (2011)).
- 3) Neurological/Nerve Symptoms: these symptoms are related to the involvement of the cranial nerves (King, Vlantis, Yuen, & Law (2015)). The incidence of cranial nerve involvement in NPC is around 20%. If the tumor extends superiorly, it will involve nerves III to VI, and if it extends laterally, it can involve cranial nerves IX to XII. The cranial nerves most commonly involved are III, V, VI and XII.
- 4) Painless lumps in the neck (King, Ai, Lam, Tse, Wong, & Chan (2024)). More than half of individuals with NPC objected of neck lumps when they first arrives. Depending on where the cancer is located, this lymph node growth is typically ipsilateral (upper neck), though it can occasionally be bilateral. Additional symptoms, such anorexia and weight loss, may be general signs of cancer. Most patients present with a neck lump that is usually at an advanced stage of nasopharyngeal carcinoma, and early symptoms are frequently vague and undetectable (Suwondo, Surarso, & Kristyono (2019)).

The diagnosis of NPC is obtained from clinical suspicion, careful examination, endoscopic examination and biopsy, CT scan and MRI. A biopsy of the major tumor confirms the diagnosis of NPC. Fresh specimens are very important to be sent immediately for histopathological examination. If the specimen taken is normal mucosa, the patient will usually feel pain during the procedure. Bleeding during biopsy can occur but is rarely massive. Negative biopsy results obtained in patients suspected of NPC or without a clear tumor shape are an indication for re-biopsy under general anesthesia by taking several specimens from bilateral *Rossemüller* fossa and from the superior / posterior wall of the nasopharynx. In practically all NPC cases in endemic areas, the tumour cells have the EBV genome. Because of their close relationship with EBV, viral nucleic acids or the host antibody response to the virus have been investigated as potential biomarkers for NPC. The circulating EBV DNA in plasma as an cancer biomarker has been widely explored for the monitoring and prognosis of NPC. It is used in conjunction with endoscopy and imaging to monitor recurrence following radical treatment. Plasma EBV DNA levels were also measured before, during, and after treatment to determine their predictive significance in NPC patients. In recent years, a large-scale prospective investigation involving 20,000 asymptomatic male subjects in an endemic region confirmed the additional role of plasma EBV DNA for examination of NPC. Subjects who had any detectable levels of plasma EBV DNA by quantitative polymerase chain reaction (qPCR)-based assay on both consecutive occasions were defined as "screen optimistic." "Screen-positive" subjects would then undergo endocopy and magnetic resonance imaging to confirm the diagnosis. It was also demonstrated that patients with NPC diagnosed through screening had a higher progression-free survival rate (PFS) than the same unscreened sample. The positive findings could serve as a foundation for additional research into the widespread implementation of a plasma EBV DNA-based screening program in endemic areas. (Bossi, Chan, Licitra, Trama, Orlandi, & Machiels (2021)).

There are differences in the area / location of biopsy for confirming NPC. Biopsies are taken from masses in the neck in patients with nasopharyngeal carcinoma that are performed before the diagnosis of nasopharyngeal carcinoma is confirmed compared to nasopharyngeal carcinoma that is confirmed after nasopharyngeal biopsy. Aside from detecting EBV DNA in plasma, researchers have demonstrated that detecting EBV DNA in nasopharyngeal brush

cytology can be employed for NPC identification with excellent sensitivity and specificity. qPCR study revealed higher quantitative levels of EBV DNA in the nasopharyngeal brush cytology of NPC patients compared to non-NPC patients. The cytology specimens were acquired via a transoral method without endoscopic supervision, therefore their usage was not limited to specialists. This may be useful in a community setting. Another case-control research used the same brush technique, and has clinical potential for detecting local recurrence in post-irradiated NPC patients. This study will compare nasopharyngeal biopsy with neck biopsy in establishing a diagnosis of nasopharyngeal carcinoma (Lam, & Chan (2018)).

Result

There are not enough tissue resources available for NPC research, despite the disease's high occurrence. NPC lesions are quite tiny and rarely need surgery, in contrast to many other cancers. Endoscopic biopsy is currently a highly dependable tissue-sampling technique for suspected tumour sites. However, tiny biopsy samples are generally utilized for histological evaluation on an initial basis and rarely left for scientific purposes following diagnosis. Furthermore, because to the invasiveness, samples of tissue from healthy people are not available. Blood and urine are examples of bodily fluids that may not be specific enough for NPC detection since they do not come into direct touch with neoplastic sites. In the majority of clinical situations, bodily fluids contain very few cancer cells. As previously demonstrated, nasopharyngeal brushing, a non-invasive and practical tissue-sampling technique, comes into close touch against the neoplastic site and can extract tumour cells or exfoliative epithelium. In high-risk groups, it has been used for NPC diagnosis and extensive EBV screening at the level of EBV-related nucleic acids, such as DNA, mRNA, and microRNA. In nasopharyngeal brushings, EBV-related indicators have a high degree of specificity and sensitivity. The mucosal lining of the nasopharynx is the site of nasopharyngeal carcinoma, an epithelial cancer. The lateral wall of the nasopharynx, including the fossa of Rosenmüller, is typically where nasopharyngeal cancer begins. After that, it may spread out into or out of the nasopharynx to the opposite lateral wall, or postero-superiorly to the nasal cavity, oropharynx, or base of the skull, or palate. Frequently, it expands to the cervical lymph nodes after that. The bones, lungs, mediastinum, and, less frequently, the liver are all susceptible to distant metastases. Nasopharyngeal carcinoma differs highly from other head and neck epithelial tumours, even though they are generated from the same tissues or cells lineage (Cai, Zhang, Hu, & Gu (1983)).

The majority of patients who seek treatment currently in advanced stages, specifically stages III and IV, and some even arrive in terrible condition because the early signs of NPC are unusual and the nasopharynx is difficult to notice. This happens because of a missed diagnosis. It is acknowledged in the medical community that determining a prompt diagnosis of NPC is challenging. This is mostly as a result it is tough to see or examine the nasopharynx, particularly the Rosen-muller fossa region on the lateral wall. Considering that the nasopharynx is a dark cavity situated above the roof of the molar mouth and behind the nasal cavity, it seems to reasonable that it would be challenging to examine. It is more challenging to detect nasopharyngeal cancer early because its symptoms, like common sinusitis or chronic rhinitis, are ambiguous (Brennan (2006)).

The most prevalent variety of epithelial cancer in adults is nasopharyngeal carcinoma. Epstein-Barr virus (EB) can spread to epithelial cells and is linked to their transformation, as evidenced by the detection of viral DNA and EBNA in NPC types 2 and 3. EBV, ethnic origin, and environmental carcinogens all seem to play a significant part in the multi-step process that appears to be the genesis of NPC, particularly endemic variants (Ng, Ngan, Wei, Gullane, & Phillips (2014)). Ninety percents of patients with non-keratinizing NPC carry plasma samples which contain EBV DNA, whereas controls contain just 7%. EBV DNA levels may be a stand-alone prognostic biomarker since they seem to be correlated with treatment response and can forecast illness recurrence. Other potential causes in adults include a genetic history and intake of foods that contain carcinogenic volatile nitrosamines, mostly salted fish. (Ng, Choi, Lee, Law, Yau, & Lee (2010)).

Many patients first show up with cervical lymphadenopathy, and lymph node biopsies are frequently used to diagnose NPC. Trismus, discomfort, otitis media, nasal regurgitation from soft palate paresis, hearing loss, and cranial nerve palsies are all symptoms linked to the underlying tumour. A "nasal buzz" and nasal blockage or bleeding may result with larger growths. Organ failure or bone pain may be the outcome of cancer metastasis. Infrequently, disseminated disease might occur in paraneoplastic osteoarthropathy syndromes (Sham, Choy, Wei, Ng, Zong, Guo, & Luo (1990)).

The World Health Organization (WHO) has identified three subtypes of NPC:

- a. Type 1: Squamous cell carcinoma, typically seen in the older adult population
- b. Type 2: Non-keratinizing carcinoma
- c. Type 3: Undifferentiated carcinoma

In childhood and adolescence, type 3 cases predominate, with a small number of type 2 cases. Epstein-Barr virus titers are higher in types 2 and 3, but not in type 1. The degree of lymphoid infiltration is part of Krueger and Wustrow's Cologne version of the WHO strategy. The term "lymphoepithelioma" refers to the inflammatory infiltration of lymphocytes, plasma cells, and eosinophils, which may be linked to types 2 and 3. There are two potential histological patterns: the Schmincke type, where cancer cells are dispersed and combined with inflammatory cells, and the Regaud type, which has a distinct collection of epithelial cells encircled by lymphocytes and connective tissue. The same neoplasm may exhibit both patterns (Brennan, 2006).

Histopathological biopsy analysis of nasopharyngeal carcinoma tissue is the gold standard for determining an NPC diagnosis. The form and presence of malignant cells can be ascertained by histopathological analysis. This approach has a very high success rate (97.25%) for determining an NPC diagnosis. It is also possible to overlook very small cancer, like in the case of early-stage NPC. In order to minimize lesions, lessen pain, and lower the risk of bleeding, a more accurate method of select the biopsy target must be developed. This method must also have high sensitivity and specificity in order to be a reliable method of identifying whether or not malignant cells are present in the nasopharynx. Because it is a protocol, the initial diagnostic evaluation is crucial. Detecting tumour gene promoter hypermethylation in nasopharyngeal brushings has been shown to be more sensitive and specific than detecting EBV DNA markers in plasma for early NPC detection. Brush cytology has also been tested for NPC detection, but the cytologic pickup is inferior to that obtained through biopsy. These findings suggest that nasopharyngeal brushing. Tissue sections from nasopharyngitis patients revealed an inflammatory epithelium infiltrated with many lymphocytes, whereas nasopharyngeal tissue sections from NPC patients revealed evident tumour nests surrounded by infiltrating lymphocytes. In brushing smears, normal nasopharyngeal mucosa from healthy participants presented typical columnar cells, squamous cells, and lymphoid cells, whereas in nasopharyngeal mucosa from NPC patients, a significant number of exfoliative tumour cells mixed with a few normal epithelial cells and lymphocytes were observed. (Tan, Phua, Soong, Oon, Chan, Lucky, & Lim (2020)).

Discussion

Nasopharyngeal and neck biopsies are the biopsy techniques that can be used. Primary lesions that have not spread can undergo nasopharyngeal biopsy. In addition, a neck biopsy is carried out if there is a possibility that nasopharyngeal carcinoma or lymph node cancer may have spread or metastasized (Tune, Liavaag, Freeman, & Dosch (1999)).

The outcome of pathology is typically homogeneous or poorly distinguished cancer. When patients are first checked, they typically have metastases in the neck lymph nodes. Typically, a biopsy from the main lesion in the nasopharynx through the mouth or nose is performed to confirm the diagnosis. An excisional biopsy is taken from the neck's lymph nodes if it fails to work. Patients typically consult a surgeon, ENT specialist, neurologist, ophthalmologist, or even a psychiatrist before being directed to the appropriate physician for therapy since NPC is sometimes concealed by unique symptoms and indicators. Patients frequently have a delay of several months before they start therapy. Furthermore, when the main site cannot be done, repeat biopsies from the nasopharynx are occasionally required. The microscopic images of pathology slides are far more complex than other types of medical images. Each type of cell on a slide has its own morphologic characteristics, including shape and size, cytoplasmic volume and features, nuclear size and shape, chromatin distribution, and the amount and size of nucleoli. The different cell types are then arranged in different patterns, and the colour and intensity of hematoxylin and eosin (H&E) staining may be affected by subtle differences in tissue thickness and staining conditions between laboratories, or even within a single laboratory. Additionally, the digital files of high-resolution pathology images are very large and complex, making computer analysis of these images extremely challenging. (Wen, Yong, Liang, Xie, Chen, & Cheng (2019)).

In general, the prognosis is unaffected by cervical lymph node biopsy, regardless of whether the lymph nodes are fixed. The rates of survival are similar. The type of biopsy seems to have an impact on prognosis in individuals with mobile lymph nodes. Removing the entire intact lymph node can stop lymphovenous spread before the malignancy has entered the clinically movable lymph node capsule. Even when the lymph node is completely removed, spread is likely to happen if the cancer has spread to the surrounding tissue and fixed the node. The five-year survival rate for individuals with mobile lymph nodes was 50% for those who had total lymph node excision and 22% for those who only had partial removal (Zhang, Zheng, Li, Tian, Hu, & Jia (2018)).

Conclusions

Biopsies are the primary method used to diagnose nasopharyngeal cancer. Since nasopharyngeal carcinoma is the most prevalent cancer in the head and neck, but may be differentiated from other forms of the disease, a biopsy should be considered. The histopathology of the biopsy, whether it be a neck biopsy or another method, determines how accurate the diagnosis is. Note that a nasopharyngeal biopsy must be performed to confirm a neck biopsy for suspected metastases.

Reducing the inaccurate diagnosis rate as much as feasible and keeping the misdiagnosed rate below an acceptable range are crucial for NPC screening and early detection. Especially compared to applying just one diagnostic marker, a combination of several diagnostic markers may result in great sensitivity, according to certain prospective and retrospective studies. Further imaging, pathological investigation, and regular follow-up visits can correctly confirm whether a patient has NPC if they have a positive screening or early diagnosis result. Therefore, future research on NPC screening and early diagnosis will concentrate on determining the optimal mix of diagnostic markers (Feng, Xia, & Yi (2020)).

Acknowledgement

We acknowledge the Department of ENT-Head and Neck Surgery, Muhammadiyah University of Surakarta for permission to use the data. We would like to thank Dr. Iwan who has guided us in compiling this literature review.

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