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THE RELATIONSHIP BETWEEM PTEN GENE EXPRESSION AND HISPATHOLOGICAL TYPES IN PATIENTS WITH NASOPHARYNGEAL CARCINOMA

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ABSTRACT

Background: Nasopharyngeal carcinoma (NPC) is a type of epithelial cancer arising from the nasopharyngeal mucosa, with tumors most commonly found in the fossa of Rosenmüller. NPC ranks as the fourth most prevalent cancer in Indonesia, after cervical, breast, and skin cancers. However, its exact pathogenesis remains unclear. Aims: This study aimed to determine the relationship between PTEN gene expression and histopathological types in NPC patients, and to explore its potential as a diagnostic and therapeutic target. Methods: This was an analytic study with a cross-sectional design. Samples were obtained from paraffin-embedded tissue blocks, followed by RNA isolation and synthesis. RT-PCR was subsequently performed and analyzed using a Rotor-Gene system. Statistical analysis was conducted using SPSS software. Results: Of 38 NPC patients, the majority were male (57.9%), with the most common age group being 41–60 years (71.1%). Based on histopathological type, 60.5% were diagnosed with non-keratinizing squamous cell carcinoma (SCC) and 39.5% with undifferentiated carcinoma. Statistical analysis of the relationship between PTEN expression levels and histopathological type yielded a p-value of 0.413 ($p > 0.05$). Conclusion: B There was no statistically significant relationship between PTEN expression levels and the histopathological type of NPC.

Keywords: gene expression, histopathology, nasopharyngeal carcinoma, PTEN, TNM

INTRODUCTION

Nasopharyngeal carcinoma (NPC) is a malignant epithelial tumor arising from the mucosal lining of the nasopharynx, a region located at the upper posterior part of the pharynx behind the nasal cavity. Unlike other head and neck malignancies, NPC has a distinct anatomical predilection, with tumors most frequently originating from the lateral wall of the nasopharynx, particularly the pharyngeal recess known as the fossa of Rosenmüller [1]. This unique anatomical location often leads to delayed diagnosis, as

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early-stage symptoms are subtle and nonspecific, contributing to the high proportion of patients presenting at an advanced stage.

NPC exhibits a markedly uneven global distribution, with the highest incidence rates observed in Southeast Asia, Southern China, and parts of North Africa and the Middle East. In Indonesia, NPC represents the fourth most common malignancy overall, following cervical, breast, and skin cancers. Marlinda et al. reported that NPC accounts for 28.4% of all head and neck cancers in Indonesia, with a male-to-female ratio of approximately 2:1 and a particularly high endemicity on the island of Java [2]. This epidemiological pattern underscores the significant public health burden that NPC imposes on the Indonesian population.

The etiology of NPC is multifactorial, involving a complex interplay between Epstein-Barr virus (EBV) infection, genetic susceptibility, and environmental carcinogens. EBV is consistently detected in nearly all cases of non-keratinizing NPC, which predominates in endemic regions, and plays a central role in driving oncogenic transformation through viral oncoproteins such as LMP1 and EBNA. Additional risk factors include regular consumption of nitrosamine-containing salted fish, occupational exposure to dust and fumes, and a family history of the disease. Understanding these etiological contributors is essential for developing effective screening and preventive strategies [3].

The World Health Organization (WHO) classifies NPC into three histopathological subtypes: Type I (keratinizing squamous cell carcinoma), Type II (non-keratinizing differentiated carcinoma), and Type III (non-keratinizing undifferentiated carcinoma). In endemic regions including Indonesia, WHO Type II and Type III predominate and are strongly associated with EBV infection, while WHO Type I is more prevalent in non-endemic Western countries and is more closely linked to tobacco and alcohol use. This histopathological heterogeneity has important implications for prognosis and therapeutic response [3].

The management of NPC relies primarily on radiotherapy, with concurrent chemotherapy reserved for locoregional advanced disease. However, because the majority of patients in Indonesia present with locally advanced or metastatic disease at the time of diagnosis, treatment outcomes remain suboptimal, with a relatively low five-year survival rate [1,3]. The lack of effective individualized therapeutic strategies

highlights the urgent need to identify reliable molecular biomarkers that can improve early detection, stratify prognosis, and guide targeted therapy in NPC patients.

At the molecular level, the phosphatase and tensin homolog (PTEN) gene, located on chromosome 10q23.3, has emerged as one of the most frequently altered tumor suppressor genes in human cancers. The PTEN gene consists of nine exons and encodes a protein of 403 amino acids that possesses both lipid and protein phosphatase activities [4–6]. As a tumor suppressor, PTEN plays a pivotal role in maintaining genomic stability and controlling intracellular signaling pathways that regulate cell growth, differentiation, and survival.

The principal biochemical function of PTEN is to dephosphorylate phosphatidylinositol-3,4,5-trisphosphate (PIP3), the lipid second messenger generated by phosphatidylinositol-3-kinase (PI3K). By converting PIP3 back to PIP2, PTEN directly antagonizes PI3K activity and thereby suppresses downstream signaling cascades including the phosphoinositide-dependent kinase-1 (PDK1)/AKT axis and the mechanistic target of rapamycin (mTOR) pathway. Since PI3K-driven signaling promotes cell proliferation and survival, PTEN functions as a critical negative regulator of cell cycle progression, angiogenesis, and resistance to apoptosis. Loss or inactivation of PTEN thus permits unchecked activation of pro-tumorigenic pathways, contributing to tumor development and progression [7].

Given the central role of PTEN in tumor suppression and its documented inactivation across multiple cancer types, investigating its expression in the context of NPC histopathological subtypes may yield important diagnostic and therapeutic insights. Variations in PTEN expression between WHO histopathological types could reflect differences in underlying molecular pathogenesis, which in turn may influence clinical behavior, treatment sensitivity, and overall prognosis. Therefore, this study aimed to determine the relationship between PTEN gene expression and histopathological types in NPC patients, and to evaluate its potential utility as a molecular marker for diagnosis and targeted therapy in NPC.

METHODS

This study was an analytic observational study employing a cross-sectional designSamples were selected using a consecutive sampling method, yielding a total of

38 subjects. The inclusion criteria were: (1) patients with complete medical records encompassing all study variables, including age, sex, clinical stage, histopathological type, extent of primary tumor, and cervical lymph node enlargement; (2) availability of formalin-fixed paraffin-embedded (FFPE) tissue blocks at the Department of Anatomical Pathology, Adam Malik General Hospital Medan, with a confirmed histopathological diagnosis of NPC; and (3) patients who had not previously received chemotherapy and/or radiotherapy.

The exclusion criteria were: (1) non-representative or inadequate FFPE tissue blocks, and (2) patients with a history of other malignancies. Histopathological classification followed WHO criteria, categorizing NPC into keratinizing squamous cell carcinoma (Type I), non-keratinizing differentiated carcinoma (Type II), and non-keratinizing undifferentiated carcinoma (Type III).

Medical record data were retrieved from Adam Malik General Hospital Medan, covering demographic characteristics, histopathological type, primary tumor extent (T stage), cervical lymph node status (N stage), and overall clinical stage based on the AJCC staging system. FFPE tissue blocks were then transported to the Integrated Laboratory of the Faculty of Medicine, Universitas Sumatera Utara, where tissue sections were cut using a microtome. Total RNA was isolated from each section using a standardized extraction protocol for FFPE specimens, followed by complementary DNA (cDNA) synthesis through reverse transcription. PTEN gene expression was subsequently quantified using quantitative reverse transcription polymerase chain reaction (RT-qPCR) on a Rotor-Gene Q system, with cycle threshold (CT) values recorded as a measure of relative gene expression and a housekeeping gene used as an internal control.

All data were analyzed using IBM SPSS Statistics software. Numerical variables were expressed as mean ± standard deviation (SD) or median with minimum–maximum range, based on data distribution normality as assessed by the Shapiro-Wilk test. The relationship between PTEN gene expression and histopathological type was evaluated using the Independent Samples t-test, with a p-value of less than 0.05 considered statistically significant.

RESULTS

This study included 38 patients with nasopharyngeal carcinoma (NPC) who sought treatment at the Subdivision of Oncology–Head and Neck Surgery, Department of Otorhinolaryngology–Head and Neck Surgery, Adam Malik General Hospital Medan. All subjects fulfilled the predetermined inclusion and exclusion criteria. Data were collected from formalin-fixed paraffin-embedded (FFPE) tissue blocks retrieved from the Department of Anatomical Pathology, and molecular analysis was subsequently performed at the Integrated Laboratory of the Faculty of Medicine, Universitas Sumatera Utara. The complete demographic and clinical characteristics of the study population are summarized in Table 1.

Table 1. Demographic and clinical characteristics of NPC patients.

Demographic and Clinical Characteristic	n=38	%
Sex		
Male	22	57.9
Female	16	42.1
Age (years)		
20 – 40 years	6	15.8
41 – 60 years	27	71.1
> 60 years	5	13.2
Histopathological type		
Non-Keratinizing SCC	23	60.5
Undifferentiated Carcinoma	15	39.5
T stage		
T1	2	5.3
T2	7	18.4
T3	15	39.5
T4	14	36.8
N stage		
N0	1	2.6
N1	2	5.3
N2	26	68.4
N3	9	23.7
Clinical stage		
III	18	47.4
IV	20	52.6

The distribution of patients by sex revealed a predominance of male patients. Of the 38 subjects, 22 patients (57.9%) were male and 16 patients (42.1%) were female, yielding a male-to-female ratio of approximately 1.4:1. This finding is consistent with

the well-established epidemiological pattern of NPC, in which male individuals are disproportionately affected compared to their female counterparts. The higher susceptibility observed in males is generally attributed to greater exposure to known environmental risk factors, including tobacco smoking, occupational hazards, and higher consumption of nitrosamine-containing preserved foods.

Patient age ranged from 28 to 71 years, with a mean age of 49.58 years (SD ± 10.03) and a median age of 50 years. The distribution of patients across age groups demonstrated that the 41–60 years cohort was the most heavily represented, accounting for 71.1% of the total sample (n = 27). This was followed by patients aged 20–40 years, who comprised 15.8% of the sample (n = 6), and those aged over 60 years, who accounted for 13.2% (n = 5). The predominance of patients in the productive age group of 41–60 years suggests that NPC tends to manifest during the fourth and fifth decades of life, consistent with the known latency period between carcinogen exposure and clinical tumor development.

Based on WHO histopathological classification, the majority of patients were diagnosed with non-keratinizing squamous cell carcinoma (SCC), accounting for 60.5% of cases (n = 23). The remaining 39.5% of patients (n = 15) were diagnosed with undifferentiated carcinoma. No cases of keratinizing squamous cell carcinoma were identified in this study population. This distribution reflects the well-recognized pattern in Southeast Asian endemic regions, where non-keratinizing subtypes predominate and are strongly associated with Epstein-Barr virus (EBV) infection, in contrast to the keratinizing subtype more commonly encountered in Western non-endemic populations.

Analysis of primary tumor staging revealed that the majority of patients presented with locally advanced disease. T3 was the most common T stage, observed in 15 patients (39.5%), followed closely by T4 in 14 patients (36.8%). T2 was recorded in 7 patients (18.4%), while only 2 patients (5.3%) presented with T1 disease. With respect to cervical lymph node involvement, N2 was the most prevalent nodal stage, affecting 26 patients (68.4%), followed by N3 in 9 patients (23.7%), N1 in 2 patients (5.3%), and N0 in only 1 patient (2.6%). Overall clinical staging demonstrated that 20 patients (52.6%) were at Stage IV, while 18 patients (47.4%) were at Stage III. Notably, no patients presented at Stage I or Stage II, underscoring the characteristic late presentation of NPC in clinical practice, which is largely attributable to its anatomically concealed

location and the nonspecific nature of early symptoms.

PTEN Gene Expression Analysis

The quantitative assessment of PTEN gene expression across the 38 NPC patients was performed using RT-qPCR, with cycle threshold (CT) values serving as the primary measure of relative gene expression. A higher CT value corresponds to lower levels of gene expression, as it reflects the number of amplification cycles required to reach a detectable signal threshold. The distribution of PTEN CT values across the study sample is presented in Table 2.

Table 2. PTEN gene expression levels in NPC patients.

PTEN Gene Expression (CT Value)	n=38
Mean (SD)	31.73 (6.27)
Median (Min-Max)	34.3 (21.09-39.46)

The mean CT value for PTEN gene expression across all patients was 31.73 (SD ± 6.27), with a median CT value of 34.3. The minimum CT value recorded was 21.09 and the maximum was 39.46, resulting in a wide inter-individual range of 18.37 CT units. This substantial range of CT values indicates considerable variability in PTEN gene expression across the study population. Such heterogeneity may reflect differences in the degree of PTEN inactivation among individual tumors, attributable to diverse mechanisms including somatic mutations, gene deletion, epigenetic silencing via promoter methylation, or post-transcriptional regulation by microRNAs such as miR-21. These molecular mechanisms of PTEN inactivation may each contribute to varying degrees of PI3K/AKT pathway dysregulation, which in turn influences tumor biological behavior and clinical outcome.

Relationship Between PTEN Gene Expression and Histopathological Type

To examine the primary research question, PTEN gene expression levels were compared between the two histopathological subtypes identified in this study: non-keratinizing SCC and undifferentiated carcinoma. The results of this comparative analysis are presented in Table 3.

Table 3. Relationship between PTEN gene expression and hispathological type in NPC patients.

Histopathological Type	n	PTEN Gene Expression		p-value
		Mean (SD)	Median (Min-Max)	
Non-Keratinizing SCC	23	30,45 (6,83)	33,02 (21.09 – 38,96)	0,413*
Undifferentiated Ca	15	33,51 (5,07)	34,58 (21,54 – 39,46)	

**T Independent*

Among the 23 patients with non-keratinizing SCC, the mean CT value of PTEN gene expression was 30.45 (SD ± 6.83), with a median of 33.02 and a range spanning from 21.09 to 38.96. In the undifferentiated carcinoma group comprising 15 patients, the mean CT value was 33.51 (SD ± 5.07), with a median of 34.58 and a range of 21.54 to 39.46. While the undifferentiated carcinoma group appeared to exhibit a marginally higher mean CT value that indicating a tendency toward lower PTEN expression, this difference did not reach statistical significance.

Statistical comparison of PTEN CT values between the two histopathological groups was performed using the Independent Samples t-test. The analysis yielded a p-value of 0.413 ($p > 0.05$), confirming that there was no statistically significant difference in PTEN gene expression between non-keratinizing SCC and undifferentiated carcinoma subtypes of NPC. This result indicates that PTEN gene expression levels, as measured by RT-qPCR CT values, did not vary meaningfully according to histopathological subtype in this study population.

It is worth noting that the relatively small sample size, combined with the unequal distribution between the two histopathological groups (23 vs. 15 patients), may have limited the statistical power of this analysis. Furthermore, the absence of a healthy control group precluded comparison of PTEN expression between tumor tissue and normal nasopharyngeal mucosa, which would have provided additional context regarding the magnitude and direction of PTEN dysregulation in NPC. These limitations should be considered when interpreting the present findings.

DISCUSSION

This study investigated the relationship between PTEN gene expression and histopathological type in 38 NPC patients treated at Adam Malik General Hospital Medan. The principal finding of this study was that there was no statistically significant

difference in PTEN gene expression, as measured by RT-qPCR CT values, between non-keratinizing squamous cell carcinoma and undifferentiated carcinoma subtypes ($p = 0.413$). Beyond this primary outcome, the demographic and clinical data yielded several noteworthy findings regarding the epidemiological profile of NPC in this population, each of which warrants detailed discussion in the context of existing literature.

The present study found a male predominance among NPC patients, with a male-to-female ratio of approximately 1.4:1. This finding aligns with the well-established global epidemiological pattern of NPC, in which males consistently bear a disproportionately higher disease burden. Nafisa et al. reported a male predominance of 70.4% with a male-to-female ratio of 2.3:1 among 273 NPC patients who underwent radiotherapy at Dr. Hasan Sadikin General Hospital Bandung during 2018–2019. Similarly, data from RSUPN Dr. Cipto Mangunkusumo recorded 68.3% male patients among 167 NPC cases in 2010, reflecting a ratio approaching 2:1. The male-to-female ratio observed in the present study (1.4:1) was somewhat lower than those reported in these previous studies, which may be attributable to the relatively small sample size or regional differences in risk factor exposure within the study population. Nevertheless, the directional consistency across studies supports the conclusion that male sex is an independent risk factor for NPC. This disparity is largely explained by higher rates of tobacco smoking, greater occupational exposure to environmental carcinogens, and more frequent consumption of nitrosamine-containing preserved foods among males, all of which have been recognized as significant contributors to NPC pathogenesis [8,9].

The mean age of patients in this study was 49.58 years, with the 41–60 years age group accounting for the majority of cases (71.1%). This is consistent with findings reported by Nafisa et al., in which the most common age group among NPC patients was 45–54 years (35.0%), followed by 35–44 years (21.9%), with a median age of 48 years. Similarly, Jayalie et al. reported that the most prevalent age group at RSUPN Dr. Cipto Mangunkusumo was 31–45 years (35.9%), followed by 46–60 years (33.5%), with an overall mean age of 43.5 years. Across these studies, the pattern consistently identifies the fourth and fifth decades of life as the peak period of NPC incidence, a finding mirrored in data from other endemic regions including Southern China (40–60 years), Singapore (41–50 years), and North Africa (approximately 50 years). The concentration of NPC cases in the productive adult age group is thought to reflect the

prolonged latency period between initial carcinogen exposure, including EBV infection and dietary nitrosamines, and the eventual clinical manifestation of malignant disease. Notably, no patients under 28 years of age were recorded in this study, though pediatric NPC has been reported to account for 1–2% of all NPC cases globally, predominantly linked to early-onset EBV infection [8,9] .

In the present study, non-keratinizing SCC was the dominant histopathological subtype, accounting for 60.5% of cases, while undifferentiated carcinoma comprised 39.5%. No cases of keratinizing SCC were identified. This distribution is broadly consistent with findings from multiple Indonesian institutions. A study conducted at RSUP Dr. Mohammad Hoesin Palembang reported that among 64 NPC patients from 2019 to 2020, 62.5% exhibited well-differentiated non-keratinizing SCC and 37.5% exhibited undifferentiated non-keratinizing SCC, with no keratinizing SCC or basaloid SCC cases identified [10] .

Further corroboration comes from studies at RSUD Mangusada, where 100% of NPC cases were classified as non-keratinizing undifferentiated carcinoma, and at RSUD Abdul Wahab Sjahranie Samarinda, where approximately 97% of 104 patients were WHO Type III. At RSUD Al-Ihsan Bandung, 61.11% of NPC patients were classified as WHO Type III, while at RSUD Abdul Moeloek Lampung, 71.4% of patients presented with non-keratinizing undifferentiated histology. The absence of keratinizing SCC in this cohort is consistent with its rarity in Southeast Asian endemic populations, where non-keratinizing subtypes predominate due to the central pathogenic role of EBV. In contrast, keratinizing SCC, which is more frequently EBV-negative and associated with tobacco and alcohol exposure, is predominantly encountered in Western non-endemic countries [10–14]. This geographic and etiological divergence in histopathological distribution has important clinical implications, as keratinizing SCC is generally associated with poorer radioresponsiveness and worse prognosis compared to non-keratinizing subtypes.

A striking finding of this study was that all 38 patients presented at either Stage III (47.4%) or Stage IV (52.6%), with no cases at Stage I or Stage II. This late-stage predominance is a well-recognized feature of NPC and reflects its anatomically concealed location within the nasopharynx, which renders early lesions clinically silent and difficult to detect without targeted screening. The anatomical proximity of the

nasopharynx to critical neurovascular structures also facilitates early locoregional extension, contributing to the high proportion of N2 (68.4%) and N3 (23.7%) nodal staging observed in this cohort. The predominance of advanced-stage disease at presentation underscores the need for population-level NPC screening programs in endemic regions such as Indonesia, as well as the development of more sensitive and specific early diagnostic biomarkers to improve detection before distant or locoregional spread has occurred.

PTEN Gene Expression

The mean CT value of PTEN gene expression across all 38 patients was 31.73 (SD ± 6.27), with a wide range of 21.09 to 39.46. This considerable inter-individual variability in PTEN expression is biologically plausible, given the multiple distinct mechanisms through which PTEN can be inactivated in cancer cells. Zhang et al. demonstrated that PTEN expression is frequently downregulated in NPC tissue, and that this downregulation is at least partly mediated by microRNA-21 (miR-21), which directly targets PTEN transcripts and suppresses their translation [15]. Additional mechanisms of PTEN inactivation include somatic point mutations, allelic deletions, and epigenetic silencing through promoter hypermethylation, each of which may contribute to varying degrees of PTEN loss across individual tumors. Xu et al. similarly documented reduced PTEN expression in nasopharyngeal carcinoma tissue, and proposed that such loss contributes to unrestrained activation of the PI3K/AKT/mTOR signaling axis, thereby promoting tumor cell proliferation, survival, and resistance to apoptosis [16]. The wide distribution of CT values observed in the present study is therefore consistent with this mechanistic heterogeneity, reflecting the diversity of molecular alterations that can converge on PTEN inactivation in NPC.

Relationship Between PTEN Expression and Histopathological Type

The central finding of this study that PTEN gene expression did not differ significantly between non-keratinizing SCC and undifferentiated carcinoma ($p = 0.413$), warrants careful interpretation. While the non-keratinizing SCC group exhibited a slightly lower mean CT value (30.45 vs. 33.51), suggesting a trend toward relatively higher PTEN expression compared to undifferentiated carcinoma, this difference was not statistically significant. This null result is partially congruent with, yet also nuanced by, findings reported in the existing literature. Krikelis et al., in a study profiling 21

biomolecules in locally advanced NPC among Caucasian patients, found that WHO Type II/III tumors (non-keratinizing, both differentiated and undifferentiated) were significantly more frequently PTEN-positive compared to Type I tumors, suggesting that PTEN loss is more characteristic of the keratinizing subtype . This observation implies that differences in PTEN expression may be more pronounced when keratinizing SCC is included as a comparator group, a comparison that was not possible in the present study due to the complete absence of Type I cases. Xu et al. similarly reported that PTEN protein loss occurred in approximately 58.1% of keratinizing SCC cases compared to approximately 30.8% in non-keratinizing subtypes, further supporting the notion that the magnitude of PTEN inactivation may differ most substantially between keratinizing and non-keratinizing categories rather than within the non-keratinizing group itself [16]. The absence of a statistically significant difference between non-keratinizing SCC and undifferentiated carcinoma in the present study may therefore reflect the fact that both subtypes share similar EBV-driven oncogenic mechanisms, which may produce comparable degrees of PTEN pathway dysregulation through overlapping molecular routes.

At the genomic level, Ali et al. conducted comprehensive genomic profiling across NPC subtypes and found that PTEN mutations were detected in approximately 11% of nasopharyngeal squamous cell carcinoma (NPSCC) cases, encompassing keratinizing histology, ranking among the top five driver gene mutations in that subtype [17]. In contrast, PTEN mutations were notably absent from the most commonly mutated genes in undifferentiated NPC (NPUC), which instead showed a predominance of mutations in genes such as IDH2 and components of the NF-κB pathway [18]. This genomic evidence lends further support to the interpretation that PTEN alterations may be a more prominent feature of keratinizing NPC, and that the distinction in PTEN expression between non-keratinizing subtypes as examined in this study, may be insufficiently large to yield statistical significance, particularly with a modest sample size. Wu et al. further demonstrated that NPC patients with negative PTEN expression had significantly shorter progression-free survival compared to PTEN-positive patients, and identified histopathological subtype as an independent predictor of PTEN-negative status on multivariate analysis, highlighting the clinical and prognostic relevance of PTEN expression in NPC management [19].

Several limitations of this study must be acknowledged. First, the sample size of 38 patients, while sufficient for initial exploratory analysis, may have been inadequate to detect a statistically significant difference in PTEN expression between the two histopathological groups, particularly given the relatively wide standard deviations observed in both groups. The unequal distribution between groups (23 vs. 15 patients) further reduced statistical power. Second, the absence of a healthy control group, comprising normal nasopharyngeal mucosal tissue, precluded direct comparison of PTEN expression between malignant and non-malignant tissue, which would have provided important context regarding the magnitude and direction of PTEN downregulation in NPC relative to normal baseline expression. Third, PTEN expression was assessed solely at the mRNA level using RT-qPCR; protein-level assessment through immunohistochemistry (IHC) or Western blotting would provide complementary data and allow for more direct correlation with functional PTEN activity. Fourth, the complete absence of keratinizing SCC cases limited the ability to compare PTEN expression across all three WHO histopathological subtypes, restricting the comparative analysis to two non-keratinizing groups that may share more molecular similarities than differences.

The findings of this study suggest several important avenues for future research. Studies with larger, more balanced sample sizes across all three WHO histopathological subtypes including keratinizing SCC are needed to more definitively characterize the relationship between PTEN expression and NPC histopathology. Future investigations should incorporate both mRNA quantification and protein-level assessment of PTEN, alongside evaluation of upstream regulatory mechanisms such as miR-21 expression and PTEN promoter methylation status, to provide a more comprehensive picture of PTEN regulation in NPC. Additionally, the inclusion of healthy control tissue would allow for normalization of PTEN expression relative to non-malignant mucosa, strengthening the interpretability of molecular findings.

CONCLUSION

This study demonstrated that the majority of NPC patients at Adam Malik General Hospital Medan were male, in the productive age group of 41–60 years, and presented with locally advanced disease at Stage III or IV at the time of diagnosis. The

predominant histopathological subtype was non-keratinizing squamous cell carcinoma (60.5%), followed by undifferentiated carcinoma (39.5%), consistent with the well-established pattern of NPC in Southeast Asian endemic regions where Epstein-Barr virus-driven non-keratinizing subtypes predominate. PTEN gene expression, as measured by RT-qPCR CT values, demonstrated considerable inter-individual variability across the study population, with a mean CT value of 31.73 (SD ± 6.27) and a wide range of 21.09 to 39.46, reflecting the molecular heterogeneity inherent to NPC pathogenesis.

The primary finding of this study was that there was no statistically significant difference in PTEN gene expression between non-keratinizing squamous cell carcinoma and undifferentiated carcinoma subtypes ($p = 0.413$), suggesting that PTEN expression does not vary meaningfully between these two non-keratinizing histopathological groups within this study population. This result may be attributable to the shared EBV-driven oncogenic mechanisms underlying both subtypes, the absence of keratinizing SCC cases as a comparator group, and the limited sample size. Future studies with larger cohorts encompassing all three WHO histopathological subtypes, combined with both mRNA and protein-level PTEN assessment alongside healthy control tissue, are warranted to more definitively establish the role of PTEN as a molecular biomarker for histopathological classification, prognostication, and targeted therapy in NPC.

DATA AVAILABILITY STATEMENT

The datasets generated and analyzed during the current study are not publicly available due to privacy and ethical considerations. Further inquiries can be directed to the corresponding author.

ETHICAL STATEMENT

This study received ethical clearance from the Research Ethics Committee of Universitas Sumatera Utara with approval number 1503/KEPK/USU/2024.

AUTHOR CONTRIBUTIONS

All authors contributed to the design and implementation of the research, data analysis, and finalizing the manuscript.

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CONFLICT OF INTEREST

Authors declares no conflict of interest.

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