P-ISSN 0215-7284
e-ISSN 25279106
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Immunohistochemistry Profile of Neuroendocrine Tumor of Five Years' Experience at Tertiary Referral Hospital in Palembang

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Received : 02-03-2024
Accepted : 21-07-2023
Published : 31-01-2026

ABSTRACT

Background
Neuroendocrine tumors (NET) are a type of uncommon neoplasms originating from the neuroendocrine cell system. Recent decades, the prevalence of NET gradually increases, attributing partially to the utilization of advanced detection procedures using modern methodologies.

Objective
The aim of this research was to assess the positivity of immunohistochemistry profile of neuroendocrine tumors based on gender and tumor location.

Methods
In this retrospective cross-sectional study, a thorough examination was performed on a total of 71 cases obtained from archives of the Department of Anatomic Pathology Mohammad Hoesin Hospital, over the period from 2017 to 2021. The Chi-square test was used for data analysis. Bivariate analysis was performed using binary logistic regression tests to investigate the correlation between the independent variables, including gender and tumor site, and the dependent variables, including expression of immunohistochemistry.

Results
Out of the 71 recorded samples, 69 samples were subjected to be analyzed while the remaining samples were excluded due to have incomplete data. Four different antibodies were evaluated to find the association between these antibodies and tumor with location (chromogranin, P=0.792; synaptophysin, P=0.100; Ki-67, P=0.026; CD56, P=0.511) and gender (chromogranin, P=0.627; synaptophysin, P=0.929; Ki-67, P=0.315; CD56, P=0.524).

Conclusion
The study showed synaptophysin has the highest positive rate on NET diagnosis. There is no association was found between chromogranin, synaptophysin, and CD56 staining to tumor location, except for Ki-67. Similarly, no association was found between staining performance (chromogranin, synaptophysin, Ki-67, CD56) with gender.

Keywords: CD56, chromogranin, Ki-67, Neuroendocrine tumors, synaptophysin

P-ISSN 0215-7284
e-ISSN 25279106
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INTRODUCTION

Neuroendocrine tumors encompass a diverse range of neoplasms, require a comprehensive approach involving several clinical and imaging investigations for optimal evaluation and treatment. The initial description of these tumors and the introduction of the word "carcinoid" (or "karzinoide") were attributed to Oberndofer in 1907.[1] Patients with NET are frequently diagnosed with metastatic disease prior to seeking medical treatment due to their perceived rarity and potential lack of specificity in their manifestation, although this circumstance does not necessarily exclude the possibility of pursuing curative surgical intervention or surgical debulking.[2]

The prevalence of NET is reported to be 2 cases per 100,000 individuals, constituting around 0.5% of all malignancies. In United States, the incidences of NET has increased five-fold over the course of the last three decades, resulting in an annual diagnosis rate of five cases per 100,000 individuals.[3] Neuroendocrine tumors show a lower incidence among pediatric populations, whereas their prevalence is comparatively higher among those aged 50 years and above. The prevalence of NET is twice in males compared to females. The prevalence of NET appears to have risen in recent years, primarily attributed to enhanced detection methods utilizing advanced techniques such as endoscopy, computed tomography (CT), magnetic resonance imaging (MRI), ultrasonography, and scintigraphy.[4,5]

Neuroendocrine tumors are a distinct category of malignant neoplasms, notable for their capacity to produce bioactive peptides that can induce symptoms such as flushing and diarrhea.[6] Neuroendocrine tumors are neoplastic proliferations originating from neuroendocrine cells. The primary sites of occurrence for these neoplasms are the gastrointestinal system (48%), lung (25%), and pancreas (9%). However, they can also manifest in several other organs, such as the breast, prostate, thymus, and skin.[7] Neuroendocrine cells possess the capacity to synthesize hormones, including serotonin, leading to manifestations such as flushing and diarrhoea.[8] Additionally, these cells create additional proteins, such as chromogranin A, which act as biomarkers for NET. Neuroendocrine tissues commonly express the presence of somatostatin receptors on their cellular membranes.[9,10]

The biological behavior of NET is influenced by three clinicopathologic criteria, including grade, differentiation, and stage.[6] The histologic grade of this tumor indicates its biological aggressiveness. There exist two primary characteristics related to the grading of cancer. Firstly, the Ki-67 index, which quantifies the proportion of cancer cells exhibiting positive staining for Ki-67, a marker indicative of cellular proliferation, and secondly the mitotic rate, which records the quantity of mitotic events observed within 10 high-power microscopic fields. Differentiation refers to the degree of resemblance exhibited by neoplastic cells to their non-neoplastic counterparts in the originating tissue. Cancer cells that are well-differentiated exhibit a close resemblance to non-neoplastic cells, whereas poorly differentiated cancer cells lack this resemblance. Typically, low-grade tumors (grades 1 and 2) have a high degree of differentiation, while high-grade tumors (grade 3) show a low degree of differentiation.[11,12] The stage of cancer is determined by the degree of tumor spread throughout the body.[13]

Chromogranin, synaptophysin, and CD56 are widely suggested as markers for the identification of lung tumors with neuroendocrine differentiation. These indicators are often used for the purpose of establishing the diagnosis of typical carcinoid, atypical carcinoid, small cell lung cancer, and large cell neuroendocrine carcinoma (LCNEC).[14] Not only that, Ki-67 index also has an important role in neuroendocrine tumor which is related to the grade of NETs. The evaluation of the grade has significant importance in the prognostication and determination of treatment strategies for NET, alongside with additional factors like tumor size, lymphovascular invasion, and disease stage.[15] The objective of this study was to assess the correlation between gender and tumor location of NET and IHC expression (chromogranin, synapthopysin, CD56 and Ki-67) at Moh. Hoesin General Hospital Palembang.

METHODS

A retrospective cross-sectional study was conducted on 71 cases of neuroendocrine neoplasms were extracted from the anatomical pathology archives of the computerized medical records of the Departments of Anatomic Pathology Mohammad Hoesin Hospital, over

Maj Patol Indones 2026; 35(1): 1010-1016
DOI: 10.55816/mpi.v35i1.664

P-ISSN 0215-7284
e-ISSN 25279106
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the period from 2017 to 2021. A comprehensive analysis was conducted on a total of 71 cases which two pathologists assessed a various number of histologic sections, ranging from three to ten hematoxylin and eosin (H&E) stained cases. The H&E-stained slides were examined for each case to identify the most representative section.

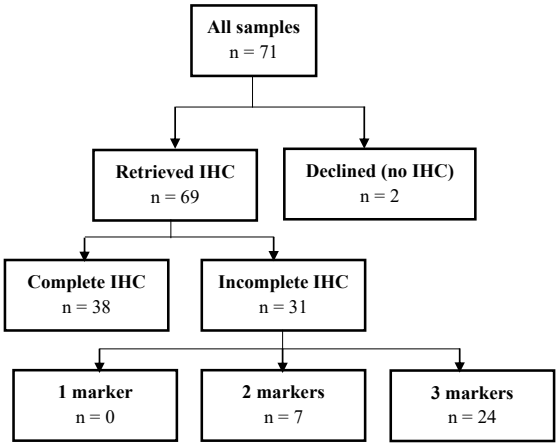

Figure 1. Flow diagram of inclusion and exclusion samples.

Only cases which the diagnosis was confirmed by the authors was included in the study. A total of 69 cases were selected for the study and they were divided into complete and incomplete IHC examinations. We classified samples as incomplete IHC when there were less than four IHC examinations and complete IHC when sample stained with chromogranin, synaptophysin, CD56 and Ki-67. Inclusion criteria for this study are all the tissues from biopsy and tissue surgery with histopathology of neuroendocrine neoplasms. Meanwhile, the exclusion criteria are neuroendocrine neoplasm without immunohistochemistry examination (Figure 1).

The statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) 26. Positivity was defined as >1% positive tumor cells. Univariate analysis was performed by displaying frequency distributions for categorical variables, and measures of central data tendency (mean/median) for numerical variables. To determine whether numerical variables were normal, the Saphiro-Wilk test was applied. Data analysis was using Chi-square test. The bivariate analysis was performed with binary logistic regression tests to examine the relationship between the independent variables (sex and tumor location) and the dependent variable (four staining outcomes of NET). Statistical significance was attributed to P-values <0,05.

RESULTS

From recorded 71 samples, 69 samples were included in the analysis. From the 71 samples, 38 were stained with all four immunohistochemical agents, 24 were stained with three immunohistochemical agents, seven were stained two, and two were not stained with any included histochemical agent. This study recorded 23 different tumor locations, which were further classified into four groups, namely intraabdominal, musculoskeletal, respiratory, and others. According to the result of this study (Table 1), intraabdominal is the most common site of tumor location with total frequency 32 out of 69 cases included. The subjects mean age was 43.96 years old with median was 45 and a standard deviation of 17.37.

Table 1. Characteristic of Study Population According to Sex and Tumor Location.

Variable	Frequency	Percentage
Tumor Location		
Intraabdominal	32	46.4
Musculoskeletal	6	8.7
Respiratory	14	20.3
Other	17	24.6
Sex		
Female	33	47.8
Male	36	52.2

Three markers were assessed (Table 2), resulting in varying outcomes. Chromogranin staining recorded in 60 samples as positive and 9 samples as negative, synaptophysin staining recorded in 60 samples as positive and 8 samples as negative, while 1 sample was not stained with it. In addition, Ki-67 staining recorded in 35 samples as positive ≥20% and 25 samples as positive <20% whereas 9 samples were not stained with it. Lastly the CD56 staining recorded in 34 samples as positive and 8 samples as negative while 27 were not stained with it.

Table 2. Positive rate of neuroendocrine markers.

IHC	Positive	Negative	Percentage of Positivity
Chromogranin	60	9	86.9
Synaptophysin	60	8	88.2
CD-56	34	8	80.9

Maj Patol Indones 2026; 35(1): 1010-1016
DOI: 10.55816/mpi.v35i1.664

P-ISSN 0215-7284
e-ISSN 25279106
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The relationship between sex and tumor location with chromogranin staining, can be observed on Table 3. The positive chromogranin staining was mostly found in female. There were 60 cases with positive result consist of intraabdominal (26 cases), musculoskeletal (5 cases), respiratory (14 cases), and others (15 cases).

Table 3. Chromogranin Staining Cross Tabulation.

Variables	Chromogranin – N (%)		P*
	Negative	Positive	
Sex			0.294
Female	6 (18.2%)	27 (81.8%)	
Male	3 (8.3%)	33 (91.7%)	
Tumor Location			0.356
Intraabdominal	6 (18.8%)	26 (81.3%)	
Musculoskeletal	1 (16.7%)	5 (83.3%)	
Respiratory	0 (0%)	14 (100%)	
Others	2 (11.8%)	15 (88.2%)	

*Fisher's Exact Test

The relationship between sex and tumor location with synaptophysin staining, can be observed on Table 4. The positive synaptophysin staining was mostly found in male. There were 60 cases with positive result consist of intraabdominal (27 cases), musculoskeletal (6 cases), respiratory (13 cases), and others (14 cases).

Table 4. Synaptophysin Staining Cross Tabulation.

Variables	Synaptophysin – N (%)		P*
	Negative	Positive	
Sex			1.000
Female	4 (12.1%)	29 (87.9%)	
Male	4 (11.4%)	31 (88.6%)	
Tumor Location			0.810
Intraabdominal	4 (12.9%)	27 (87.1%)	
Musculoskeletal	0 (0%)	6 (100%)	
Respiratory	1 (7.1%)	13 (92.9%)	
Others	3 (17.6%)	14 (82.4%)	

*Fisher's Exact Test

The relationship between sex and tumor location with CD56 staining, can be observed on Table 5. The positive CD56 staining in female was higher than male. There were 34 cases with positive result consist of intraabdominal (14 cases), musculoskeletal (3 cases), respiratory (10 cases), and others (8 cases).

Table 5. CD56 Staining Cross Tabulation.

Variables	CD56 – N (%)		P*
	Negative	Positive	
Sex			0.700
Female	3 (15%)	17 (85%)	
Male	5 (22.7%)	17 (77.3%)	
Tumor Location			0.588
Transabdominal	4 (22.2%)	14 (77.8%)	
Musculoskeletal	0 (0%)	3 (100%)	
Respiratory	1 (9.1%)	10 (90.9%)	
Others	3 (30%)	7 (70%)	

*Fisher's Exact Test

The relationship between sex and tumor location with Ki-67 staining, can be observed on Table 6. The positive Ki-67 staining was mostly found in male. There were 42 cases with high grade positivity result consist of intraabdominal (19 cases), musculoskeletal (3 cases), respiratory (12 cases), and others (8 cases).

Table 6. Ki-67 Staining Cross Tabulation.

Variables	Ki-67 – N (%)		P
	Positive <20%	Positive ≥20%	
Sex			0.315*
Female	12 (41.4%)	17 (58.6%)	
Male	6 (19.4%)	25 (80.6%)	
Tumor Location			0.015**
Intraabdominal	12 (38.7%)	19 (61.3%)	
Musculoskeletal	1 (25%)	3 (75%)	
Respiratory	1 (7.7%)	12 (92.3%)	
Others	4 (33.3%)	8 (66.7%)	

*Chi-Square Test; **Fisher's Exact Test

Chi-square analysis found no association between sex, tumor location, and staining performance illustrated on Table 3, 4, 5, and 6. Logistic regression test found similar results, in which neither sex nor tumor location contributes to the prediction of staining performance. The logistic regression was done with each independent bivariate variable (Table 7).

Table 7. Binary Logistic Regression Analysis between Sex, Tumor Location, and Staining.

Dependent Variable	Independent Variable	P value	Odds Ratio (95% CI)
Chromogranin staining	Sex (male)	0.235	0.409 (0.093–1.790)
	Tumor Location (non-intraabdominal)	0.159	0.305 (0.059 – 1.592)
Synaptophysin staining	Sex (male)	0.929	0.935 (0.214– 4.091)
	Tumor Location (non-intraabdominal)	0.790	0.818 (0.187– 3.581)
Ki-67 staining	Sex (male)	0.317	0.589 (0.209–1.659)
	Tumor Location (non-intraabdominal)	0.109	0.422 (0.147 – 1.213)
CD56	Sex (male)	0.527	1.667 (0.343 – 8.103)
	Tumor Location (non-intraabdominal)	0.651	0.700 (0.149–3.282)

DOI: 10.55816/mpi.v35i1.664

P-ISSN 0215-7284
e-ISSN 25279106
Accredited by KEMENRISTEKDIKTI/Sinta-4

DISCUSSION

The objective of this study is to find out the profile of neuroendocrine tumors of 5 years experiences in our hospital. The data was acquired from a tertiary referral hospital that located in Palembang. In the beginning, a total of 71 patients diagnosed with NET were included in the dataset. Furthermore, the study was restricted to 69 data as a result of constraints in the available data. Four different staining procedures were assessed in order to examine the relationship between staining procedures and as well as tumor location. Similar results also found in the research that conducted by Kriegsmann et al,[14] where there are no significant difference of sex and age were observed with and without expression of neuroendocrine markers.

The intraabdominal region is the primary location for tumor development, accounting for a total frequency of 32 out of the 69 cases included in the study, followed by the other 3 tumor locations. Study that performed by Muralidhar et al[16] shows that the duodenum was found to be the most frequently affected site, resulting in 28.8% (n=17) of cases, followed by the rectum at 22% (n=13). The esophagus and gastroesophageal junction showed the lowest frequency. Similar result also performed in study by Stephanie et al,[17] that indicates rectum as the most frequent site for NET, followed by the pancreas. Another study that from Dasari et al[18] reveals that the small intestine, rectum, pancreas, stomach, and appendix are the most often primary locations in NET, listed in that order. According to study by Yao et al,[19] there was a significant difference in the sites of the primary tumors among the patients determined by their sex (P=0.001). The incidence of NET in several anatomical sites differed between female and male patients. Female patients showed a greater probability of having a primary NET in the lung, stomach, appendix, or cecum. On the other hand, male patients demonstrated a higher possibility of having primary tumor in the thymus, duodenum, pancreas, jejunum/ileum, or rectum.

CONCLUSION

In summary, our study revealed synaptophysin has the highest positive rate on NET. Results indicated no association found between staining positivity (chromogranin, synaptophysin, Ki-67, CD56) with gender. There is no association found between chromogranin, synaptophysin, and CD56 staining to tumor location, except for Ki-67.

Acknowledgements

We have received ethical approval from the institutional board review of Mohammad Hoesin General Hospital (Ref. No. DP.04.03/D.XVIII.06.08/ETIK/168/2024)

Funding

Not applicable.

Authors' contributions

Sandria, as an author, that substantially contributed to the conception and the design of the study, she been contributed to manuscript drafting, approved of the final manuscript version to be published, and agreed to be accountable for all aspects of the work, so that any questions relating to research integrity or scientific accuracy in any part of the study are appropriately investigated and resolved. Krisna Murti as a co-author, that substantially contributed to the acquisition, analysis and interpretation of the data; she been contributed to critical revisions on the intellectual content, approved of the final manuscript version to be published, and agreed to be accountable for all aspects of the work, so that any questions relating to research integrity or scientific accuracy in any part of the study are appropriately investigated and resolved.

Conflict of interests

The authors declare that they have no conflict of interests.

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Maj Patol Indones 2026; 35(1): 1010-1016
DOI: 10.55816/mpi.v35i1.664