The Relationship of SRY Determining Region Y Box 2 (SOX2) Immunohistochemical Expression with Stromal and Intratumoral TILs (Tumor Infiltrating Lymphocytes) in Patients with Ovarian Serous Tumors

Abdul Hamid Hasan*, Delyuzar, Tengku Kemala Intan, Joko S Lukito, Jessy Chrestella, Tengku Ibnu Alferraly

[a]Master in clinical medicine, Anatomical Pathology, Faculty of Medicine, University of North Sumatra, University of North Sumatra Hospital
[b]Department of Anatomical Pathology, Faculty of Medicine, University of North Sumatra, Hospital, University of North Sumatra
email: hamidhasannas@gmail.com

Abstract

Background: Ovarian serous tumors are the most common epithelial tumors in premenopausal and postmenopausal, 60% of the most common cases are ovarian cystadenoma, 25% of low grade and highgrade serous carcinoma. Tumor infiltrating lymphocytes (TILs) is used to predict the prognosis some solid tumors. SRY (sex determining region Y)-box 2 (SOX2) is a transcription factor. High SOX2 in ovarian tumors associated with reduced disease-free survival.
Research Objective: To determine the relationship between SOX2 expression and TILs in patients with a diagnosis of ovarian serous tumor at the Anatomic Pathology Laboratory, USU Medical Faculty and RSUP. H. Adam Malik Medan.
Materials and Methods: 39 samples histopathological slides with a diagnosis of ovarian serous tumor, slide review was performed and TILs assessed and then SOX2 immunohistochemical staining and then analyzed for correlation between variables using Eta test ($p<0.001$) and Somer'sd test ($p=0.120$).
Results: The highest expression of SOX2 high was in the highgrade serous carcinoma subtype in 9 (23.1%) cases. Most cases were also found in low SOX2 expression with low iTILs in 20 (51.3%) cases and low SOX2 expression with low sTILs in 16 (41.0%) cases. There was a significant relationship between subtypes and SOX2 expression ($p < 0.001$) and the Somers'd correlation showed no significant relationship between SOX2 and TILs ($p = 0.120$).
Conclusion: In this study, there was a correlation between tumor subtypes and SOX2 expression and there was no correlation between SOX2 expression and TILs in ovarian serous tumors.

Keywords: Sex determining region Y box 2, ovarian serous tumor.

INTRODUCTION

Ovarian tumors are neoplasms found in the female genital system with an incidence of 30% of all cancers in the female genitalia.[1] These tumors can originate from the epithelium, germ cells, stromal cells and tumor metastases to the ovaries.[2] Epithelial ovarian tumors are the result of a group of changes and genetic mutations that cause unusual transformation of epithelial cells, stem cells or metaplasia in the primary tumor area, either from the ovary or fallopian tube.[3] One type of ovarian epithelial tumor is ovarian serous tumor. Based on the WHO classification 2020, serous ovarian tumors are divided into 3 parts, namely serous cystadenoma NOS, borderline serous tumor and serous carcinoma.[4] Almost 90% of all serous ovarian tumors are epithelial types characterized by diverse and molecular histopathological features.[5]

Based on data from the Global Burden of Cancer (GLOBOCAN) released by the World Health

Organization (WHO) stated that the number of new cases discovered in 2020 was 313,959 cases and 207,252 deaths in the world.6 In Indonesia, the incidence of ovarian cancer in 2020 was recorded as 14,896 (3.8%) new cases with an incidence rate of 10.0 per 100,000 population. Ovarian cancer also has a high mortality rate, which is 6.6 per 100,000.[6] Based on data from Litbangkes (2019), ovarian cancer ranks 3rd most cases of cancer in women in Indonesia after breast cancer and cervical cancer.[4] Ovarian serous tumors are the most common type of the 4 common types of epithelial tumors on the ovary as much as 35-40% of all epithelial ovarian tumors with variations in patient age ranging from 40-60 years.[7] Ovarian serous tumors also are the most common epithelial tumors in premenopausal and postmenopausal, 60% of the most common cases are ovarian cystadenoma, 25% of low grade and highgrade serous carcinoma.[8]

Sex-determining region Y box containing (SOX) is a transcription factor that plays an important role as a tumor suppressor or promoter in carcinogenesis. Based on some evidence shows that SOX protein plays a role in various tumor events such as migration, development, proliferation, regulation and differentiation of cells and apoptosis. The role of SOX-genes is currently a focus in the field of research due to an increase in morbidity and mortality from the incidence of gynecological cancer from year to year. The level of expression of SOX-genes is considered a biomarker associated with clinical features in gynecologic cancer patients. Therefore, SOX-genes are very important in the development of diagnostic, therapeutic and prognostic patients.[9,10]

Sex-determining region Y (SRY)-box 2 (SOX2) is a group of SOX genes consisting of transcription factors that are important in the regulation of developmental processes and cell type specification. Overexpression of the SOX2 gene was found in at least 25 types of cancer.[11] In advanced ovarian cancer, SOX2 expression was found to be higher. High SOX2 overexpression in ovarian cancer is associated with decreased disease-free survival.[12] The SOX2 gene (sex-determining region Y (SRY)-box 2) is located on chromosome 3p26.3-q27 and encodes a protein of 317 amino acids consisting of three the main domains, namely: the high mobility group (HMG) domain at the N-terminal, the dimerization domain (DIM) at the center and transactivation (TAD) and the C-terminal domain. As a transcription factor, SOX2 recognizes and binds to the promoter of various target genes via its TAD domain to transactivate or suppress their expression thereby regulating various physiological processes. SOX2 has an important role in maintaining the stem cell phenotype of embryonic stem cells (ESCs).[13]

High SOX2 expression may serve as a prognostic biomarker. This is due to the importance of SOX2 in the initiation and progression of tumorigenesis. Overexpression or amplification of SOX2 is frequently observed in various tumor types but is still correlated with prognostication of patient survival.[13] Lee, J, et al (2021) conducted a study on the prognostic value of SOX2 and CD8+ TILs in small cell lung carcinoma (SCLC). SOX2 is a transcription factor that regulates the neuronal differentiation of pluripotent and embryonic stem cells into neuroendocrine cells during lung development. The number of CD8+ TILs and the expression level of SOX2 were evaluated by immunohistochemistry using paraffin-embedded tissue sections. SOX2 is involved in carcinogenesis including small cell lung carcinoma (SCLC). In in vitro studies, suppression of the SOX2 gene blocks the proliferation of SCLC cell lines. In a clinical study, high SOX2 expression in SCLC was significantly associated with poor prognosis.[14]

Tumor Infiltrating Lymphocytes (TILs)consists of a heterogeneous collection of lymphoid cells that exhibit diverse antitumor activity and spatial distribution, characterized by the expression of several molecular biomarkers such as CD8, CD3, CD4, CD103 and PD-1.[15] Accumulation of TILs in ovarian cancer is prognostic for increased survival while increasingimmunosuppressive regulatory T cells (Tregs)associated with poor outcomes. Approaches that favor tumor-reactive TILs may limit tumor progression. However, identifying tumor-reactive TILs in ovarian cancer remains a challenge.[16]

To date, there has been no research on the relationship between SOX2 expression and TILs in ovarian cancer. Therefore, the researcher wanted to know the expression and relationship based on SOX2 subtype to histopathological tissue TILs with the diagnosis of serous ovarian tumors in patients in Medan.

MATERIALS AND METHODS

There were 39 samples histopathological slides with a diagnosis of ovarian serous tumor that were collected in Adam Malik General Hospital Medan, after obtaining approval from the Health Research Ethics Committee, Faculty of Medicine, University of North Sumatra.

Slides were reviewed,then serous ovarian tumor TILs were assessed double blind by the researcher and two anatomic pathologists, then SOX2 immunohistochemical staining was performed SOX2 monoclonal mouse antibody (Bioassay Technology Laboratory) at a dilution of 1:200 and the expression was assessed. Bivariate analysis is used to see the relationship between two variables. The relationship of SOX2 with ovarian serous tumor subtypes using the ETA correlation test, while to see the relationship of SOX2 with iTILs and sTILS using the Somers correlation test. The p value < 0.005 was stated to be statistically significant.

RESULTS

In this study, the number of samples obtained was 39 samples that met the inclusion criteria in this studyAdam Malik General Hospital Medanwhich aims to determine the expression of SOX2 (sex-determining region Y (SRY)-box 2) with TILs (Tumor Infiltrating Lymphocytes) in ovarian serous tumors.

Table 1. Frequency Distribution of Age, Tumor Subtype, Size, SOX2 Expression, TILs Expression.

	Amount	Percentage
age		
● <50 years	18	46.2
● 50 – 60 years	14	35.9
● >60 years	7	17.9
Ovarian involvement and tumor size		
Unilateral ovary		
Right Ovary		
<8cm	4	10.2
8cm	4	10.2
Left Ovary		
<8cm	8	20.5
8cm	10	25.6
Bilateral ovaries		
<8cm	5	12.8
8cm	8	20.5
Ovarian serous tumor subtype		
● Benign	20	51.3
● Borderline	0	0
● Low Grade	2	5.1
● High Grade	17	43.6
SOX2 Expression		
● Low Grade	28	71.8
● High Grade	11	28.2
iTIL expression		
● Low	30	76.9
● High	9	23.1
sTILs . expression		
● Low	24	61.5

● High	16	38.5

Based on Table 1, the distribution of ovarian serous tumor samples was the most in the age group<50 years were 18 cases (46.2%), followed by the age group 50-60 years with 14 cases (35.9%), and >60 years with 7 cases (17.9%).The mean age of the patients in this study ranged from52.23±8.16years, where the youngest is 40 years old and the oldest is 70 years old. In this study also found the most benign serous tumors at the age <50 years as many as 10 cases and low grade serous tumors at the age> 50 years as many as 2 cases. In high grade serous tumors, there was no age difference between >50 and <50 years, as many as 9 and 8 cases, respectively.

This study investigated the size of ovarian serous tumors and divided them based on unilateral and bilateral ovarian involvement, where ovarian serous tumors were more common in 26 (66.6%) cases unilaterally than bilaterally in 13 (33.3%) cases. Unilateral serous ovarian tumors were more common in the left ovary as many as 18 cases with the most tumors measuring 8 cm in 10 cases (25.6%) compared to tumors measuring <8 cm in 8 (20.5%) cases. On the unilateral right ovary, an even distribution was found between tumors measuring 8 cm and <8 cm, in 4 (10.2%) cases. Bilateral serous ovarian tumors were more common with tumors measuring 8 cm in 8 (20.5%) cases compared to tumors measuring <8 cm in 5 (12.8%) cases.

Based on microscopic examination of ovarian serous tumor samples with hemaktoxylin and eosin staining, sovarian tumor subtypes were divided into four groups. Most of the patients had benign serous tumors in 20 cases (51.3%), followed by high grade serous tumors in 17 cases (43.6%), low grade serous tumors in 2 cases (5.1%) and no cases found. -cases of serous borderline tumors.

Based on the expression of SOX2, the majority of cases expressed low grade as many as 28 cases (71.8%) compared to high grade which were found to be 11 cases (28.2%). Assessment of iTILs expression was found to be mostly low expressed in 30 (76%) cases compared to high expression which was found in 9 cases (23.1%). Expression of sTILs was also found mostly in low expression in 24 cases (61.5%) compared to high expression in 16 cases (38.5%).

Table 2. Distribution and Correlation of Ovarian Serous Tumor Subtypes with SOX2 Expression.

Variable	SOX2 Expression		Total	value	p*
	Low	High			
	f(%)	f(%)	f(%)		
Serous Tumor					
Benign	20 (51.3)	0 (0,0)	20 (51.3)		
Borderline	0 (0,0)	0 (0,0)	0 (0,0)	0.681	<0.001
Low Grade	0 (0,0)	2 (5,1)	2 (5,1)		
High Grade	8 (20.5)	9 (23.1)	17 (43.6)		
Total	28 (71.8)	11 (28.2)	39 (100.0)		

*) Eta correlation test

In table 2, the analysis between SOX2 expression and ovarian tumor subtypes found that cases with high SOX2 expression were mostly found in the high grade serous carcinoma subtype as many as 9 (23.1%) cases, followed by low grade serous carcinoma which was found in 2 (5 ,1%) cases and found no positive benign serous tumor with high SOX2 expression. On the other hand, most of the SOX2 expression was low in the subtype of benign serous tumor in 20 (51.3%) cases followed by high grade serous carcinoma which was found in 8 (20.5%) cases. The results of the Eta correlation test between ovarian serous tumor subtypes and SOX2 expression showed that there was a significant correlation, with $p < 0.001$ ($p < 0.005$).

Table 3. Distribution and Correlation of SOX2 Expression with iTILs Expression

Variable	iTIL expression		Total	value	p*
	Low	High			
	f(%)	f(%)	f(%)		
SOX2 Expression					
Low	20 (51.3)	8 (20.5)	28 (71.8)	-0.195	0.120
High	10 (25.6)	1 (2.6)	11 (28.2)		
Total	30 (76.9)	9 (23.1)	39 (100.0)		

*) Somers'd correlation test

In table 3, the analysis of the correlation between SOX2 expression and TILs in this study shows that high SOX2 expression was more commonly found in the group with low iTILs expression in 10 (25.6% cases) compared to high iTILs expression which was found in 1 (2 ,6%) cases. Likewise, low SOX2 expression was also more commonly found in the group with low iTILs expression in 20 (51.3%) cases compared to high iTILs expression in 10 (25.6%) cases. The results of the Somers'd correlation test between SOX2 expression and iTILs did not show a significant correlation (p>0.005).

Table 4. Distribution and Correlation of SOX2 Expression with Expression of sTILs.

Variable	sTILs . expression		Total	value	p*
	Low	High			
	f(%)	f(%)	f(%)		
SOX2 Expression					
Low	16 (41.0)	12 (30.8)	28 (71.8)	-0.166	0.346
High	8 (20.5)	3 (7,7)	11 (28.2)		
Total	24 (61.5)	16 (38.5)	39 (100.0)		

*) Somers'd correlation test

Table 4 shows that the highest expression of SOX2 was found in the low expression of sTILs in 8 cases (20.5%) compared to the high expression of sTILs in 3 cases (7.7%). The lowest expression of SOX2 was found in the low expression of sTILs in 16 (41%) cases compared to the high expression of sTILs in 12 (30.8%) cases. The low expression of SOX2 was expressed the most in the low expression of str-TILs in 16 (41%) cases compared to the high expression of sTILs in 12 (30.8%) cases. The results of the correlation test of SOX2 expression with sTILs, it was found that there was no significant correlation between SOX2 expression and sTILs, with a p value of 0.346 (<0.005).

DISCUSSION

In this study, controversial results were found where patients with high grade ovarian serous tumors were most commonly found in the <50 years age group (46.2%). Based on the literature, it was found that the majority of patients with ovarian serous tumors were 40-60 years old.4 Research by Nicole et al. found a mean age of 33 - 88 years.[18] This is in contrast to the study conducted by Kim et al. which showed that serous ovarian tumors were more common in the age group >60 years (35.8%), followed by the age group 50-59 years (32.2%), and <50 years (32.1%).[17] Some Age differences are caused by several etiological factors, including genetic deviations that are influenced by hormone exposure and inherited susceptibility genes.

Based on the histopathological subtype of ovarian serous tumor, the most common benign subtype found in this study. Nicole et al. found that the most cases were found in serous ovarian tumor with high grade subtype as many as 19 samples followed by cystadenoma in 11 samples and borderline in 1 sample.[18] Research by Xua et al. found 55 cases (67%) of high grade subtype, while in 27 cases (33%) other types.[19]

This study investigated the size of ovarian serous tumors and divided them based on unilateral and bilateral ovarian involvement, where ovarian serous tumors were more common in 26 (66.6%) cases unilaterally than bilaterally in 13 (33.3%) cases. Unilateral serous ovarian tumors were more common in the left ovary in 18 cases with the most tumors measuring 8 cm in 10 cases (25.6%) compared to tumors measuring <8 cm in 8 cases (20.5%). On the unilateral right ovary, an even distribution was found between tumors measuring 8 cm and <8 cm, in 4 (10.2%) cases. Bilateral serous ovarian tumors were more common in 8 cases (20.5%) with tumors measuring 8 cm compared to 5 cases (12.8%) with tumors measuring <8 cm. The size of the tumor is radiologically important for examination and can provide clues for diagnosing serous ovarian tumors, both benign and malignant. Thus, the radiologist should be aware of this entity and familiar with its radiological findings in order to optimize the imaging protocol in order to obtain appropriate treatment. The size of the tumor in this study, both unilateral and bilateral ovarian involvement, the results were the same, which was more commonly found in the size 8 cm and mostly found in the left ovary (25.6%). The research of Amante et al. explained that the tumor size radiologically in serous ovarian tumors was >5cm.20 The radiologist should be aware of this entity and familiar with its radiological findings in order to optimize the imaging protocol in order to obtain appropriate treatment. The size of the tumor in this study, both unilateral and bilateral ovarian involvement, the results were the same, which was more commonly found in the size 8 cm and mostly found in the left ovary (25.6%). The research of Amante et al. explained that the tumor size radiologically in serous ovarian tumors was >5cm.[20] The radiologist should be aware of this entity and familiar with its radiological findings in order to optimize the imaging protocol in order to obtain appropriate treatment. The size of the tumor in this study, both unilateral and bilateral ovarian involvement, the results were the same, which was more commonly found in the size 8 cm and mostly found in the left ovary (25.6%). The research of Amante et al. explained that the tumor size radiologically in serous ovarian tumors was >5cm.20Pannu's study found that the size of the serous ovarian tumor was borderline different with unilocular and multilocular CT scans, found to be 1-5 cm in size with bilateral ovarian involvement.[21]

This study found low grade SOX2 expression in benign serous tumors as much as 51.3%. On Research Ye et al. Immunohistochemical results showed that the positive ratio of SOX2 expression gradually increased from benign and borderline ovarian tumors to malignant as much as 55.81% normal ovarian epithelium 65% serous and mucinous cystadenomas, 70% borderline serous and mucinous cystadenomas, and 91% serous and mucinous cystadenocarcinomas, respectively each expresses SOX2.[22]

High SOX2 expression may serve as a prognostic biomarker. This is due to the importance of SOX2 in the initiation and progression of tumorigenesis. Overexpression or amplification of SOX2 is often observed in various tumor types but is still correlated with prognostication of patient survival. During lung tumorigenesis, SOX2 amplification is more common in high-grade lesions than in low-grade lesions that develop into malignant tumors.[11]

Research conducted by James et al. showed that TILs were associated with histopathological subtypes for all tumors whereas high expression of iTILs and sTILs was associated with a better prognosis. The better prognostic effect on iTILs may be due to activation of iTILs with target cells at the T cell receptor. The lower prognostic effect on sTILs may be due to sTILs not belonging to the tumor microenvironment secreted by tumor cells and/or other stromal cells, to avoid attacks by the immune system.[23]

In this research, hthere was no association between SOX2 expression and intratumoral TILs and stromal TILs. To date, there have been no studies examining the relationship between SOX2 expression and TILs in serous ovarian tumors. However, several studies have shown that high SOX2 expression in ovarian serous tumors is associated with tumor aggressiveness. This indicates the important role of SOX2 in maintaining the basic characteristics of ovarian serous tumors. Expression of SOX2 in cells that cause ovarian serous tumor spread allows tumors to withstand conventional chemotherapy and enhances their tumorigenicity77 However, a study by Le et al on small cell lung carcinoma that did not differentiate between intratumoral and stromal TILs found that high SOX2 and CD8+ TIL expression indicated high overall survival (OS) and progression free survival (PFS). [24]

CONCLUSION

This study showed that there was a correlation between tumor subtypes and SOX2 expression and there was no correlation between SOX2 expression and TILs in ovarian serous tumors.

COMPETING INTEREST

The author has no financial interests that are relevant to the products or company described in this article.

ACKNOWLEDGEMENT

We acknowledge to all staff and resident of Anatomical Pathology Department of North Sumatra University, H. Adam Malik Hospital, Medan, Indonesia for all its help and cooperation.

ETHICAL APPROVAL

The Health Research Ethical Committee, University of North Sumatra, Medan, Indonesia approved this study.

REFERENCES

1. Arania, R., Windarti, I., Characteristics of Ovarian Cancer Patients at Dr. Hospital. H. Abdoel Moeloek Bandar Lampung Year 2009-2013. Juke Unila, 2015.
2. Ravindran, Febina & Choudhary, Bibha. Ovarian Cancer: Molecular ClassificationandTargetedTherapy, 2021. https://doi.org/10.5772/intechopen.95967
3. Kim, J., Park, EY, Kim, O., Schilder, JM, Coffey, DM, Cho, CH, & Bast, RC, Jr. Cell Origins of High-Grade Serous Ovarian Cancer. Cancers, 2018;10(11),433. https://doi.org/10.3390/cancers10110433
4. Indonesian Ministry of Health. Infodatin. RI Health Information and Data Center: The Burden of Cancer in Indonesia. 2019.
5. Mescher AL. Junqueira's Basic Histology Text & Atlas. McGraw Hill. 2017.
6. World Health Organization International Agency for Research on Cancer (IARC). GLOBOCAN 2020: Global Cancer Observatory. 2020. Available from:https://gco.iarc.fr/today/data/factsheets/cancers/25-Ovary-fact-sheet.pdf
7. Folkins AK, Longacre TA. Low-grade Serous Neoplasia of the Female Genital Tract. Surgical pathology 12. 2019; pp.481-513
8. Jones, J. Epithelial ovarian tumors. Reference article, Radiopaedia.org. 2022. https://doi.org/10.53347/rID-18735
9. Sakuragi N, Takeda N, Hareyama H, Fujimoto T, Todo Y, Okamoto K, et al. A multivariate analysis of blood vessel and lymph vessel invasion as predictors of ovarian and lymph node metastases in patients with cervical carcinoma. Cancer. 2000;88:2578-2583.
10. Ashrafizadeh, M., Taeb, S., Hushmandi, K., Orouei, S., Shahinozzaman, M., Zabolian, A., Najafi, M. Cancer and SOX proteins: New insight into their role in ovarian cancer progression/inhibition . Pharmacological Research, 105159. 2020 doi:10.1016/j.phrs.2020.105159
11. Hendry S, Salgado R, Gevaert T, et al. Assessing Tumor-Infiltrating Lymphocytes in Solid Tumors: A Practical Review for Pathologists and Proposal for a Standardized Method from the International Immuno-Oncology Biomarkers Working Group: Part 2: TILSs in Melanoma, Gastrointestinal Tract Carcinomas, Non-Small Cell Lung Carcinoma and Mesothelioma, Endometrial and Ovarian Carcinomas, Squamous Cell Carcinoma of the Head and Neck, Genitourinary Carcinomas, and Primary Brain Tumors. Adv Anat Pathol. 2017;24(6):311-335. doi:10.1097/PAP.0000000000000161.
12. Zhang S, Xiong X, Sun Y. Functional characterization of SOX2 as an anticancer target. Signal Transduct Target Ther. 2020; 5:135. Doi: 10.1038/s41392-020-00242-3
13. Novak D, Hüser L, Elton JJ, Umansky V, Altevogt P, Utikal J. SOX2 in development and cancer biology. Semin Cancer Biol. 2020 Dec;67(Pt 1):74-82. doi:10.1016/j.semcancer.2019.08.007.
14. Lee, J., Jung, YY, Lee, HJ, Hong, M., Hwang, HW, Hong, SA, et al. The prognostic value of sex-determining region Y-Box 2 and CD8+ tumor infiltrating lymphocytes in limited stage small cell lung cancer. oncology. 2021.99:528-538.10.1159/000516444.
15. Santoiemma, PP, & Powell, DJ, Jr. Tumor infiltrating lymphocytes in ovarian cancer. Cancer biology & therapy, 2015;16(6), 807 – 820. https://doi.org/10.1080/15384047.2015.1040960
16. Hao, J., Yu, H., Zhang, T., An, R., & Xue, Y. Prognostic impact of tumor-infiltrating lymphocytes in high grade serous ovarian cancer: a systematic review and meta-analysis. Therapeutic advances in medical oncology, 2020:12, https://doi.org/10.1177/1758835920967241
17. Kim SI, Ha HI, Eoh KJ, Lim J, Won YJ, Lim MC. Trends in the Incidence and Survival Rates of Primary Ovarian Clear Cell Carcinoma Compared to Ovarian Serous Carcinoma in Korea. Front Oncol. 2022 Apr 7;12:874037. doi:10.3389/fonc.2022.874037. PMID: 35463304; PMCID: PMC9021727.
18. Nicole, SA, Leslie, T., Sandra, L., Ren, C., Santo, VN., Patricia, AK, BCL2 expression is altered with ovarian tumor progression : an Immunohistochemical evaluation. Journal of Ovarian Research 2009
19. Xua Y, Chena L, Xua B, Xionga Y, Yanga M, Shia XRL, et al. Higher Numbers of T-Bet+ Tumor-Infiltrating Lymphocytes Associate with Better Survival in Human Epithelial Ovarian Cancer. Cell Physiol Biochem, 2017; 41: pp. 475-483.
20. Amante, S., Santos, F., Cunha, TM., Low-grade serous epithelial ovarian cancer: a comprehensive review and update for radiologists. 2021. Insight imaging. https://doi.org/10.1186/s13244-021-01004-7
21. Pannu, KH., CT Features of low grade serous carcinoma of the ovary. 2015. European Journal of Radiology. 39-45.
22. Mamun MA, Mannoor K, Cao J, Qadri F, Song X. SOX2 in cancer stemness: tumor malignancy and therapeutic potentials. J Mol Cell Biol. 2020;12(2):85-98. doi:10.1093/jmcb/mjy080
23. James, FR, Jiminez-Linan, M., Alsop, J., Mack, M., Song, H., Brenton, JD, Pharoah, P., & Ali, HR (2017). Association between tumor infiltrating lymphocytes, histotype and clinical outcome in epithelial ovarian cancer. BMC cancer, 17(1), 657. https://doi.org/10.1186/s12885-017-3585-x

24. Lee, J., Jung, Y., Lee, J H., Hong, M., Hwang, W H., Hong, AS et al. The Prognostic Value of Sex-Determining Region Y-Box2 and CD8+ Tumor Infiltrating Lymphocytes in Limited Stage Small Cell Lung Cancer. 2021. Clinical Translation Research. doi:10.1159/000516444.

AUTHOR DETAILS

First Author– dr. Abdul Hamid Hasan, resident of Anatomical Pathology Department, Faculty of Medicine, University of North Sumatra, Medan, Indonesia, email id:21dec84@gmail.com

Second Author– Dr. dr. Delyuzar, M.Ked(PA), Sp.PA(K), Lectures and Staff Anatomical Pathology Department, Faculty of Medicine, University of North Sumatra, Medan, Indonesia

Third Author– dr. T. Kemala Intan, M.Pd, M.Biomed, Lectures and Staff Anatomical Pathology Department, Faculty of Medicine, University of North Sumatra, Medan, Indonesia

Fourth Author- dr. Joko S Lukito, Sp.PA (K), Lectures and Staff Anatomical Pathology Department, Faculty of Medicine, University of North Sumatra, Medan, Indonesia

Fifth Author– dr. Jessy Chrestella, M.Ked(PA), Sp.PA, Lectures and Staff Anatomical Pathology Department, Faculty of Medicine, University of North Sumatra, Medan, Indonesia
Fifth Author– Dr. dr. T. Ibnu Alferraly, M.Ked(PA), Sp.PA, D.Bioeth, Lectures and Staff Anatomical Pathology Department, Faculty of Medicine, University of North Sumatra, Medan, Indonesia

Corresponding Author–Abdul Hamid Hasan, resident of Anatomical Pathology Department, Faculty of Medicine, University of North Sumatra, Jl. University. No. 1 Abdul Hakim building, Medan, Indonesia, E-mail ID: hamidhasannas@gmail.com