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Incidence and Prognostic Significance of Signet Ring Cell Histology in Gastric Cancer: A Cross-Sectional Study in Turkey

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Abstract

Background: The prognostic significance of an SRC histology in gastric cancer is still a matter of debate. There have been only limited studies of SRC gastric cancer based on the new definition.

Objectives: The current research was targeted toward investigating the incidence of signet ring cell (SRC) histology in patients with gastric cancer and its prognostic significance for disease staging.

Methods: This retrospective research was performed on 309 patients at the Kartal Koşuyolu High Specialization Training and Research Hospital Gastroenterology Surgery Clinic in Turkey, between November 2006 and September 2019. For the purpose of the study, the clinicopathological features and survival status of the patients were examined in the presence of SRC histology.

Results: According to the results, 71.4% of the patients had gastric cancer with non-SRC histology, and the rest (28.6%) had SRC histology. The presence of SRC histology was found to be correlated with young age (P=0.007), advanced depth of wall invasion (P=0.001), number of positive lymph nodes (P=0.022), and presence of vascular invasion (P=0.044). In addition, SRC histology presence was found to be in association with a good prognosis of stage I gastric cancer (P=0.045) but a poor prognosis of stage III disease (P=0.034). However, the results revealed no significant association between stage II gastric cancer and overall survival.

Conclusion: Our findings were indicative of the association of survival with good prognosis of stage I and poor prognosis of stage III among patients with gastric cancer and SRC histology. However, no prognostic significance could be established for overall survival.

Keywords: Gastrectomy, Gastric cancer, Gastric signet ring cell carcinoma

1. Background

Based on the Global Cancer Statistics 2018, the incidence of gastric cancer is on a decreasing trend. However, this disease still remains one of the most significant public health problems and one of the leading causes of cancer mortality (1). Recent epidemiological data suggest that there has been a shift in the frequency of the various histopathological subtypes of gastric cancer (2). In particular, the evidence is indicative of the decreasing incidence of distal gastric tumors and increasing incidence of proximal tumors and Lauren diffuse-type histology (2). Recent studies have also reported an increase in the incidence of gastric cancer with a signet ring cell (SRC) histology (3). Signet ring cell carcinoma is a form of adenocarcinoma, the histological diagnosis of which is defined by the World Health Organization (WHO) as the presence of more than 50% intracytoplasmic mucin and a microscopic appearance of signet cell as a result of nuclear shift (4).

The SRC carcinoma has been also termed as poorly cohesive carcinoma, Lauren diffuse-type carcinoma, infiltrative carcinoma, and undifferentiated carcinoma (4, 5). Accordingly, the SRC gastric cancer or poorly differentiated gastric cancer definitions are used, depending on the dominant SRC histology in the tumor, without any discrimination or standardization (6). Poorly cohesive tumors are divided into three categories based on the European Consensus of Experts (6). According to this classification, SRC1, SRC2, and SRC3 are defined as the SRC histology rates of ≥ 90%, 10-90%, and ≤ 10%, respectively (6). Pure SRC1 histology is observed in early-stage gastric cancer and often associated with *CDH1* mutation (7). The SRC2 and SRC3 histology is often observed in advanced stage gastric cancer, exhibiting a high frequency of aggressive phenotypical characteristics, such as *TP53* mutation and Ki67 proliferation index (7). As a result, gastric cancer with a pure SRC histology is associated with better prognosis when compared to other poorly cohesive gastric cancers (7).

The prognostic significance of SRC histology, showing a growing prevalence in recent years, is still a matter of debate. There have been studies claiming that SRC histology is a poor prognostic factor, while others claim the opposite (8, 9). Recent studies have shown the disease stage as the most significant prognostic factor in patients with gastric cancer with SRC histology (10). There have been only limited studies on SRC gastric cancer considering its new definition.

2. Objectives

The current research was performed to establish

a comparison between gastric cancer patients with SRC and non-SRC histology in terms of clinicopathological characteristics in order to determine the prognostic significance of SRC histology.

3. Methods

This retrospective study was carried out on the medical records of 309 patients, undergoing total or subtotal gastrectomy and D2 lymph node dissection at the Gastroenterological Surgery Clinic of Kartal Koşuyolu Higher Specialty Training and Research Hospital in Turkey between November 2006 and September 2019 due to gastric adenocarcinoma. The cut-off date for the survival analysis was December 31, 2019. The D2 dissection was carried out following the principles of the Japanese Research Society for the Study of Gastric Cancer (11). Tumor staging was accomplished using the tumor, node, and metastasis (TNM) classification system determined by the American Joint Committee on Cancer (8th ed, 2017).

The data were collected based on the follow-up forms uploaded onto the database of our clinic, and the pathology results were recorded. The patients diagnosed with distant organ metastasis at the time of surgery (8 cases of liver metastasis), positive peritoneal cytology (n=11), and positive surgical margins (n=4), as well as those who passed away within 30 days of surgery (n=7), were removed from the research, even if they had undergone a gastric resection. Finally, 280 cases were entered into the research. The patients were allocated into two groups of gastric cancer with SRC histology (n=80) and non-SRC histology (n=200). Among the non-SRC gastric cancer patients, 18, 72, 84, and 25 cases had well-differentiated, moderately-differentiated, poorly-differentiated, and mucinosis cell histology, respectively. The clinicohisto-pathological characteristics of the two groups were compared, and the differences in survival were evaluated against disease stages. İn addition, the prognostic factors affecting survival were examined.

3.1. Statistical Analysis

The normality of the distribution of the numerical variables was evaluated using the Kolmogorov-Smirnov test. The median values were taken if there was no normal distribution when the p-value was less than 0.05. Categorical variables were expressed as numbers and percentages. Furthermore, the groups were analyzed on the basis of the presence of SRC histology using the Chi-square and Mann-Whitney U tests. Interstage survival, based on SRC histology status, was analyzed by means of the Kaplan-Meier pairwise comparison for each stratum. In addition, the overall survival analysis was carried out using the Kaplan-Meier pooled over strata test. A log-rank test was also utilized to identify any differences. The other prognostic factors were investigated using a stepwise Cox regression analysis. The data were analyzed in SPSS software (version 22) at a significance level of < 0.05.

4. Results

Out of the 280 included patients, 80 (28.6%) cases had SRC gastric cancer, while 200 (71.4%) patients had non-SRC gastric cancer. Comparison of the two groups regarding the clinicopathological characteristics is presented in Table 1. The presence of SRC histology was associated with young age (59 vs. 63 years; P=0.007), advanced disease stage (stage III: 62.5% vs. 50%; P=0.041), presence of vascular invasion (69.6% vs. 56.5%; P=0.044), and number of positive lymph nodes (4 vs. 2; P=0.022; Table 1).

The median follow-up duration of the study participants was 26 months (range: 1-156). After follow-up, 155 (51.4%) patients passed away, while 136 (48.6%) cases survived. The median durations of follow-up were 52 (range: 2-153), 37 (2-148), and 19 (range: 1-156) months in the patients with stage I, II, and III disease, respectively. A log-rank analysis revealed a mean survival duration of 96.145±14.203 months (P=0.505) for stage II gastric cancer with SRC histology, while overall survival was 72.361±8.1 months for all patients with gastric cancer with SRC histology, revealing no statistical difference (P=0.350). All patients with stage I gastric cancer with SRC histology survived the follow-up period (P=0.045), while survival was 34.239±6.209 months (P=0.034) for those with stage III gastric cancer with SRC histology, showing a statistically significant difference (Table 2). Accordingly, the SRC histology indicated a good prognosis of early-stage gastric cancer but a poor prognosis of stage III disease. The overall survival in the entire study group and in patients with stage I-III disease based on the presence of SRC histology is presented in Figure 1.

The results of multivariate Cox regression analysis involving other prognostic factors dismissed SRC as a prognostic factor for neither overall survival nor stage II and III disease (OR=1.064, P=0.767; OR=0.959, P=0.951; OR=1.167, P=0.688, respectively; Table 3). The prognostic factors for the stage II disease included tumor diameter (P=0.018) and a high number of positive lymph nodes (P=0.011). Regarding the stage III of the disease, the prognostic factors were proximal tumor localization (P=0.028), increased depth of tumor invasion (P=0.007), total number of removed lymph nodes (P=0.001), and high number of positive lymph nodes (P=0.000). Additionally, for overall survival, these factors were the increased depth of tumor invasion (P=0.001), total number of removed

Table 1. Clinicopathologic features of patients stratified based on signet-ring cell and non-signet-ring cell histology

	Non-signet ring cell	Signet ring cell	P-value
	Count (%)	Count (%)	
Gender			
Male	139 (69.5%)	52 (65.0%)	0.465
Female	61 (30.5%)	28 (35.0%)	
Location			
Upper	54 (27.0%)	13 (16.2%)	0.155
Middle	47 (23.5)	23 (28.8%)	
Bottom	99 (49.5%)	44 (55.0%)	
Type of surgery			
Subtotal	99 (49.5%)	43 (53.8%)	0.520
Total	101 (50.5%)	37 (46.2%)	
Depth of invasion			
T1	21 (10.5%)	13 (16.2%)	0.001*
T2	24 (12.0%)	6 (7.5%)	
T3	97 (48.5%)	21 (26.2%)	
T4	58 (29.0%)	40 (50.0%)	
Lymph node metastasis			
N0	75 (37.5%)	27 (33.8%)	0.004*
N1	40 (20.0%)	8 (10.0%)	
N2	33 (16.5%)	10 (12.5%)	
N3a	37 (18.5.0%)	17 (21.3%)	
N3b	15 (7.5%)	18 (22.5)	
Stage			
Stage I	32 (16.0%)	15 (18.8%)	0.041*
Stage II	68 (34.0%)	15 (18.8%)	
Stage III	100 (50.0%)	52 (62.5%)	
Neoadjuvant therapy			
No	162 (81.0%)	71 (88.8%)	0.117
Yes	38 (19.0%)	9 (11.2%)	
Vascular ınvasion			
Negative	87 (43.5%)	24 (30.4%)	0.044*
Positive	113 (56.5%)	55 (69.6%)	
Perineural invasion			
Negative	76 (38.2%)	22 (27.8%)	0.104
Positive	123 (61.8%)	57 (72.2%)	
Complication			
No	148 (72.5%)	58 (71.6%)	0.933
Yes	56 (27.5%)	23 (28.4%)	
	Median Min-Max	**Median Min-Max**	
Age	63 (30–86)	59 (28–91)	0.007**
Tm Diameter (cm)	5 (0.5–18)	4.5 (0.5–13)	0.768
Total number of lymph nodes	24 (6–74)	24 (9–73)	0.926
Number of positive lymph nodes	2 (0–38)	4 (0–48)	0.022**
Length of hospital stay	10 (0–158)	10 (7–65)	0.264

*Chi-square test, P<0.05, ** Mann-Whitney U test, P<0.01

Table 2. Kaplan-Meier analysis of patients with stage II, stage III, and all disease stages according to signet-ring cell status

	All Stages			Stage II			Stage III		
	Estimate (SE)	95% CI	P-value	Estimate (SE)	95% CI	P-value	Estimate (SE)	95% CI	P-value
Non-signet-ring cell	75.786±5.214	(65.566–86.005)	0.303	86.353±8.134	(70.410–102.297)	0.505	56.705±6.755	(43.465–69.945)	0.034*
Signet-ring cell	72.361±8.100	(56.485–88.237)		96.145±14.203	(68.307–123.983)		34.239±6.209	(22.069–46.408)	
Overall	74.696±4.451	(65.972–83.420)		88.573±7.521	(73.832–103.314)		51.324±5.329	(40.880–61.769)	

*P<0.05

lymph nodes (P=0.000), and high number of positive lymph nodes (P=0.000; Table 3).

5. Discussion

Traditionally, gastric cancer has two morphological types of either intestinal or diffuse (12). Based on the WHO classification, the diffuse type is defined as gastric cancer with poorly cohesive SRC histology (4), having an incidence rate of 3.4-39% (13). Gastric cancer with SRC histology is in association with female sex, young age, distal tumor localization, poor tumor differentiation, microscopically positive surgical margins (R1 resection margin), presence of perineural invasion, advanced stage, and adjuvant therapy (14). The prognostic significance of SRC histology is currently an issue of debate. According to a study performed by Chon et al., early-stage gastric cancer with SRC histology is correlated with a better prognosis than intestinal-type carcinoma following a

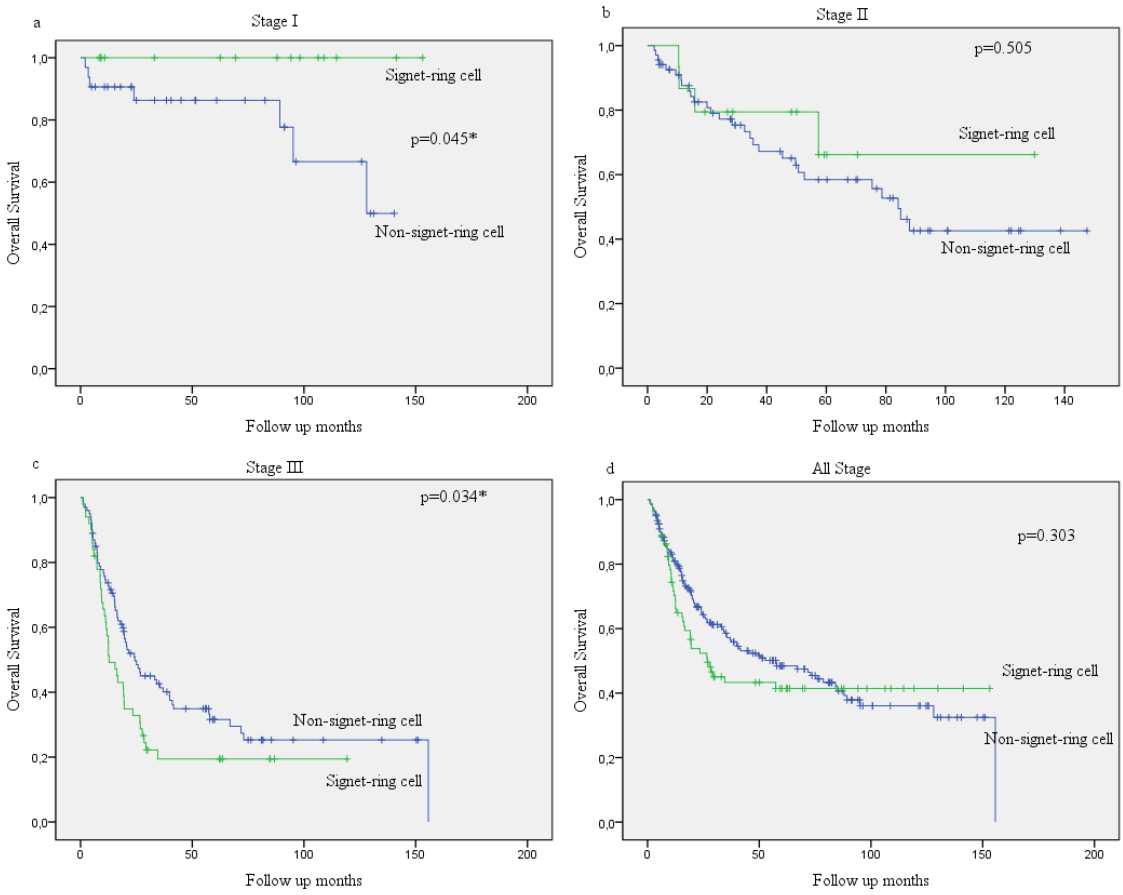

Figure 1. Kaplan-Meier survival curves stratified by signet-ring cell histology status. a)stage I, b) stage II, c) stage III, d) Overall survival for all patients

Table 3. Multivariate Cox regression analysis of stage 2 and stage 3 patients and all patients

	Stage II		Stage III		All patients	
	OR (95.0% CI)	**P-value**	**OR (95.0% CI)**	**P-value**	**OR (95.0% CI)**	**P-value**
Gender	0.625 (0.239–1.636)	0.338	1.343 (0.842–2.144)	0.148	1.173 (0.781–1.761)	0.441
Age	1.009 (0.975–1.045)	0.598	1.013 (0.993–1.034)	0.252	1.013 (0.997–1.030)	0.106
Signet-ring cell	0.959 (0.253–3.627)	0.951	1.167 (0.750–1.817)	0.688	1.064 (0.707–1.600)	0.767
Localization						
Proximal		0.611		0.028*		0.056
Middle	1.706 (0.438–6.646)	0.441	1.151 (0.640–2.069)	0.603	1.448 (0.859–2.444)	0.165
Distal	1.711 (0.581–5.035)	0.330	0.586 (0.344–1.000)	0.085	0.869 (0.554–1.364)	541
Tumor Diameter	1.159 (1.025–1.310)	0.018*	0.934 (0.854–1.022)	0.308	1.016 (0.949–1.087)	0.655
T Stage						
T1		0.601		0.007*	4.203 (0.870–20.209)	0.001*
T2		0.926	0.298 (0.04–2.211)	0.236	5.371 (1.241–23.251)	0.074
T3		0.931	0.490 (0.308–.780)	0.003	10.415 (2.331–46.538)	0.025
T4		0.924				0.002
Vascular invasion	952 (0.405–2239)	0.910	1.152 (0.637–2.083)	0.640	1.152 (0.753–1.765)	0.514
Perineural invasion	1.077 (0.445–2605)	0.870	1.329 (0.724–2.440)	0.359	1.351 (0.850–2.149)	0.203
Total number of lymph nodes	0.970 (0.922–1.021)	0.245	0.963 (0.941–0.986)	0.001**	0.962 (0.943–0.981)	<0.001**
Number of positive lymph nodes	1.974 (1.167–3.339)	0.011*	1.081 (1.050–1.112)	<0.001**	1.076 (1.050–1.103)	<0.001**

* indicates statistical significance at P<0.05;** indicates statistical significance at p<0.001
OR=odds ratio, CI=confidence interval

curative resection. Nonetheless, advanced stage gastric cancer is linked with poor prognosis, and SRC is of prognostic significance (10).

In a study, Kau et al. demonstrated a relationship between SRC histology and good prognosis in early-stage gastric cancer; however, in advanced stage gastric cancers, SRC histology was found to be an independent predictor of poor prognosis (15). On the

other hand, SRC histology is not an independent risk factor for disease-free and overall survival, if not evaluated together with other poor prognostic factors (e.g., poor differentiation, advanced TNM stage, and positive microscopic margins) (14). Kwon et al. reported no statistically significant difference between SRC histology and non-SRC histology in early-stage gastric cancer in terms of 10-year survival (76% vs. 65.7%).

The SRC histology is linked with deep tumor invasion, large tumor diameter, and a high rate of lymph node metastasis in advanced stage gastric cancer (16). Zhou et al. reported poorer survival in patients with a tumor diameter of 49 mm but greater survival among those with gastric cancer with SRC histology. They also reported a large tumor diameter as a poor prognostic factor (17). A Cox regression analysis in the same study identified the depth of tumor wall invasion, increased number of positive lymph nodes, and tumor diameter as other poor prognostic factors (17). In the current research, the patients with SRC histology comprised 28.6% of the patient population. In addition, gastric cancer with SRC histology was found to be associated with young age, increased number of lymph nodes, advanced disease stage, presence of vascular invasion, and low serum carbohydrate antigen 19-9.

In a study carried out by Pokala et al., gastric cancer with SRC histology was found to be correlated with good prognosis at an early-disease stage and poor prognosis at an advanced disease stage (18). Postlewait et al. identified no statistical difference between stage I-III gastric cancer patients with SRC and non-SRC histology in terms of survival rate (P=0.777, P=0.190, and P=0.756, respectively). However, the two groups were significantly different considering the overall survival rate (P=0.011) (14). In the mentioned research, D0 and D1 lymph node dissections were considered; however, in the present research, the patients undergoing a D2 lymph node dissection as standard were investigated.

The study conducted by Bamboat et al. reported statistically better survival in stage Ia gastric cancer with SRC histology (P<0.0001). However, they identified no statistical difference among patients with stage Ib, II, and III in this regard. Nonetheless, they established SRC histology as a factor for statistically poor survival considering overall survival (P<0.0001) (19). In a meta-analysis performed by Zhao et al., while some studies reported no difference between gastric cancer patients with SRC and non-SRC histology regarding the survival rate, others established differences, concluding that the studies were highly heterogeneous (20). In the same meta-analysis, a subgroup assessment revealed a statistical difference between gastric cancer patients with SRC and non-SRC histology in terms of the survival rate (21). While the *CDH1* mutation is common in early SRC gastric cancer, the Ki67 index, indicating tumor aggressiveness, is increased, and *TP53* mutation is more frequent in the advanced stages.

Although SRC histology in the present study was correlated with a good prognosis of stage I disease, it was an indicator of a poor prognosis of stage III of the disease. Moreover, it had no prognostic value for stage II disease and overall survival. Although SRC histology has been identified as a poor prognostic factor for survival in stage III gastric cancer, a multivariate Cox regression analysis evaluating SRC histology together with other prognostic factors failed to identify SRC histology as a risk factor for stage III gastric cancer.

The limitations of the present study included the adoption of a single-center and retrospective study design, small sample size, and failure to examine the impacts of chemotherapy and radiotherapy on survival. Therefore, it is essential to perform prospective, randomized, multi-center studies to clarify prognosis in gastric cancer patients with SRC histology to determine the actual number of gastric cancer cases with pure SRC histology and reveal their responses to chemotherapy and radiotherapy.

6. Conclusion

In conclusion, the incidence and prognostic nature of gastric cancer with pure SRC histology, as per the new definition, are not sufficiently known. The present study revealed that SRC histology is correlated with a good prognosis of early gastric cancer and a poor prognosis of stage III gastric cancer. This variable was also found to have no association with poor prognosis in stage II gastric cancer or overall survival. There is a need to perform further multicenter studies of different subtypes in order to obtain a better comprehension of the prognostic significance of poorly cohesive SRC histology.

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Footnotes

Authors' Contribution: Uzun O., Senger A.S., and Gülmez S.,Omeroglu S performed most of the study; Uzun O., Gülmez S., Sert Kurt O.Z., Oz A, designed the study and analyzed the data; Uzun O., Senger A.S., wrote the manuscript;and Polat E. and Duman M. revised the manuscript. Uzun O. and Duman M. approved the final version of the manuscript.

Ethical Approval: The study protocol was approved by the Kartal Koşuyolu High Specialty Training and Research Hospital Ethics Committee with the number 2020.4 /25-330. A written informed consent was obtained from each participant. The study was conducted in accordance with the principles of the

Declaration of Helsinki.

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References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2018;**68**(6):394-424. doi: 10.3322/caac.21492. [PubMed: 30207593].
2. Treppiedi V, Treppiedi E, Mariagiulia M, Dal Cero M, Giacopuzzi S. Tailored treatment for signet ring cell gastric cancer. *Updates Surg*. 2018;**70**(2):167-71. doi: 10.1007/s13304-018-0550-4. [PubMed: 29948660].
3. Pernot S, Voron T, Perkins G, Lagorce-Pages C, Berger A, Taieb J. Signet-ring cell carcinoma of the stomach: Impact on prognosis and specific therapeutic challenge. *World J Gastroenterol*. 2015;**21**(40):11428-38. doi: 10.3748/wjg.v21.i40.11428. [PubMed: 26523107].
4. Nagtegaal ID, Odze RD, Klimstra D, Paradis V, Rugge M, Schirmacher P, et al. The 2019 WHO classification of tumours of the digestive system. *Histopathology*. 2020;**76**(2):182-8. doi: 10.1111/his.13975. [PubMed: 31433515].
5. Jiang CG, Wang ZN, Sun Z, Liu FN, Yu M, Xu HM. Clinicopathologic characteristics and prognosis of signet ring cell carcinoma of the stomach: results from a Chinese mono-institutional study. *J Surg Oncol*. 2011;**103**(7):700-3. doi: 10.1002/jso.21878. [PubMed: 21308685].
6. Mariette C, Carneiro F, Grabsch HI, van der Post RS, Allum W, de Manzoni G, et al. Consensus on the pathological definition and classification of poorly cohesive gastric carcinoma. *Gastric Cancer*. 2019;**22**(1):1-9. doi: 10.1007/s10120-018-0868-0. [PubMed: 30167905].
7. Bencivenga M, Treppiedi E, Dal Cero M, Torroni L, Verlato G, Iglesias M, et al. The amount of signet ring cells is significantly associated with tumour stage and survival in gastric poorly cohesive tumours. *J Surg Oncol*. 2020;**121**(7):1084-9. doi: 10.1002/jso.25885. [PubMed: 32153051].
8. Piessen G, Leteurtre E, Jean-pierre T, Mariette C. Signet ring cell histology is an ındependent predictor of poor prognosis in gastric adenocarcinoma regardless of tumoral linical presentation. *Ann Surg*. 2009;**250**(6):878-87. doi: 10.1097/SLA.0b013e3181b21c7b. [PubMed: 19855261].
9. Taghavi S, Jayarajan SN, Davey A, Willis AI. Prognostic significance of signet ring gastric cancer. *J Clin Oncol*. 2012;**30**(28):3493-8. doi: 10.1200/JCO.2012.42.6635. [PubMed: 22927530].
10. Chon HJ, Hyung WJ, Kim C, Park S, Kim JH, Park CH, et al. Differential prognostic ımplications of gastric signet ring cell carcinoma: stage adjusted analysis from a single high-volume center in Asia. *Ann Surg*. 2017;**265**(5):946-53. doi: 10.1097/SLA.0000000000001793. [PubMed: 27232252].
11. Japanese Gastric Cancer Association. Japanese gastric cancer treatment guidelines 2014 (ver. 4). *Gastric Cancer*. 2017;**20**(1):1-19. doi: 10.1007/s10120-016-0622-4. [PubMed: 27342689].
12. Machlowska J, Pucułek M, Sitarz M, Terlecki P, Maciejewski R, Sitarz R. State of the art for gastric signet ring cell carcinoma: From classification, prognosis, and genomic characteristics to specified treatments. *Cancer Manag Res*. 2019;**11**:2151-61. doi: 10.2147/CMAR.S188622. [PubMed: 30936747].
13. Theuer CP, Nastanski F, Brewster WR, Butler JA, Anton-Culver H. Signet ring cell histology is associated with unique clinical features but does not affect gastric cancer survival. *Am Surg*. 1999;**65**(10):915-21. [PubMed: 10515534].
14. Postlewait LM, Squires MH 3rd, Kooby DA, Poultsides GA, Weber SM, Bloomston M, et al. The Prognostic value of signet-ring cell histology in resected gastric adenocarcinoma. *Ann Surg Oncol*. 2015;**22**(Suppl 3):S832-9. doi: 10.1245/s10434-015-4724-8. [PubMed: 26156656].
15. Kao YC, Fang WL, Fang R, Anna W, Yau F, Yang MH, et al. Clinicopathological differences in signet ring cell adenocarcinoma between early and advanced gastric cancer. *Gastric Cancer*. 2018;**22**(2):255-63. doi: 10.1007/s10120-018-0860-8. [PubMed: 30069742].
16. Kwon KJ, Shim KN, Song EM, Choi JY, Kim SE, Jung HK, et al. Clinicopathological characteristics and prognosis of signet ring cell carcinoma of the stomach. *Gastric Cancer*. 2014;**17**(1):43-53. doi: 10.1007/s10120-013-0234-1. [PubMed: 23389081].
17. Zhou L, Li W, Cai S, Yang C, Liu Y, Lin Z. Large tumor size is a poor prognostic factor of gastric cancer with signet ring cell: results from the surveillance, epidemiology, and end results database. *Medicine (Baltimore)*. 2019;**98**(40):e17367. doi: 10.1097/MD.0000000000017367. [PubMed: 31577736].
18. Pokala SK, Zhang C, Chen Z, Gamboa AM, Cristofaro SL, Keilin SA, et al. Incidence, survival, and predictors of lymph node ınvolvement in early-stage gastric signet ring cell carcinoma in the US. *J Gastrointest Surg*. 2018;**22**(4):569-77. doi: 10.1007/s11605-017-3500-4. [PubMed: 29313289].
19. Bamboat ZM, Tang LH, Vinuela E, Kuk D, Gonen M, Shah MA, et al. Stage-stratified prognosis of signet ring cell histology in patients undergoing curative resection for gastric adenocarcinoma. *Ann Surg Oncol*. 2014;**21**(5):1678-85. doi: 10.1245/s10434-013-3466-8. [PubMed: 24394986].
20. Zhao B, Lv W, Zhang J, Zhang J, Huang B, Lin J. Different prognostic significance of signet ring cell histology for early and advanced gastric cancer patients: a systematic review and meta-analysis. *Expert Rev Gastroenterol Hepatol*. 2020;**14**(6):499-509. doi: 10.1080/17474124.2020.1769476. [PubMed: 32421372].
21. Jansen M, Wright NA. Stem cells, pre-neoplasia, and early cancer of the upper gastrointestinal tract. Berlin, Germany: Springer; 2016. P. 331-46. doi: 10.1007/978-3-319-41388-4.