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HISTOLOGICAL CRITERIA FOR "INTRAEPITHELIAL SQUAMOUS CELL CARCINOMA" OF THE ESOPHAGUS: CONTINUED DIALOGUE BETWEEN UKRAINIAN AND JAPANESE PATHOLOGISTS

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***Background*: Patients with esophageal squamous cell carcinoma (SCC) have a poor prognosis mostly due to the late diagnosis. A morphological method is still the main diagnostic method for SCC. *The aim* of the study was to find out which histological criteria, namely Western or Japanese criteria, for early stage SCC are used by pathologists in Ukraine as compared with their Japanese colleagues. *Methods*: 14 Ukrainian and 6 Japanese pathologists have participated in this study. Virtual slides for research were provided by National Cancer Research Center (Tokyo, Japan) in 2018. Each of the pathologists has used these slides and presented the conclusion *via* the Internet. *Results*: Essential diagnostic discrepancies were revealed: a number of biopsy specimens was diagnosed by Japanese pathologists as "noninvasive carcinoma", while Ukrainian pathologists classified the specimens as high-grade or low-grade dysplasia, indefinite for neoplasia, or reactive/regenerative lesions. *Conclusion*: The adoption of a unified concept of criteria for non-invasive (intraepithelial) carcinoma underlies early endoscopic/surgical treatment, which significantly increases the survival rate of patients with SCC. A solid common approach to the diagnosis between Western and Japanese pathologists, as well as endoscopists, is necessary to ensure timely treatment and increase survival rate of patients with SCC.**

***Key Words*: noninvasive (intraepithelial) carcinoma, esophageal squamous cell carcinoma, Western histological criteria, Japanese histological criteria, high/low-grade dysplasia.**

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Esophageal cancer (EC) remains a serious public health problem. There are two main histological EC subtypes: squamous cell carcinoma (SCC) and adenocarcinoma (EA). It is known that patients with EC have a poor prognosis due to the late diagnosis. According to a recent USA study, majority of EA cases (42%) were diagnosed as poorly differentiated tumors of grade III, and majority of SCC cases (39.5%) — as moderately differentiated tumors of grade II. The most common stage of presentation was stage IV (for EA — 36.9%, for SCC — 26.8%) [1].

EC is recognized as one of the most aggressive forms of malignant tumors and the eighth most common cancer in the world with a 5-year survival rate of less than 25%. In recent years, among all cancer mortality causes worldwide EC has steadily kept the 6th place [2]. The clinical features of the EC course make physicians focus on early diagnosis. The introduction of modern endoscopic technologies, such as narrow band imaging endoscopy or confocal laser endomicroscopy, makes it possible to increase efficiency of disease detection. Attempts are being made to noninvasive diagnosis of an early stage EC using blood biomarkers [3–5]. At the same time, a morphological method is still the main diagnostic method for EC.

The Seminar on the classification of gastrointestinal epithelial neoplasia of the gastrointestinal tract was held in 1998 in Vienna, Austria, with following publication in GUT journal in 2000 [6]. It is known that there are different opinions on histological criteria of early stage EC/EA among Western and Japanese pathologists. These different approaches lead to differences in neoplasm detection and patients' management. SCC was one of the topics in this discussion. Polish, German, and Japanese pathologists had evaluated accuracy of SCC diagnosis and clarified its significance for clinical practice [7]. It has been argued that the Western approach might lead to defects in early diagnosis and unnecessary delay in starting treatment of patients with SCC. However, the use of Japanese criteria in European countries, where the prevalence of EC is lower than in Japan, is regarded by European experts as a way to overdiagnosis and unreasonable treatment of such patients.

More than 20 years have passed since the discussion on morphological criteria of the early stage SCC, but the disease does not give up. In this regard, it is important to understand whether this is due to the inertia of specialists in adopting more "stringent" guidelines for the morphological diagnosis of EC. Understanding the real situation in terms of morphological norm has fundamental importance for the diagnosis of this disease. This assessment was carried out in Ukraine.

The aim of this study was to find out which histological criteria for early stage SCC, namely Western or Japanese criteria, are used by pathologists in Ukraine as compared with their Japanese colleagues.

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Abbreviations used: carcinoma (SM~) – carcinoma with invasion to submucosal or deeper layer; EA – esophageal adenocarcinoma; EC – esophageal cancer; ESD – endoscopic submucosal dissection; reactive/regenerative – reactive lesion or regenerative lesion; R/I – reactive lesion/indefinite for neoplasia; SCC – esophageal squamous cell carcinoma.

MATERIALS AND METHODS

Questionnaire. 14 Ukrainian and 6 Japanese pathologists participated in answering the questionnaire. The question on histological criteria of the SCC used in everyday diagnostic work, was proposed for the participants as following:

Question: "Your histological criterion of EC is":

Answer:

A1: Stromal invasion of neoplastic cells.

A2: Invasion of neoplastic cells to submucosa.

A3: Nuclear/Architectural atypia regardless of stromal invasion.

A4: Others (describe).

Morphological evaluation of virtual slides. 14 Ukrainian and 6 Japanese pathologists participated in morphological evaluation of virtual slides. Virtual slides for research were provided by National Cancer Research Center (Tokyo, Japan) in 2018. Each of the pathologists has used these slides and presented his conclusion *via* the Internet. All participants were provided with the same information about each sample: localization, color and shape of the lesion, endoscopic images, biopsy zones and macroscopic images allocated to the esophagus for endoscopic submucosal dissection (ESD)/surgical samples.

In this study, non-invasive carcinoma was defined as intraepithelial SCC without visible stromal invasion. The definite carcinoma was determined as SCC with obvious stromal invasion. Histological samples of the mucous membrane of the digestive tract of patients, proposed for evaluation by pathologists, were obtained from Hitachi General Hospital in Hitachi city and Cancer Center in Shizuoka Prefecture in Japan. Materials consisted of 6 endoscopic biopsies, 4 ESD samples, and also of 8 surgical samples obtained from patients with squamous lesions. The samples were taken of eight male patients 59–73 years old, with different stages of the esophageal squamous epithelial lesions located at middle thoracic esophagus or esophagocardiac junction.

The interrelation between biopsy and ESD/surgically resected specimens for each case was known to the investigators, but the pathologists were not aware of about the interrelation before diagnosis. Changes in Barrett's esophagus were not included in this study.

Statistical analysis. Statistical analysis was performed by the Yeats-corrected Chi-Square test to compare the distribution of diagnoses. $p < 0.05$ was considered statistically significant. All statistical tests were performed using SAS version 9.4 (SAS Institute, USA).

RESULTS

By the histological criteria for SCC, which participants use in their daily practice, their answers to questionnaire were distributed as follows: among 14 Ukrainian pathologists, 4 chose the answer A1, 4 — A2, and 6 — A3, while all Japanese pathologists chose A3. Thus, before the start of the assessment of morphological samples, the unanimous opinion of Japanese specialists coincided with that of only 6 Ukrainian participants.

In total, each pathologist has analyzed 18 histological slides. Of those, 73.4% and 95.4% lesions were diagnosed as malignant lesions by Ukrainian and Japanese pathologists, respectively. The category "malignant lesions" included the following: (5) suspicious carcinoma, (6) non-invasive carcinoma, (7) carcinoma in dysplasia, (8) definite carcinoma and (9) carcinoma with invasion to submucosal or deeper layer (carcinoma (SM~)) (Table 1). So, Ukrainian pathologists diagnosed "benign" lesions in 26.6% cases, while Japanese pathologists — only in 4.6% ($p < 0.001$).

Ukrainian pathologists established the diagnosis of high-grade dysplasia essentially more often than their Japanese colleagues: 15.1% *vs* 1.9% ($p = 0.001$). The difference in diagnoses between Ukrainian and Japanese pathologists was even more evident if only biopsy specimens were analyzed (Table 2). In particular, Ukrainian pathologists diagnosed 48.8% of the biopsy specimens as malignant while Japanese pathologists — 86.1% ($p < 0.001$). Correspondingly, benign diagnoses were established in 51.2% cases by Ukrainian pathologists, and only in 13.9% cases by Japanese pathologists ($p < 0.001$). Many biopsy specimens classified as noninvasive carcinoma by Japanese pathologists, were diagnosed by Ukrainian pathologists as high-grade dysplasia, low-grade dysplasia, indefinite for neoplasia, or reactive/regenerative lesions.

There were 5 esophageal cases in which ESD or surgical specimens showed a definite stromal invasion. Japanese pathologists diagnosed the biopsies of 5 esophageal invasive carcinomas as carcinoma

Table 1. Distribution of diagnoses for esophageal lesions: all specimens (including biopsy, ESD and surgically resected specimens)

N	Diagnoses	Ukrainian pathologists, n = 14		Japanese pathologists, n = 6	
		№ of cases	%	№ of cases	%
1	Reactive/regenerative	11	4.4	0	0
2	Indefinite for neoplasia	3	1.1	0	0
3	Low-grade dysplasia	15	6.0	3	2.8
4	High-grade dysplasia	38	15.1	2	1.9
	Subtotal (benign)	67	26.6	5	4.6
5	Susp. of carcinoma	11	4.4	2	1.9
6	Noninvasive carcinoma	39	15.4	37	34.3
7	Carcinoma in dysplasia	15	6.0	0	0
8	Definite carcinoma	60	23.8	51	47.2
9.	Carcinoma (SM~)	60	23.8	13	12
	Subtotal (malignant)	185	73.4	103	95.4
	Total number	252	100	108	100

Table 2. Distribution of diagnoses for esophageal lesions: biopsy specimens

N	Diagnoses	Ukrainian pathologists, n = 14		Japanese pathologists, n = 6	
		№ of cases	%	№ of cases	%
1	Reactive/regenerative	10	11.9	0	0
2	Indefinite for neoplasia	1	1.2	0	0
3	Low-grade dysplasia	14	16.7	3	8.3
4	High-grade dysplasia	18	21.4	2	5.6
	Subtotal (benign)	43	51.2	5	13.9
5	Susp. of carcinoma	9	10.7	2	5.6
6	Noninvasive carcinoma	15	17.9	20	55.6
7	Carcinoma in dysplasia	2	2.4	0	0
8	Definite carcinoma	9	10.7	9	25
9	Carcinoma (SM~)	6	7.1	0	0
	Subtotal (malignant)	41	48.8	31	86.1
	Total number	84	100	36	100

(including non-invasive carcinoma) in 97% cases, and high-grade dysplasia in 3% cases (1/30), while Ukrainian pathologists diagnosed them as carcinoma in 69%, high-grade dysplasia in 14%, low-grade dysplasia in 11%, and as a reactive lesion/indefinite for neoplasia (R/I) in 6%. Ukrainian pathologists diagnosed biopsy specimens of 31% of the esophageal invasive carcinoma as benign. The differences between Ukrainian and Japanese pathologists for the diagnosis of high-grade dysplasia or low-grade dysplasia or R/I were statistically significant ($p = 0.005$), as well as for the diagnosis of low-grade dysplasia or R/I ($p = 0.037$).

DISCUSSION

By analogy with the previous study with Polish and German pathologists [7], the differences in diagnoses between Ukrainian and Japanese pathologists are based on differences in the acceptance of the concept of non-invasive (intraepithelial) carcinoma. According to Western criteria, the histological diagnosis of SCC includes the mandatory presence of stromal invasion of tumor cells [8]. Japanese pathologists consider cellular and structural disorders as more important criterion for intraepithelial SCC, regardless of the presence of stromal invasion [6, 8].

Early SCC is defined as intramucosal carcinoma with or without metastasis. In the subclassification based on depth of cancer invasion, m1 and m2 carcinomas are metastasis-free and are considered curable by endoscopic mucosal resection alone, whereas < 10% of m3 carcinomas and about 20% of sm1 carcinomas produce lymph node metastasis [9]. Our study confirmed that despite adoption of the Vienna classification, Ukrainian pathologists are still reluctant to use the diagnostic criteria, in particular, for diagnosis of intraepithelial SCC of the esophagus.

Attention should be paid for changing treatment options for the EC patients. Several years ago, partial esophagectomy was considered as a main surgical treatment. Modern endoscopic operations make it possible to preserve the esophagus.

Comparison of application of histological diagnostic criteria for early stage EC by Ukrainian and Japanese pathologists has shown that Western and Japanese pathologists still have different approaches. The Japanese diagnostic criteria allow more accurate correspondence of biopsy evaluation to resected specimens of esophageal SCC, and use of the Western criteria may lead to a delay in early diagnosis of esophageal SCC thus postponing the start of the treatment.

It seems necessary to emphasize once again the importance of diagnosis on the early stage carcinoma. Currently, the five-year survival rate of EC is 15–25%, but the survival rate can reach 80% if EC is detected at the early stages [10–12].

Sufficient experience has been accumulated in a number of issues related to the early diagnosis of SCC. We think it is necessary to propose organizational consensus meeting between Japanese and Western pathologists and endoscopists in order to achieve a solid common approach to the nomenclature and tactics of managing such patients [13]. Such consensus is necessary to ensure timely treatment and increase the survival rate of patients with SCC.

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CONFLICT OF INTERESTS

All authors report no conflict of interest to disclose regarding this article.

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ETHICS APPROVAL

The present study was conducted in accordance with the Declaration of Helsinki (1964) and later versions and Good Clinical Practice guidelines and with the approval of the Institutional Review Boards of Hitachi General Hospital. All the patients of the Shizuoka Prefectural Cancer Center provided written informed consent for ESD or surgery, as well as for the possibility of using their specimens in future medical studies as long as their privacy was protected.

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