Pathology – Research and Practice 212 (2016) 410–414

Contents lists available at ScienceDirect

Pathology – Research and Practice

journal homepage: www.elsevier.com/locate/prp

Original article

Are new criteria for mixed histology necessary for endoscopic resection in early gastric cancer?

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ARTICLE INFO

Article history:
Received 30 September 2015
Received in revised form 2 February 2016
Accepted 7 February 2016

Keywords:
Early gastric cancer
Mixed histology
Endoscopic resection
Lymph node metastasis

ABSTRACT

Purpose: Early gastric cancer (EGC) of mixed histology is more aggressive than other histologies. In addition, signet ring cell (SRC) mixed histology shows more submucosal invasion and greater lymph node metastasis (LNM). However, there are no criteria for endoscopic resection (ER) in mixed histology. Therefore, this study investigated whether new criteria for mixed histology are necessary for ER in EGC.
Methods: From January 2005 to December 2012, 3419 patients with EGC underwent surgery. Lesions were classified using three histological classifications: the Japanese classification; World Health Organization (WHO) classification including SRC mixed histology; and Lauren classification. The mixed type in the Lauren classification was also reclassified according to the proportion of differentiated and undifferentiated components. Clinicopathological characteristics were compared according to histological classifications, with special reference to the ER criteria.
Results: With the Lauren classification, 179 (5.3%) lesions were classified as mixed type, including 54 (30.2%) lesions as the differentiated-predominant mixed type. There were 361 (10.6%) lesions classified as SRC mixed histology. Mixed-type lesions in the Lauren classification and SRC mixed lesions were significantly associated with larger size and a greater LNM. Among the lesions meeting the ER criteria, 20 (1.6%) and 55 (4.7%) were categorized as mixed type by the Lauren classification and SRC mixed histology, respectively. However, there was no LNM among the lesions recategorized into mixed histology.
Conclusions: Mixed histology showed no LNM among the lesions met the present ER criteria. Thus, separate criteria for mixed histology might be not necessary in the criteria for ER in EGC.

Introduction

Endoscopic resection (ER) can be curative for selected cases of early gastric cancer (EGC) [1]. The risk of lymph node metastasis (LNM) is the most important factor when deciding on ER in EGC [2]. Therefore, the criteria for ER consist of factors related to the risk of LNM, including histological differentiation. Histological classifications of gastric cancer include the World Health Organization (WHO), Lauren, and Japanese classifications [1–4]. Many studies have reported that the biological behavior of EGC differs according to the histological differentiation [5,6].

Hanaoka et al. reported that the rate of LNM was higher in the mixed type than in the pure differentiated type [7]. We also reported that SRC mixed histology, which was defined as adenocarcinoma with a minor component less than 50% of the SRC, had a higher LNM rate than other histologies [6]. Kozuki et al. reported that mixed-type carcinoma had a greater proportion of LNM than diffuse carcinoma of the stomach [8].

However, the present criteria for ER simply categorize EGC into differentiated or undifferentiated histology based on the Japanese classification. There are no criteria for ER for mixed histology in EGC. Therefore, this study analyzed the clinicopathological behavior of mixed histology in EGC to investigate whether new criteria of ER are necessary for mixed histology.

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http://dx.doi.org/10.1016/j.prp.2016.02.013
0344-0338/

Patients and methods

Patients

The study enrolled 3419 patients diagnosed with EGC who underwent surgery at Severance and Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Korea, between January 2005 and December 2012.

Pathology

The subjects' EGC was classified using three histological classifications: the Japanese, WHO, and Lauren classifications [2–4,7]. The 2000 WHO classification recognizes four major histological patterns: tubular, papillary, mucinous, and signet ring cell carcinoma (SRC). It then classifies EGC by histological as well, moderate, and poorly differentiated. We added SRC mixed histology (called partly SRC, p-SRC) to the WHO classification as mixed histology based on a previous report [6]. Based on the WHO classification, p-SRC can be defined as an adenocarcinoma with a minor component less than 50% of the SRC [6]. That is, if adenocarcinoma has a minor component less than 50% of the SRC, that adenocarcinoma is categorized as p-SRC irrespective of predominant histologic types (well, moderate, or poorly differentiated adenocarcinoma).

In the Japanese classification, well- and moderately differentiated tubular adenocarcinoma and papillary adenocarcinoma were classified as 'differentiated type' and poorly differentiated adenocarcinoma and SRC was classified as the 'undifferentiated type' based on the predominant patterns of the tumor [9]. That is, different histological types seen in a tumor are recorded according to their quantitative predominance [10]. The present criteria of ER use the Japanese classification such as differentiated or undifferentiated-type based on the predominant histology.

In the Lauren classification, intestinal and diffuse-type adenocarcinomas are the two major histological subtypes, including another subtype of mixed type as non-homogenous mixtures. The mixed type from the Lauren classification was divided into differentiated dominant and undifferentiated dominant types, which we termed the modified Lauren classification based on a previous study by Hanaoka et al. [7]. That is, the lesions were classified into the following four categories according to the modified Lauren classification: differentiated type, differentiated dominant mixed type, undifferentiated dominant mixed type, and undifferentiated type [7]. The category was classified based on the percentages of undifferentiated-type components [7].

Therefore, mixed histology was defined in each histological classification as follows: p-SRC in the WHO classification, mixed type in the Lauren classification, and predominantly differentiated or undifferentiated mixed types in the modified Lauren classification. We analyzed the clinicopathological characteristics of each histological classification, with special reference to the LNM rate, as criteria for ER.

Statistical analysis

The chi-square test was used to examine associations among categorical variables and the *t*-test was used for non-categorical variables. A p-value <0.05 was considered statistically significant. All analyses were performed using SPSS ver. 12.0 for Windows (SPSS, Chicago, IL, USA).

Results

Baseline clinicopathological characteristics of the subjects (Table 1, Fig. 1)

Table 1 shows the clinicopathological features of the subjects. The mean tumor diameter was 25 mm and LNM was observed in 355 (10.4%). According to the Japanese classification currently used as ER criteria, 1700 (49.7%) were differentiated type and 1719 (50.3%) were undifferentiated type.

Fig. 1 shows the proportion of mixed histology in each histological classification. Mixed histology cannot be classified with the Japanese classification currently used as ER criteria because the Japanese classification has been categorized based on the predominant histological type. However, according to each classification, mixed histology was reclassified as shown Fig. 1. In accordance with the WHO classification, 361 (10.6%) were reclassified as partly SRC. According to the Lauren classification, 179 (5.3%) were reclassified as mixed type. According to the modified Lauren classification, 54 (1.6%) were reclassified as differentiated-predominant mixed type and the remainder (3.7%) were undifferentiated-predominant mixed type.

Clinicopathological features according to histology (Table 2)

The Japanese classification currently used for ER shows no difference in LNM between differentiated and undifferentiated adenocarcinoma. However, submucosa invasion and lymphovascular invasion (LVI) are more frequent in differentiated type (Table 2a).

Table 1
Baseline clinicopathological characteristics of the subjects.

	n	%		*n*	%
Gender			WHO classification		
Male	2224	65.0	AWD/AMD	1643	48.0
Age (years, mean ± SD)	57.4 ± 11.5		APD	485	14.2
Tumor location			SRC	930	27.2
Upper	366	10.7	Partly SRC	361	10.6
Middle	617	18.0	Tumor diameter (mm, mean ± SD)	25.0 ± 16.1	
Lower	2436	71.3			
Japanese classification			Depth of invasion		
Differentiated	1700	49.7	Mucosa (T1a)	1781	52.1
Undifferentiated	1719	50.3	Submucosa (T1b)	1638	47.9
*Lauren classification			Lymphovascular invasion	414	12.1
Intestinal	1873	55.9			
Diffuse	1301	38.8	Perineural invasion	82	2.4
Mixed	179	5.3	Lymph node metastasis	355	10.4
Modified Lauren			N1	223	6.5
Mixed-differentiated	54	1.6	N2	102	3.0
Mixed-undifferentiated	125	3.7	N3	30	0.9

AWD/AMD, Well/moderate differentiated adenocarcinoma; APD, Poorly differentiated Adenocarcinoma; SRC, Signet ring cell carcinoma.
* Lauren classification could be evaluated in 3353 cases among 3419 patients.