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ORIGINAL ARTICLE

Clinicopathological features and outcomes in patients undergoing radical resection for early gastric cancer with signet ring cell histology

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KEYWORDS
Early gastric cancer;
Signet ring cell histology;
Prognosis

Summary
Background: The signet ring cell histology is regarded as an independent predictor of poor prognosis in advanced gastric adenocarcinomas, but its biologic behavior in early gastric cancer remains highly controversial.
Objective: Our objective was to compare the clinicopathological features and outcomes in patients undergoing curative resection between SRCs and non-SRCs histologic types of early gastric cancer.
Methods: Clinicopathologic features and the overall survival rates of 334 patients with early gastric cancer undergoing D2 curative resection from January 1994 to December 2008 were retrospectively reviewed and compared according to the histologic type.
Results: Clinicopathologic features were comparable between two groups, except age, ulcer findings and the presence of lymph node metastasis. The incidence of recurrence for SRCs group was significantly lower than that for non-SRCs group (10.4% vs 19.6%; $P < 0.05$). The overall 5-year survival rate was 88.6% in all cases. The overall survival rate of patients in SRCs group was significantly better than that of patients in non-SRCs group (5-year survival, 93.9% vs 85.8%; $P = 0.027$). Multivariable analysis revealed that SRCs subtype, lymphovascular invasion, and lymph node metastasis were independent prognostic factors.
Conclusion: Our analysis revealed that the biological behavior of SRCs was different from other undifferentiated cancer histologic subtypes in early stage. Early gastric cancer with signet ring cell histology had low incidence of lymph node metastasis and a relatively favorable prognosis.

Introduction

In 1962, the Japanese Society of Gastroenterological Endoscopy defined early gastric cancer as a lesion confined

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to the mucosa and/or submucosa, regardless of lymph node metastatic status [1]. The need to define this category of gastric cancer is related to the difference in prognosis between early and advanced gastric cancer. The prognosis is generally favorable in early gastric cancers after radical surgery, with a 5-year survival rate of more than 90% [2,3]. The proportion of early gastric cancer among all gastric cancers has increased to nearly 50% in Japan and Korea [4—6]. With more widespread mass screenings, as well as advances in endoscopic techniques and equipment, similar trends have been observed during the past few decades in China.

According to the Japanese Gastric Cancer Association, undifferentiated gastric carcinoma includes poorly differentiated adenocarcinoma, mucinous adenocarcinoma and signet ring cell carcinoma [7]. Signet ring cell carcinomas (SRCs) are defined as gastric cancers in which the predominant component consists of isolated or small groups of malignant cells containing intracytoplasmic mucins [8]. Generally, SRCs and poorly differentiated adenocarcinomas, mucinous adenocarcinoma are associated with an ominous outcome. However, the prognostic significance of SRCs histologic subtype in early stage remains controversial. Some studies have reported that SRCs have a lower incidence of lymph node metastasis and favorable prognosis than other undifferentiated cancer histologic subtypes [9,10]. For this reason, undifferentiated early gastric carcinoma includes SRCs subtype and non-SRCs subtype should be investigated separately with regard to oncologic outcomes. The aim of this retrospective study was to compare the clinicopathologic features and outcomes between SRCs group and non-SRCs group in patients undergoing radical resection for early gastric cancer.

Patients and methods

Patients

Institutional review board approval was obtained before conducting this study. A total of 334 patients who had undergone radical (R0) gastrectomy with D2 lymph node dissection for histologically proven undifferentiated early gastric cancer from January 1994 to December 2008 at the Department of Abdominal Surgical Oncology, Cancer Hospital of the Chinese Academy of Medical Sciences, Peking Union Medical College were selected for this study. Cases with recurrence or multifocal gastric cancer were excluded. Histology was classified according to the Japanese Gastric Cancer Association [7].

All the patients routinely underwent an upper alimentary tract barium meal and electronic gastroscope examination before surgery to identify the diseased region and the pathologic type to confirm the diagnosis of malignant neoplasm of the stomach after pathologic examination. The preoperative routine chest X-ray, abdominal ultrasound, and upper abdominal CT examination showed no pulmonary, hepatic, or other distant metastases and no tumor directly invading the pancreas, spleen, liver, or colon. Endoscopic ultrasound examination was not performed routinely. All patients underwent radical subtotal or total gastrectomies, depending on the tumor location and intraoperative verification of tumor-free resection margins, as well as D2 lymphadenectomies. Those with tumors located in the lower third of the stomach underwent distal gastrectomy. Patients with tumors in the middle third of the stomach underwent either distal gastrectomy or total gastrectomy according to the direction of the tumor invasion. Proximal gastrectomy was used for patients with tumors in the upper third of the stomach, and total gastrectomy was used for those with tumors occupying the entire stomach. In this series, distal gastrectomy was performed in 283 patients, total gastrectomy was performed in 33 patients, and proximal gastrectomy was performed in 18 patients. No patient has received neoadjuvant therapy before surgery. The methods of reconstruction after distal gastrectomy include Billroth I, II or Roux-en-Y. Roux-en-Y reconstruction and jejunal interposition are the most common methods used after a total gastrectomy. All specimens were examined after resection. World Health Organization criteria for histological typing of gastric tumors were used, where signet ring cell carcinoma is defined as an adenocarcinoma in which a predominant component (more than 50% of the tumor) is made up of isolated or small groups of malignant cells containing intracytoplasmic mucin. The formalin-fixed specimens were cut into multiple slices, principally parallel to the lesser curvature, at an interval of 3 mm. The hematoxylin and eosin stained sections of tumor were examined. A single pathologist retrieved all lymph nodes by palpation under gross inspection. The lymph nodes were cut into two pieces along the long axis, embedded in paraffin blocks, and stained with haematoxylin and eosin.

Of these patients, SRCs group had 115 patients (34.4%), and non-SRCs had 219 patients (65.6%). The patients' clinical characteristics, histopathological parameters and follow-up data were analyzed. Clinicopathological factors, such as sex-ratio, age, tumor size, tumor location, macroscopic appearance, histological type, ulceration, depth of tumor invasion, lymph node status and lymphovascular invasion were defined according to the Japanese Classification of Gastric Carcinoma [7]. The maximum diameter of tumor was recorded as tumor size. Macroscopic type includes elevated (I, protruded; IIa, superficial elevated), flat (IIb, superficial flat), and depressed (IIc, superficial depressed; III, excavated). Lesions with ulceration or scarring from previous ulceration (converging folds or deformity of the muscularis propria, or fibrosis in the submucosal or deeper layer) within them were regarded as ulcerated lesions. The depth of tumor invasion was classified as mucosa and submucosa carcinoma. Lymphovascular invasion was defined as the presence of tumor emboli either in the lymphatic duct or the vascular lumen. Overall survival and the pattern of recurrence were compared between the two groups. Patients with SRCs were considered as the reference group for statistical analysis.

Follow-up

All patients who survived the operation were followed until death or the cutoff date (March 31, 2014). All patients were followed up regularly at 3-month intervals in the first 2 years and the every 6 months thereafter for clinical examination including chest X-ray, abdominal and pelvic ultrasound or CT and tumor markers. Follow-up evaluation was implemented by means of outpatient service, telephone calls, and letters. Median follow-up period were 97 months (range, 66—236). Only deaths due to early gastric cancer were considered. Deaths due to other causes were censored at the date of death. Three patients were lost to follow-up. These patients were excluded from the present study.