Distribution of the Deepest Penetrating Point of Minute Submucosal Gastric Cancer

Souya Nunobe1,2, Takuji Gotoda1, Ichiro Oda1, Hitoshi Katai2, Takeshi Sano2, Tadakazu Shimoda3 and Mitsuru Sasako2

1Endoscopy Division, 2Department of Surgical Oncology and 3Department of Clinical Laboratory, National Cancer Center Hospital, Tokyo, Japan

Received April 21, 2005; accepted August 10, 2005; published online September 19, 2005

Background: Accurate assessment of depth of invasion is critical in decision-making for additional surgery after endoscopic resection of early gastric cancer (EGC). Although this depth of invasion is determined at the deepest point of submucosal invasion (DPSI), there is no literature describing the distribution of deepest invasion point.

Objective: To describe the location of the DPSI, and to determine whether it is possible to predict this point by clinicopathological features before treatment.

Methods: One hundred and ninety-five lesions of EGC with minute submucosal invasion, which had been resected en bloc between 1991 and 2003, were reviewed. For each lesion, we recorded the location of the DPSI as being in one of three areas demarcated by three concentric equal distance rings. We also examined the correlation between the location of the deepest penetration and the clinicopathological characteristics.

Results: The DPSI was located most often (53%) in the central, less often (31%) in the middle and least often (16%) in the outermost area. There was no significant correlation between the distribution of the deepest point and any clinicopathological features.

Conclusions: The DPSI was not always in the central area, and it was impossible to predict its location by clinicopathological features alone. To obtain an accurate measure of depth of tumor invasion, we must histologically assess the entire lesion by thin sections.

Key words: minute submucosal penetration – early gastric cancer – depth of invasion – endoscopic mucosal resection

INTRODUCTION

Because the presence of lymph node metastasis has a strong adverse influence on a patient’s prognosis (1,2), gastrectomy with lymph node dissection had been the gold standard treatment for patients who had early gastric cancer (EGC) in Japan (3–5). Recent studies, however, have identified the subgroup of patients in whom the risk of lymph node metastasis is minimal (6,7). These patients’ lesions are ideal candidates for local resection through endoscopic mucosal resection (EMR), a procedure associated with rates of morbidity and mortality significantly lower than those of surgery. Today in Japan, EMR has become the standard treatment for patients who meet certain endoscopic and pathologic criteria.

EMR is the most reliable technique not only to remove mucosal lesions but also to ensure complete histological assessment of these resected specimens. Considering the limit of imaging techniques currently available (8), histological examination of the entire lesion is mandatory to assess the risk of residual disease (mainly lymph node metastasis) and the need for additional surgical treatment.

Traditionally, clinicians have assumed that the deepest point of submucosal invasion (DPSI) of gastric cancer with minute invasion occurs most commonly near the center of the lesion. However, we are not aware of any studies that support this assumption. Determination of the potential locations of minute submucosal invasion is important if we are to develop strategies to resect EGC and to examine the resected materials. There are several useful techniques of EMR (9), such as conventional strip biopsy (10), EMR using cap (11) or EMR using a ligation device (12). These allow resection of a limited-size area only, so often a piecemeal resection is required (13–15). If we could predict the area where DPSI is located, whether that area is always in the center or is strongly correlated with clinicopathological features, then we should be able to resect the identified area in one piece to ensure accurate histological assessment.
assessment of the true tumor depth, even when we perform piecemeal resection, which can otherwise be problematic because of the burn effect at the resection margins. Thus, our goal was to describe the distribution of the DPSI in patients who underwent resection of minute penetrating submucosal gastric cancer.

METHODS

From a prospectively entered database that contained findings of all patients who were treated for EGC in the National Cancer Center Hospital between 1991 and 2003, we selected 195 patients (152 male, 43 female; mean age ± SD, 65.2 years ± 1.02) who had differentiated adenocarcinoma with a minute submucosal invasion. Histologically, we classify differentiated adenocarcinoma to include well and moderately differentiated tubular adenocarcinoma and papillary adenocarcinoma (16). Surgery with lymph node dissection or differentiated adenocarcinoma and papillary adenocarcinoma was performed in 106 and 89 patients, respectively. EMR was performed in 106 and 89 patients, respectively. All specimens obtained by EMR were resected in one piece. Minute submucosal penetration was defined as invasion to the submucosal layer <500 μm from the muscularis mucosa; it was measured at the deepest level of penetration of the cancer cells including lymphatic–vascular involvement with an ocular lens scale, as previously described (17).

All pathological procedures were performed according to the Japanese classification of gastric carcinoma (18). Pathological examination of EGC specimen includes a photographic documentation of the specimen before and after serial 2 mm (EMR) or 5 mm (surgery) sectioning. These images allowed us to map the location of the cancer and DPSI. We divided each lesion into three equal width concentric rings, and identified the deepest penetration as being located in the central, middle or outermost areas.

We performed univariate analyses to test for correlation between the location of the DPSI and these clinicopathological features: macroscopic type, tumor size, presence or absence of peptic ulceration, location of the tumor in stomach and lymphatic–vascular involvement. The presence of peptic ulcer or peptic ulcer scar (defined endoscopically as converging folds and histologically as a deformity of the muscularis propria or fibrosis in the submucosal or deeper layer) within a cancerous lesion was defined as a positive ulcerative finding. The location of the tumor was also classified as being in one of the three areas (upper, middle or lower third of the stomach).

We performed our statistical analyses using the SAS program (SAS Institute, Cary, NC, USA). We assessed the association between the location of DPSI and the clinicopathological variables using a simple \( \chi^2 \) test as univariate analysis; we considered \( P < 0.05 \) as significant. We applied the Bonferroni’s correction to adjust for multiple comparisons.

RESULTS

Among the 195 lesions examined, 194 (99%) were endoscopically evaluated as intramucosal cancer before resection. The locations of the DPSI within their lesions are shown in Fig. 1: 103 (53%) were in the central, 60 (31%) were in the middle and 32 (16%) were in the outermost area. Table 1 shows the largest dimension of each lesion; the mean was 29.8 mm.

Table 2 showed the correlation between the clinicopathological features and the location of DPSI. Univariate analysis showed no significant association of the clinicopathological features with the distribution of DPSI. In 73 cases with ulcerative findings of this study, there was no correlation between ulcer location and DPSI.

DISCUSSION

We found that minute submucosal invasion in EGC is not always located at the center. We also found that the DPSI could not have been predicted before pathological examination. Thus, the only way to assess true tumor depth is to resect the entire lesion in one piece, avoiding burn effects inside the lesion. Our results support the notion that standard techniques using strip biopsy, EMR with ligation and EMR with cap are reliable only when they are applied to small lesions. Endoscopic submucosal dissection (ESD) is the optimal technique to resect larger lesion (19). In ESD, the endoscopist makes a circumferential cut ~5 mm beyond the border of the tumor. He or she then carefully dissects the lesion off the muscularis propria using a specialized endoscopic knife (20). Thus, even large lesions can be resected in one piece, with surrounding non-cancerous mucosa as the margins (21,22).

Differentiation of mucosal from submucosal EGC is known to be difficult. We reviewed images of the cases we presented in this study multiple times. We found only one case that we could diagnose as submucosal cancer. Our data are in
Table 2. Relationship between clinicopathological factors and distribution of the deepest points of minute submucosal invasive carcinoma

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Number</th>
<th>Central</th>
<th>Middle</th>
<th>Outer</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macro type</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Raised</td>
<td>66</td>
<td>35</td>
<td>23</td>
<td>8</td>
<td>0.967</td>
</tr>
<tr>
<td>Depressed</td>
<td>129</td>
<td>68</td>
<td>37</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>Tumor size (mm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤20</td>
<td>93</td>
<td>47</td>
<td>25</td>
<td>21</td>
<td>0.542</td>
</tr>
<tr>
<td>&gt;20</td>
<td>102</td>
<td>56</td>
<td>35</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Ulcer finding</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>122</td>
<td>65</td>
<td>35</td>
<td>22</td>
<td>0.868</td>
</tr>
<tr>
<td>Yes</td>
<td>73</td>
<td>38</td>
<td>25</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Location</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>U</td>
<td>37</td>
<td>22</td>
<td>13</td>
<td>2</td>
<td>0.105</td>
</tr>
<tr>
<td>M</td>
<td>99</td>
<td>57</td>
<td>23</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>L</td>
<td>59</td>
<td>24</td>
<td>24</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>ly–v</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>162</td>
<td>86</td>
<td>46</td>
<td>30</td>
<td>0.869</td>
</tr>
<tr>
<td>Yes</td>
<td>33</td>
<td>17</td>
<td>14</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Histological type</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Well</td>
<td>162</td>
<td>84</td>
<td>47</td>
<td>31</td>
<td>0.156</td>
</tr>
<tr>
<td>Mod</td>
<td>30</td>
<td>18</td>
<td>11</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Pap</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>195</td>
<td>103</td>
<td>60</td>
<td>32</td>
<td></td>
</tr>
</tbody>
</table>

Location, location in stomach; U, upper third; M, middle third; L, lower third; ly–v, lymphatic or vascular involvement. Histological type: Well, well differentiated adenocarcinoma; Mod, moderately differentiated adenocarcinoma; Pap, papillary adenocarcinoma.

*We assessed whether or not the deepest point was located at the central area using a simple χ² test as univariate analysis.

agreement with those reported in the literature. Previous studies showed that the accuracy of endoscopic assessment has been only ~80% (23,24), even when endoscopic ultrasonography is used (25,26). Mitsunaga et al. (27) reported that beneath granular elevation within shallow depressed lesions suggested submucosal invasion. However, this finding was not reported in all cases of the present study. It would be expected that such an assessment is even more difficult for EGC with minute submucosal invasion. Additionally, for the pathologists, our analyses indicate the importance of meticulous serial thin sectioning, the technique currently used to determine the DPSI and possible lymphatic or vascular invasion.

Recently, the correlation between the progress and the phenotype of gastric cancer has been reported (28). However, the phenotype was not routinely investigated, and the correlation reported in the present study was not examined. In future, it is important to examine the pattern of invasion including DPSI from the immunohistochemical perspective.

In conclusion, the location of the DPSI in the differentiated gastric cancer with minute invasion was not always in the central area, and could not be predicted a priori. Cancers with minute submucosal invasion could not be distinguished from intramucosal cancer based only on endoscopic findings. If we are to ensure accurate assessment of the risk of residual disease, we must perform histological examination by thin sections for whole block specimens that potentially include minute submucosal invasion.

References