Clinicopathological Study on Poorly Differentiated Adenocarcinoma of the Colon

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Summary: Clinicopathological characteristics and grading of poorly differentiated colon adenocarcinoma (Por) were discussed. A total of 1074 patients with colon cancer underwent surgical treatment at Kurume University Hospital in Fukuoka, between 1985 and 2005. Clinicopathological characteristics of 88 cases (8%) of Por and 986 cases (92%) of well differentiated tubular adenocarcinoma/moderately differentiated tubular adenocarcinoma (Tub1/Tub2) were studied. A multiple classification analysis showed that Por was more frequently observed in the right colon than Tub1/Tub2, and that the ratio of macroscopic types 3 and 4 was significantly higher in Por. Significant differences were also observed with regard to lymph vessel and perineural invasion. There were no significant differences between recurrence-free survivals of Por and Tub1/Tub2 after radical resection in Stages II and III. Recurrence of Por was significantly higher in peritonea and lymph nodes. These findings indicate that Por, which is generally considered to have a poor prognosis, has a similar recurrence rate to that of Tub1/Tub2 after the performance of radical surgery.

Key words poorly differentiated colon adenocarcinoma, prognosis, perineural invasion

INTRODUCTION

Most colon cancers are classified as either well differentiated tubular adenocarcinoma (Tub1) or moderately differentiated tubular adenocarcinoma (Tub2). According to a nationwide study by Yasutomi [1], the prevalence of poorly differentiated adenocarcinoma (Por) in Japan is 4.8%. Other reports have stated it to be 2.7% to 10% in this country [2-16], while it is estimated to be approximately 20% in Europe and the United States [17,18]. There has been little discussion of the clinicopathological characteristics of Por, which is considered to have a poor prognosis. We found the prevalence of Por to be 8%, which was slightly higher than that in Yasutomi’s report. The present study compared the prognosis and clinicopathological characteristics of Por with those of Tub1/Tub2. This comparison revealed abundant and significant statistical differences, which are discussed with reference to the literature.

SUBJECTS AND METHODS

A total of 1074 patients with colon cancer underwent surgical treatment at Kurume University Hospital in Fukuoka, between 1985 and 2005. All cases were associated with sporadic colon cancer. Informed consent was obtained from all patients before surgical resection was performed, and this study was approved by the Institutional Review Committee for Research on Human Subjects in Kurume University Hospital. In our department excised samples were completely segmented and the detailed characteristics of each cancer were depicted. Tumor differentiation, the degree of invasion, venous invasion, lymph vessel invasion and perineural invasion were examined by pathologists.
and histopathological classifications were performed according to the General Rules for Clinical and Pathological Studies on Cancer of the Colon, Rectum, and Anus published by the Japanese Society for Cancer of the Colon and Rectum [19]. Venous invasion was evaluated by Elastica van Gieson (EVG) stain. Adenocarcinoma tissues were classified as Por or Tub1/Tub2 in accordance with the dominant tissue images. The subjects in this study were patients suffering recurrence or survival according to our department database. The cases were classified as either Tub1/Tub2 or Por, and the clinicopathological characteristics of each adenocarcinoma were studied. The prevalence of Por was 8% (88/1074 cases). The statistical significance of differences between Tub1/Tub2 and Por were examined using the chi-square test, Fisher’s exact test, and the t-test. Cumulative survival rate was calculated using the Kaplan-Meier method with comparisons performed using the log-rank test. A logistic analysis and the Cox proportional hazard model were used for a multiple classification analysis. A p value of <.05 was considered significant. For statistical analysis, JMP 8 version 8.0 (SAS Institute Inc., USA) was used.

RESULTS

Clinicopathological characteristics (Table 2)

The average age of subjects with Por was 63 years, and males tended to be more susceptible as compared with Tub1/Tub2; however, these differences were not significant. No cases of Stage 0 or I Por were found. Fisher’s exact test demonstrated significant differences (p<.001) in the following categories: stage (p<.001), location (p<.001), macroscopic type (p<.001), tumor size (p<.001), invasion depth (p<.001), lymph node metastasis (p<.001), lymph vessel invasion (p<.001), venous invasion (p<.001), and perineural invasion (p<.001). Logistic regression analysis extracted the following 4 items as independent factors for Por: location (right colon) (p<.001, confidence interval [CI]: –0.764 - –0.275, odds ratio [OR]: 2.812), macroscopic type (types 3 and 4) (p<.001, CI: –0.780 - –0.238, OR: 2.779), lymph vessel invasion (positive) (p<.001, CI: –1.397 - –0.390, OR: 5.376), and perineural invasion (positive) (p=.032, CI: –0.570 - –0.022, OR: 1.818). There were no significant differences in preoperative carcinoembryonic antigen (CEA) values.

Recurrence-free survival rate

Figures 1 and 2 show recurrence-free survival rates in cases where radical surgery was performed (CurabilityA (CurA)).

In Stage II, 14 Por and 280 Tub1/Tub2 cases were observed. Postoperative chemotherapy was given to 3 Por cases (21%) and 107 Tub1/Tub2 cases (38%). The recurrence-free survival rate of Por was lower than that of Tub1/Tub2; however, the difference was not significant (log-rank p=0.354).

In Stage III, 36 Por and 255 Tub1/Tub2 cases were observed. Postoperative chemotherapy was given to 14 Por cases (39%) and 122 Tub1/Tub2 cases (48%). As in Stage II, the recurrence-free survival rate of Por was lower than that of Tub1/Tub2; however, the difference was not significant (log-rank p=0.354).

Similarly, no significant differences in the recurrence-free survival rate were observed in Stage IV.

First recurrent pattern (Table 3)

Fisher’s exact test showed significant differences in peritonea (p=.018) and lymph nodes (p<.001) in
THE PROGNOSIS OF POORLY DIFFERENTIATED COLON ADENOCARCINOMA

TABLE 2.
Clinicopathological features of histological types

<table>
<thead>
<tr>
<th>Variable</th>
<th>Tub1, Tub2</th>
<th>Por</th>
<th>χ²</th>
<th>Odds ratio</th>
<th>CI</th>
<th>Multivariate analysis p value</th>
<th>Univariate analysis p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age±SD (y)</td>
<td>65±11</td>
<td>63±12</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>0.127</td>
</tr>
<tr>
<td>Sex F/M</td>
<td>401/585</td>
<td>38/50</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>0.652</td>
</tr>
<tr>
<td>Stage</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>III, IV/0, I, II</td>
<td>441/540</td>
<td>73/15</td>
<td>0.10</td>
<td>1.288</td>
<td>-0.840 - 0.840</td>
<td>0.756</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Location</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>V, C, A, T, D, S, Rs</td>
<td>342/644</td>
<td>51/37</td>
<td>17.27</td>
<td>2.812</td>
<td>-0.764 - -0.275</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Macroscopic type</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3, 4/1, 2</td>
<td>99/881</td>
<td>31/56</td>
<td>13.73</td>
<td>2.779</td>
<td>-0.780 - -0.238</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Tumor size (cm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.5≤/4.5&gt;</td>
<td>509/463</td>
<td>62/25</td>
<td>0.01</td>
<td>0.974</td>
<td>-0.274 - 0.289</td>
<td>0.926</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Primary tumor si, se, ss, mp, sm, m</td>
<td>707/278</td>
<td>85/2</td>
<td>2.05</td>
<td>3.158</td>
<td>-1.531 - 0.118</td>
<td>0.152</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Lymph node metastasis +/−</td>
<td>403/555</td>
<td>70/17</td>
<td>0.54</td>
<td>1.766</td>
<td>-1.221 - 0.372</td>
<td>0.462</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Lymph vessel invasion +/−</td>
<td>537/444</td>
<td>82/5</td>
<td>11.11</td>
<td>5.376</td>
<td>-1.397 - -0.390</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Venous invasion +/−</td>
<td>673/309</td>
<td>80/7</td>
<td>0.00</td>
<td>0.999</td>
<td>-0.531 - 0.457</td>
<td>0.998</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Perineural invasion +/−</td>
<td>110/842</td>
<td>30/55</td>
<td>4.59</td>
<td>1.818</td>
<td>-0.570 - -0.022</td>
<td>0.032</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>CEA (ng/ml)</td>
<td>299/536</td>
<td>31/44</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>0.380</td>
</tr>
</tbody>
</table>

Tub1,2: Well and moderately differentiated tubular adenocarcinoma, Por: Poorly differentiated adenocarcinoma.

Fig. 1. Recurrence-free survival rate for patients in stage II.
Tub1: Well differentiated type, Tub2: Moderately type, Por: Poorly differentiated adenocarcinoma.
comparisons of first recurrence patterns. When lymph nodes and peritonea were subjected to logistic regression analysis, peritonea (p=.011, CI: –2.058 - –0.298, OR: 9.475) and lymph nodes (p=.003, CI: –2.597 - –0.560, OR: 20.408) were extracted as independent factors. The recurrence locations overlapped.

**DISCUSSION AND CONCLUSIONS**

Patients who underwent surgery for Por were younger than those with Tub1/Tub2 [20,21]. Differences in gender vary depending on the report. In our case, no significant statistical differences were found with regard to median age or gender. The clinicopathological characteristics of Por reported so far are as follows: (1) Por frequently occurs in the right colon [3-16,22]. (2) Macroscopic types 3 and 4 are frequently observed [3,4,6,7,10]. (3) Cancer invasion is deep and infiltrative [3-5,7-15]. (4) Por metastasizes at high rates [3-5,7-9,11-16]. (5) Lymph vessel and venous invasion are severe [5,7-15]. (6) The ratio of peritoneal dissemination is high [4,8,9,11-13,15,16]. (7) Clinicopathological staging is advanced [4,7-9,11-15]. (8) Prognosis is poor [3-5,7-16].

Tumor locations were concentrated in the right colon in our multiple classification analysis. Shimizu et al. [22] reported animal carcinogenesis experiments in which Por occurred in the cecum and proximal colon.
and Tub1 occurred in the distal colon. A report of hereditary nonpolyposis colorectal cancer showed that bowel cancer with microsatellite instability caused by DNA replication error had Por in the right colon [23,24]. These reports suggest a need for a study of the microsatellite instability in our case. Macroscopic types 3 and 4 were frequently observed in our multiple classification analysis, as in previous reports. For cancer invasion depth, 2 of 87 Por cases were mp, while 85 of 87 cases were se and si. The depth was greater than that of Tub1/Tub2. Statistically, there were no significant differences in the multiple classification analysis. In Por, multiple classification analysis showed significantly higher rates of lymph vessel and perineural invasion. First recurrence patterns showed significantly higher rates of Por in the peritonea and lymph nodes. Positive lymph nodes and deeper invasion implied that Por included more advanced cases with Stage III or higher disease compared with Tub1/Tub2. The recurrence-free 5-year survival rate of Cur A cases was discussed as to prognosis. In Stage II, the prevalence of Por was 83.1% and that of Tub1/Tub2 was 89.6%; the difference was not significant. The recurrence-free 5-year survival rate in Stage III was 65.7% for Por and 72.0% for Tub1/Tub2; again the difference was not significant. Some studies have reported that the prognosis of Por was poorer than that of Tub1/Tub2, even after radical surgery [3-5,7-16]. To compare prognoses according to tissue type, a wider study is necessary.

In the present study, no significant difference was observed between the prognoses of Por and Tub1/Tub2 when radical surgery was performed. In the treatment guidelines for colon cancer [25], Por is defined as a Stage II colon cancer with a high risk of recurrence. No significant differences were observed in the prognosis of Por when compared with the prognosis of Tub1/Tub2. Hence, our findings suggest that postoperative adjunctive chemotherapy may not be necessary in cases where radical surgery is provided, even in cases that are determined to be Por. However, the number of cases studied was small, and further prospective studies in multiple facilities are necessary.

A summary of this study was delivered at the 34th Annual Meeting of The Japanese Society of Coloproctology in Kyushu, Japan.

REFERENCES


