The Relationship between Involved Lymph Nodes, Metastatic Nest Diameters and Prognosis in Colorectal Cancer

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Abstract

Introduction. Several studies evaluated the relation between colorectal cancer prognosis and various factors such as: depth of tumor invasion, involved lymph nodes size, counts and locations, metastatic nest expansion. We assessed the prognostic significance of the ratio between metastatic nest and involved lymph node diameter in colorectal cancer cases. Methods. A historical cohort study was conducted on patients with known colorectal cancer and metastatic lymph nodes (Astler Coller’s stage C), in whom diagnosis was confirmed at least one year before the study. Less than two months following surgery, patients were treated with the same chemotherapy protocol. Metastatic lymph node sizes were recorded in 63 pathologic samples. Metastatic nest borders were marked using a marker and a 40x magnifying microscope. The greatest metastatic nest to involved lymph node diameter ratio was obtained. The data were analyzed with SPSS analytic software. Actuarial and Kaplan-Meier methods were used to estimate survival. Survival functions were compared by Log rank and Cox regression tests. Results. There was no significant relation between colorectal cancer prognosis and: the greatest involved lymph node diameter, the metastatic nest diameter and the ratio metastatic nest to involved lymph node diameter (p-values in sequence: 0.1, 0.07, 0.2). Conclusion. We found no significant relationship between the colorectal cancer prognosis and the greatest lymph node diameter, the greatest metastatic nest diameter and the greatest metastatic nest to involved lymph node diameter ratio. Further studies are required in order to reach a decisive conclusion.

Keywords

Colorectal cancer – metastatic nest – lymph node size – prognosis.

Introduction

Nowadays, colorectal cancer is the third cause of mortality due to carcinoma worldwide [1]. According to one study performed in our country (1996-2000), age adjusted incidence rate in men and women with colorectal cancer was 8.2% and 7% in 100,000, as the third and fourth common cancer in each gender, respectively [2]. Staging is the most significant factor to select supplement therapy measures following tumor resection. Based on TNM staging the most important factors which influence prognosis are local tumor extension, lymph node involvement and distance metastasis [3, 4].

Prognosis is heterogeneous among patients having lymph node involvement [5, 6]. Several attempts have been made to subclassify metastatic lymph nodes and these have led to dividing N in the TNM staging system into two subgroups, N1 (1 to 3 involved nodes) or N2 (4 or more involved nodes) [7]. On the other hand, some recent studies have evaluated the prognostic significance of lymph node size in patients with esophageal and gastric cancers [8, 9].

There are a few controversial studies regarding the role of metastatic lymph node size on prognosis [10, 11]. However, further studies are required in order to evaluate this criterion of metastatic lymph node sub-classifying.

Materials and method

This study is a historical cohort one. The samples are 65 known cases of colorectal cancer with metastatic lymph nodes Astler Coller’s stage C hospitalized in the Alzahrı hospital, in whom diagnosis had been confirmed at least 1 year before the beginning of our study. In less than two months following surgery, they had been treated with the same chemotherapy protocol, based on 5-FU. Those with an additional carcinoma or metastasis were excluded.

All patients who had the eligibility criteria during 1996-
2005 in Alzahra hospital were selected. None of the rectal cases had received preoperative radiotherapy. Then in March 2007, their survival rates were calculated. We looked at their files available in Alzahra hospital to gather data, to record the pathology sample number and their phone number for following them up. In order to confirm the diagnosis, to obtain the number and size of involved lymph nodes and the greatest metastatic nest to lymph node diameter ratio, all the pathologic samples were reviewed.

Metastatic lymph node diameter was measured and the metastatic nest was marked with a marker and a 40x magnifying microscope. Its size was measured by using a standard ruler, too. Finally, the greatest metastatic nest to involved lymph node diameter ratio was obtained. All the samples were checked by two pathologists. The data was analyzed with SPSS analytic software. Actuarial and Kaplan-Meier methods were used to estimate the survival. Survival functions were compared by using the Log rank and Cox regression tests.

Results

One hundred and sixty nine known cases of colorectal cancer during 1996-2005 were evaluated. Sixty three patients in Astler Coller’s stage C who had received the same adjuvant chemotherapy based on 5-FU in less than two months following surgery entered this study. From these 63 cases, 28 patients (44.4%) were females. The mean age of patients was 62.53 years (59.09-65.97). The mean count of recovered lymph nodes was 4.45 (CI: 3.7-5.1). Thirty-four patients (54%) had died up to March 2007 and 29 (46%) were still alive.

In Table I survival analysis data are listed. The patients’ survival median was 43 months.

By using the ROC curve analysis, none of the variants such as lymph node counts, the greatest lymph node diameter, and the greatest metastatic nest diameter was appropriate in predicting death.

For the greatest metastatic nest to lymph node diameter ratio, the ROC curve analysis was also used. Its AUC was 0.57; therefore this variant does not seem to be appropriate in predicting death.

Considering ROC analysis, the best cut off point was 0.73 for the metastatic nest to lymph node diameter ratio. The survival mean was 40.97 months (31.08-50.85) for the group with metastatic nest to lymph node diameter ratio below 0.73, while for the group above 0.73, it was 59.5 months (39.0-80.0). So, in the log rank test results, there was no statistical difference (p=0.13) (Fig. 1). In addition, there was no significant difference in survival between lowest and highest cut off values.

With regard to ROC analysis, the best cut off point was 4.5 mm for the greatest metastatic nest size. Survival mean was 38.68 months (32.65-44.70) for the group with the greatest metastatic nest size below 4.5, while for the group above 4.5 mm it was 54.98 months (39.07-70.89). Thus, the log rank test results showed no statistical difference (p=0.9). There was also not a significant difference in survival between lowest and highest cut off values.

Considering ROC analysis, the best cut off point was 6 mm for the greatest nodal size. Survival mean was 41.07 months (34.52-47.62) for the group with the greatest metastatic nest size below 6 mm, while for the group above 6 mm it was 54.73 months (38.33-71.14). There was no statistical difference according to the Log rank test results (p=0.7).

The Cox-Regression analysis showed that only age was an independent prognostic factor (p <0.01, Odds Ratio 0.96). Other variables such as greatest nodal size, greatest metastatic nest size and metastatic nest to lymph node diameter ratio were excluded in our model.

Table I. Survival analysis in colorectal cancer studied cases

<table>
<thead>
<tr>
<th>Time interval (year)</th>
<th>Entered cases count</th>
<th>Censored cases count</th>
<th>Mortality count per interval</th>
<th>Survival rate per interval</th>
<th>Cumulative survival</th>
<th>Standard Error</th>
<th>Hazardous rate per interval</th>
<th>Standard Error</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1</td>
<td>63</td>
<td>0</td>
<td>6</td>
<td>0.90</td>
<td>0.90</td>
<td>0.03</td>
<td>0.0083</td>
<td>0.0034</td>
</tr>
<tr>
<td>1-2</td>
<td>57</td>
<td>9</td>
<td>11</td>
<td>0.79</td>
<td>0.72</td>
<td>0.09</td>
<td>0.0195</td>
<td>0.0058</td>
</tr>
<tr>
<td>2-3</td>
<td>37</td>
<td>9</td>
<td>9</td>
<td>0.72</td>
<td>0.52</td>
<td>0.07</td>
<td>0.0268</td>
<td>0.0088</td>
</tr>
<tr>
<td>3-4</td>
<td>19</td>
<td>5</td>
<td>2</td>
<td>0.87</td>
<td>0.46</td>
<td>0.07</td>
<td>0.0108</td>
<td>0.0076</td>
</tr>
<tr>
<td>4-5</td>
<td>12</td>
<td>3</td>
<td>3</td>
<td>0.71</td>
<td>0.32</td>
<td>0.08</td>
<td>0.278</td>
<td>0.0158</td>
</tr>
<tr>
<td>5-6</td>
<td>6</td>
<td>2</td>
<td>1</td>
<td>0.80</td>
<td>0.26</td>
<td>0.08</td>
<td>0.0185</td>
<td>0.0184</td>
</tr>
<tr>
<td>&gt; 6</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>0.20</td>
<td>0.05</td>
<td>0.06</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Fig 1. Survival functions according to metastatic nest to lymph node size ratio (Kaplan-Meyer).
Discussion

For the colorectal cancer prognosis, regional lymph node involvement is a significant factor. Several random studies have shown that patients in TNM III stage (with lymph node involvement) may require supplement therapies [12, 13]. This group of patients is a heterogeneous population with a variable 5 year survival ranging from 22% to 66% [13, 14].

The aim of this study was to evaluate the relationship between colorectal cancer prognosis and metastatic nest to involved lymph node diameter ratio. According to our results in known cases of Astler Coller’s stage C colorectal cancer which had been treated by the same chemotherapy protocol based on 5-FU in the first two months following surgery, the lymph node diameter, the metastatic nest diameter of involved lymph nodes and metastatic nest to involved lymph node diameter ratio have no role in the survival outcome.

Rodrigues-Bigas et al have evaluated the relationship between the involved lymph node size and prognosis. They studied 77 patients in Duke’s C stage and considered the size of 5 mm as a cut point, then divided the patients into two groups. They did not find any significant difference in overall survival and disease free survival between the two groups [11]. Our findings are similar to their results.

Dhar et al evaluated 107 patients with Duke’s C stage in a prospective study. They measured the diameter of the largest metastatic lymph node and assessed the cut point and prognosis. There was a significant difference in the survival of patients which had metastatic lymph node size ≤ 9 mm and those with size ≥ 10 mm. They proposed sub-classification of metastatic lymph node based on size to n1 ≤ 9 mm and n2 ≥ 10 mm [10].

In another study it was showed that the sizes of metastatic lymph nodes were significantly larger than of the free ones [15].

Our findings and those of Rodrigues-Bigas et al are similar, but they differ from the study of Dhar et al [9]. There are two differences in our methods: their study was prospective and they studied more patients. However, we evaluated both metastatic nest diameter and metastatic nest to involved lymph node diameter ratio.

One limitation of our study was the low mean recovery of lymph nodes. The minimum of lymph node recovery suggested for considering a patient as lymph node free is 14 or 15, but all our cases had lymph node involvement and had taken adjuvant chemotherapy (stage III) [16,17]. Whether a higher number of lymph nodes could have influenced our study remains undecided. The only possibility was to recover a larger involved lymph node which contained a larger metastatic nest. Practically, this possibility is less likely, because when a pathologist is searching for rapid lymph node recovery, he or she will find large lymph nodes usually more than 7 mm. The time consuming part of work is searching for small lymph nodes which may be missed. Therefore, it seems that this limitation did not significantly influence our study.

Conclusion

We found no significant relationship between colorectal cancer prognosis and the greatest lymph node diameter, the greatest metastatic nest diameter, the greatest metastatic nest to involved lymph node diameter ratio, but considering the controversies existing among different studies, further research and meta-analytic studies based on the existing data are required for a decisive conclusion.

Conflicts of interest

None to declare.

References
