Histologic Growth Patterns of Metastatic Carcinomas of the Liver
Noboru Terayama, Tadashi Terada and Yasuni Nakanuma
Second Department of Pathology, Kanazawa University School of Medicine, Kanazawa

One hundred autopsied livers containing metastatic cancers were studied pathologically. Macro-
scopically, the cancers were of the multinodular type in 65.0% of cases, massive type in 17.0%
and portal tract type in 8.0%. Among liver metastases from colon and lung cancers, most cases
showed predominantly intraparenchymal growth (92.3% and 87.5%, respectively). In contrast,
among liver metastases from gallbladder/bile duct cancer, intraparenchymal growth was less fre-
quent (35.7%). With regard to the histologic growth pattern at the boundary of the liver
metastases, in micrometastases less than 1 mm in diameter a replacement growth pattern was
predominant among metastases from lung, colon and pancreas cancers (69.7%, 79.3% and
66.7%, respectively), whereas a sinusoidal growth pattern was predominant in those from gas-
tric and gallbladder/bile duct cancers (48.5% and 66.7%). Among macrometastases of the liver
over 20 mm in diameter, an expansive growth pattern was predominant, irrespective of the
cancer primary site. Thus metastatic liver cancers showed changes in growth patterns accord-
ing to the size of the metastatic tumors.

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Key words: Liver—Metastasis—Pathology

Introduction

Many malignant neoplasms often metastasize to
the liver, and the frequency of liver metastasis is
much higher than that of primary liver cancers.1) Egge
classified primary liver cancer as nodular
type, massive type, or diffuse type according to its
gross appearance.2) The histologic patterns of
tumor growth of hepatocellular carcinoma at
tumor-non-tumor boundaries were described by
Nakashima et al.3) as follows: sinusoidal pattern,
cancer cells growing in sinusoids at the boundary
and compressing the liver cell cords; replacement
pattern, cancer cells replacing hepatocytes along the
liver cell cords, and the cancer cells adhering to
each other; encapsulated pattern, cancer cells growing
in an expansive manner and acquiring a fibrous
capsule. Certain metastatic cancers in the liver show
sinusoidal growth and a few have surrounding fi-
brous capsules.4) However, little attention has been
directed toward the replacement growth pattern of
metastatic liver cancer. Furthermore, the difference

Materials and Methods

Histologic Specimens

One hundred autopsied livers with metastatic
cancers were studied. The background factors are
summarized in Table I. The patients comprised 71
men and 29 women, with a mean age of 65.7 <
12.3 years. The mean weight of the liver was
1729±942 g. Cancer primary sites were as follows:
lung 24; pancreas 21; stomach 18; gallbladder/bile
duct 14; colon 13; kidney 3; other cancers 7. There
was no difference in liver weight or patient age
among the primary sites. Each liver was cut into 1-cm slices and fixed in 10% buffered formalin. From each liver, we obtained several specimens containing various sizes of metastatic tumors, and embedded them in paraffin. Several 5-μm-thick sections were obtained from each paraffin-embedded block and stained with hematoxylin-eosin, Gomori's reticulin and elastica van Gieson.

Macroscopic Findings

Livers with metastatic tumors were classified by gross macroscopic appearance in accordance with Eggel's classification into nodular, massive and diffuse types. Nodular type was subdivided into solitary, multinodular and fused types. Livers showing enlarged portal tracts and linear or small nodular tumors in the vicinity of the portal tracts considered to be lymphangiosis carcinomatosa were classified as having portal tract-type metastases.

Microscopic Evaluation

Predominant Sites of Growth: The growth sites of metastatic liver cancer were classified into two types according to light microscopic findings: portal tract growth, metastatic tumors growing within and/or along the portal tracts; parenchymal growth, metastatic tumors growing in and/or toward the hepatic parenchyma with no or little portal tract growth; intermediate type, including both of the precious types of growth.

Histologic Growth Patterns: Histologic growth pattern at the boundary between the tumor and hepatic parenchyma was classified into five types: sinusoidal, replacement and encapsulated growth patterns, which were described in hepatocellular carcinoma by Nakashima et al., expansive growth pattern and unclassified pattern. The histologic features of the individual growth patterns are as follows. Sinusoidal growth pattern; tumor cells infiltrate into the sinusoids at the boundary of the metastasis, and liver cells are left inside the boundary of the tumor. Replacement growth pattern; tumor cells grow within the liver-cell plates, and replacing tumor cells are in continuity with liver cells. In this pattern, compression and destruction of the liver cells close to the tumor cells are a little more prominent than in the replacement growth pattern in hepatocellular carcinoma. Expansive growth pattern; tumor cells compress the liver-cell plates and sinusoids and make the liver cells atrophic. In this pattern, the border of the tumor is somewhat even and smooth. Encapsulated growth pattern; metastatic tumor foci have an enclosing fibrous capsule. The correlation of the ratios of the individual growth patterns and the sizes of the metastatic tumors were evaluated at each primary site.

Results

Macroscopic Findings

Table II shows the ratios of the macroscopic types of metastatic liver cancers. Massive type and nodular type comprised 17 (17%) and 73 (73%) cases, respectively. There were no cases showing the diffuse type in the present study. Among nodular-type metastases, there were 3 of the solitary type (3%), 65 of the multinodular type (65%) and 5 of the fused multinodular type (5%). The portal tract type was seen in 8 cases (8%). In a case of pancreatic cancer and a case of uterine cancer, metastases in the liver were invisible, macroscopically. Among all primary sites, the multinodular type was most frequent. Primary sites of metastatic liver cancers showing the portal tract type included 2 cases of pancreatic cancer, 2 cases of gastric cancer and 4 cases of gallbladder/bile duct cancer. Four of 8 cases were poorly differentiated adenocarcinoma.

Microscopic Evaluation

Predominant Sites of Growth: Cases showing predominant parenchymal growth were seen in 92.3% of colon cancers, 87.5% of lung cancers, 66.7% of pancreas cancers, 61.1% of stomach
Table II. Macroscopic Classification of Liver Metastases

<table>
<thead>
<tr>
<th>Primary site</th>
<th>Number of cases</th>
<th>Massive type</th>
<th>Solitary</th>
<th>Multiple</th>
<th>Fused multiple</th>
<th>Total</th>
<th>Portal tract type</th>
<th>Invisible type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>24</td>
<td>0</td>
<td>0</td>
<td>22 (91.7)</td>
<td>2 (8.3)</td>
<td>24 (100)</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Pancreas</td>
<td>21</td>
<td>3 (14.3)</td>
<td>0</td>
<td>15 (71.4)</td>
<td>0</td>
<td>21 (100)</td>
<td>3 (14.3)</td>
<td>14.3</td>
</tr>
<tr>
<td>Stomach</td>
<td>17</td>
<td>5 (27.8)</td>
<td>1 (5.6)</td>
<td>9 (50.0)</td>
<td>1 (5.6)</td>
<td>17 (100)</td>
<td>5 (27.8)</td>
<td>27.8</td>
</tr>
<tr>
<td>GB/Bile duct</td>
<td>14</td>
<td>4 (28.6)</td>
<td>0</td>
<td>6 (42.8)</td>
<td>0</td>
<td>14 (100)</td>
<td>4 (28.6)</td>
<td>28.6</td>
</tr>
<tr>
<td>Colon</td>
<td>13</td>
<td>2 (15.4)</td>
<td>2 (15.4)</td>
<td>7 (53.8)</td>
<td>2 (15.4)</td>
<td>13 (100)</td>
<td>2 (15.4)</td>
<td>15.4</td>
</tr>
<tr>
<td>Others</td>
<td>10</td>
<td>3 (30.0)</td>
<td>0</td>
<td>6 (60.0)</td>
<td>0</td>
<td>10 (100)</td>
<td>6 (60.0)</td>
<td>60.0</td>
</tr>
</tbody>
</table>

GB, gallbladder. Diffuse type not found.

cancers, and 35.7% of gallbladder/bile duct cancers. Among liver metastases from colon cancer and lung cancer, the proportion of the cases showing parenchymal growth was higher than that for gallbladder/bile duct cancer ($P < 0.05$). On the other hand, cases showing predominant portal tract growth were seen in 35.7% of gallbladder/bile duct cancers (Fig. 1), 19.0% of pancreas cancers, 16.7% of stomach cancers, and 4.2% of lung cancers. In the remaining cases: 28.6% of gallbladder/bile duct cancers, 22.2% of stomach cancers, 14.3% of pancreas cancers, 8.3% of lung cancers and 7.7% of colon cancers, both parenchymal growth and portal tract growth were seen equally.

Histologic Growth Patterns: In small metastases in the liver less than 1 mm in diameter, a replacement growth pattern (Fig. 2) was predominant for lung cancer (69.7%), pancreas cancer (79.3%) and colon cancer (66.7%). In these cases, the proportion showing an expansive growth pattern increased as the metastatic tumors grew. In metastases over 20 mm in diameter, an expansive growth pattern (Fig. 3) was seen in 62.5%, 50.0% and 76.9%, respectively. On the other hand, a sinusoidal growth pattern (Fig. 4) was predominant in liver metastases less than 1 mm in diameter from gastric cancer and gallbladder/bile duct cancer (48.5% and 66.7%), followed by a replacement growth pattern (39.4% and 26.7%, respectively). The proportion showing an expansive growth pattern also increased as the metastatic tumors grew. In these cases, an expansive growth pattern was also predominant in lesions over 20 mm in diameter (84.6% and 47.4%). Table III shows the proportions of the individual growth patterns.

A fibrous capsule around the metastatic liver cancer was seen in two cases of colon cancer (Fig. 5) and two cases of renal cell cancer. Fibrous septa in the metastasis were seen in two cases of colon cancer and one case of small cell lung cancer. One case of follicular carcinoma of the thyroid and papillary carcinoma of the stomach showed a partial fibrous capsule and fibrous septa. A case of transitional cell carcinoma of the renal pelvis showed microscopic intraductal growth.

Discussion

In this study, we classified macroscopically cases of metastatic carcinoma of the liver resembling lymphangiosis carcinomatosa of the lung$^{5,8}$ as the portal tract type. In such cases, tumor cells enter the lymphatics in the portal tracts, spread to the interstitium along the lymphatics, spread from the hepatic hilum to the peripheral liver along the portal tracts, and linear or small nodular tumors are observed in the vicinity of the portal tracts$^{7,8}$. Poorly differentiated adenocarcinoma was most frequent in the portal tract type. Particularly in gastric cancer, pancreas cancer, and gallbladder/bile duct cancer, the portal tract type was more frequent than in other primary sites. With regard to
Fig. 2. Replacement growth pattern, metastasis from adenocarcinoma of the lung. (a) HE and (b) reticulin stain. Metastatic carcinoma cells within liver-cell plates covered with reticulin fibers. M, metastasis.

Fig. 3. Expansive growth pattern, metastasis from colon cancer. (a) HE and (b) reticulin stain. Metastatic carcinoma shows expansive growth. Liver-cell plates are compressed and atrophic. M, metastasis.

Fig. 4. Sinusoidal growth pattern, metastasis from colon cancer. (a) HE and (b) reticulin stain. Metastatic carcinoma cells show intrasinusoidal growth and are present between liver-cell plates. M, metastasis.
Table III. Proportion of Five Types of Growth Patterns in Relation to Size of Metastatic Tumor

<table>
<thead>
<tr>
<th>Primary site</th>
<th>Size of metastasis (mm)</th>
<th>Replacing (%)</th>
<th>Expansive (%)</th>
<th>Sinusoidal (%)</th>
<th>Encapsulated (%)</th>
<th>Unclassified (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>20 ≤</td>
<td>31.3</td>
<td>62.5</td>
<td>0</td>
<td>6.3</td>
<td>0</td>
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<tr>
<td></td>
<td>&lt; 20</td>
<td>18.9</td>
<td>75.7</td>
<td>0</td>
<td>5.4</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>&lt; 3</td>
<td>40.4</td>
<td>51.1</td>
<td>2.1</td>
<td>0</td>
<td>6.4</td>
</tr>
<tr>
<td></td>
<td>&lt; 1</td>
<td>69.7</td>
<td>10.6</td>
<td>13.6</td>
<td>0</td>
<td>6.1</td>
</tr>
<tr>
<td>Pancreas</td>
<td>20 ≤</td>
<td>25.0</td>
<td>50.0</td>
<td>4.2</td>
<td>0</td>
<td>20.8</td>
</tr>
<tr>
<td></td>
<td>&lt; 20</td>
<td>37.5</td>
<td>40.6</td>
<td>3.1</td>
<td>0</td>
<td>18.8</td>
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<tr>
<td></td>
<td>&lt; 3</td>
<td>60.0</td>
<td>34.3</td>
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<td>5.7</td>
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<td>&lt; 1</td>
<td>79.3</td>
<td>0</td>
<td>17.2</td>
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<td>3.4</td>
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<tr>
<td>Stomach</td>
<td>20 ≤</td>
<td>0</td>
<td>84.6</td>
<td>7.7</td>
<td>0</td>
<td>7.7</td>
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<tr>
<td></td>
<td>&lt; 20</td>
<td>22.2</td>
<td>59.3</td>
<td>7.4</td>
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<td>11.1</td>
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<tr>
<td></td>
<td>&lt; 3</td>
<td>23.5</td>
<td>52.9</td>
<td>20.6</td>
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<td>2.9</td>
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<tr>
<td></td>
<td>&lt; 1</td>
<td>39.4</td>
<td>6.1</td>
<td>48.5</td>
<td>0</td>
<td>6.1</td>
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<tr>
<td>GB/bile duct</td>
<td>20 ≤</td>
<td>15.8</td>
<td>47.4</td>
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<td>10.5</td>
<td>26.3</td>
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<tr>
<td></td>
<td>&lt; 20</td>
<td>31.6</td>
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<td>&lt; 3</td>
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<td>44.0</td>
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<td>&lt; 1</td>
<td>26.7</td>
<td>6.7</td>
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<tr>
<td>Colon</td>
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<tr>
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<td>12.5</td>
<td>75.0</td>
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<tr>
<td></td>
<td>&lt; 1</td>
<td>66.7</td>
<td>6.7</td>
<td>26.7</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

The present study demonstrated that a replacement growth pattern was not rare in metastatic liver cancers. Especially in those from the lung, pancreas and colon, the smaller the size of the metastatic tumor, the higher the frequency of a replacement growth pattern. Compared with the replacement growth of hepatocellular carcinoma noted by Nakashima et al., even the tumors grew within the liver-cell plates, although destruction and compression of hepatocytes were more prominent than in hepatocellular carcinoma. In the cases of gastric cancer and gallbladder/bile duct cancer, a sinusoidal growth pattern was predominant in small metastases. Similar to the other primary sites, the proportion of the expansive growth pattern increased as the size of the metastases increased. It is suggested that metastatic liver cancers grow in the liver-cell plates and/or sinusoids at first, then the speed of growth exceeds the rate of hepatocyte replacement by tumor cells or invasion of tumor cells into the sinusoids. Otherwise, the size of the metastatic tumor and growth pattern might be associated with the intensity of adhesion among tumor cells. That is, tumor cells with strong adhesion form large metastatic nodules and show expansive growth, and those with weak adhesion form small nodules and show a replacement growth pattern.

Small metastatic liver cancers are supplied by surrounding hepatic sinusoids, and as the metastatic...
tumor grows, newly formed blood vessels supply them. That is, metastatic liver cancers showing a replacement or sinusoidal growth pattern are possibly supplied by sinusoidal blood flow. The switching of the blood supply to metastatic liver cancers is thought to be closely related to the change in proportion of the growth pattern at the metastasis periphery. This seems to be one of the reasons why the effect of arterial infusion or arterial chemoembolization of metastatic liver cancer is limited.

A few cases of metastatic liver cancer showed a fibrous capsule and fibrous septa, particularly in those from colon cancer. Furthermore, microscopic portal venous tumor thrombi were often seen in metastatic liver cancers in the present study. Indeed, these are known to be features of hepatocellular carcinoma, although a few cases of metastatic liver cancer can also show them.

References