INFLUENCE OF LOCATION AND MITOTIC INDEX ON PROGNOSIS IN PATIENTS WITH GASTROINTESTINAL STROMAL TUMORS

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Gastrointestinal stromal tumors (GIST) arise from the pacemaker, the interstitial Wells of Cajal. These tumors constitute 1 to 3% of gastrointestinal neoplasms, and may occur in each portion of the gastrointestinal tract. The most useful prognostic factors are tumor size, mitotic index, cell structure and location within the gastrointestinal tract.

The aim of the study was to assess the chosen prognostic factors (location in the gastrointestinal tract and mitotic index) in patients with GIST.

Material and methods. Between 1989 and 2002, 74 patients (37 men and 37 women) with an average age of 54.9 years (range from 13 to 89 years) were operated for GIST in the Department of Gastrointestinal Surgery. Two- and five-year survival rates during observation were analyzed, as well as the location within the gastrointestinal tract and mitotic index. Based on the intraoperative and postoperative investigations, the tumor size, presence of metastases and histological type of predominant cells were estimated in each patient. Results were subjected to statistics, where \( p < 0.05 \) was considered to be significant.

Results. Of the 74 patients included in the study, 3 patients (4%) had a primary tumor located in the lower oesophagus, 42 patients (56.8%) in the stomach, 4 patients (5.4%) in the duodenum, and 13 patients (17.6%) had tumors originated from the small intestine. In an additional 12 patients (16.2%), the tumor originated from the large intestine. The most frequent (51%) mitotic index was 2, and 9/50 hpf was considered an intermediate malignant potential risk. Two-year survival was common in patients with GIST located in the oesophagus, stomach, and duodenum, totalling 34 (79%) patients. A lower than two-year survival rate was noted in patients with GIST arising from the small intestine: 7 (63.6%) patients had tumors arising from the colon and 4 (36.3%) patients had rectal tumors. Five-year survival was also the most frequent in patients with GIST located in the upper part of gastrointestinal tract (37.2%), in the median part of gastrointestinal tract (36.3%), and in the lower part of the gastrointestinal tract (27.7%). Correlation between location, mitotic index and survival of patients was assessed. The correlation studies showed a statistically significant influence of tumor location in the gastrointestinal tract (\( p=0.0264 \)) and mitotic index (\( p=0.0003 \)) with the survival of patients operated for GIST. Thus, the lower location and higher mitotic index of GIST are associated with shorter survival of patients.

Conclusions. The mitotic index and location in the gastrointestinal tract are essential prognostic factors in analyzed patients with GIST. In the analyzed group, the lower locations and higher mitotic indices of GIST were associated with shorter survival of patients.

Key words: GIST, prognostic factors, mitotic index

Gastrointestinal stromal tumors make up 1 to 3% of gastrointestinal neoplasms, and are the most frequently occurring tumors originating from the connective tissue (mesenchymal tissue) (1, 2). Approximately 2.5% of gastric neoplasms are diagnosed as GIST (3). The
morbidity/year is estimated to be about 20/million people (4), with 5-6 thousand new cases being registered annually in the US (5). These tumors occur in patients of various ages, are more frequent in patients older than 50 years old, and seem to be independent of race (4, 5).

GIST may occur in any portion of the gastrointestinal tract, from the oesophagus to the anus. Stromal tumors most frequently occur in the stomach (60-70%) and in the small intestine (25-35%), and less frequently in the oesophagus (1-3%), the rectum (about 5%) and the colon (1%) (4, 6, 7). Primary GIST rarely occur outside the wall of the gastrointestinal tract in the omentum, the mesenterium and the retroperitoneal space. These tumors are termed EGIST (8, 9).

Malignant stromal tumors most commonly metastasize to the liver, omentum, mesentery and peritoneum. Distal metastases outside the abdominal cavity are rare and are located most frequently in the bones, the lungs and soft tissues. Metastases to the lymph nodes occur sporadically (10-13). Most frequently, the primary stromal tumor occurs as a singular tumor, although it may have multifoci in about 5% of tumors. In this form, even an autopsy is insufficient in locating the primary neoplasm focus (4).

The tumors of the gastrointestinal interstitial tissues have been diagnosed in routine histopathological investigations as a benign or malignant neoplasm originating from the smooth muscle tissue or the peripheral neural covers. The presence of the KIT protein (CD117) in association with characteristic histological features are the most important for recognition of GIST (4, 5). KIT is the receptor of the cell membrane tyrosine kinase, which binds to the growth factor stem cell factor (SCF). SCF is also known as the mastocytes growth factor, Steel factor (SLF) and ligand c-KIT (KL).

The c-KIT receptor is located in the stromal gastrointestinal cells known as the interstitial cells of Cajal (interstitial Cajal cells – ICC’s) (4). ICC occur between layers of smooth muscles of the gastrointestinal tract wall in the Auerbach and Meissner plexi. They act as pacemaker cells of the gastrointestinal tract and regulate intestine movements. It has recently been suggested that ICC or their precursor matrix mesenchymal cell may be the origin of the stroma tumors. Therefore, GIST are sometimes called the gastrointestinal pacemaker cell tumors (GIPACT) (4, 5, 14-17).

Stromal tumors are a heterogeneous group of benign, intermediate malignant and malignant neoplasms. The actually used diagnostic criteria in the stromal tumors frequently do not allow for description of the malignancy level or clinical outcome. The most useful diagnostic morphological factors are tumor diameter, location in the gastrointestinal tract, cell structure and mitotic index counted in 50 visual fields at 400x (8, 12, 13, 18-32).

Discovery of the basic role of KIT activation in GIST pathogenesis led clinical investigations to the development of an inhibitor of tyrosine kinases, Imatinib (STI571, Glivec, Gleevec). Imatinib is an inhibitor of three tyrosine kinases, ABL kinase, whose overproduction is observed in chronic leukemia, KIT and PDGFR / platelet-derived growth factor receptor/ receptor of tyrosine kinase activity, whose mutation occurs in about 5% of GIST (33, 34, 35).

Results from international clinical trials show Imatinib to be highly effective in patients with non-resectable stromal gastrointestinal tumors (36, 37).

The aim of the current paper is to assess the use of mitotic index and location of GIST within the gastrointestinal tract as prognostic factors.

MATERIAL AND METHODS

From January 1989 to March 2002, 74 patients with GIST underwent operations in the Department of Gastrointestinal Surgery. Medical histories of patients were obtained and the retrospective analyses of 37 women (50%) and 37 men (50%), from 13 to 89 years old (mean – 54.9), was performed. Survival data were obtained directly from the patients, or their families in 65 patients (87.3%).

The patients were divided into two groups according to age (≤50 years old or >50 years old). The duration of postoperative hospitalization ranged from 1 to 65 days (mean 16 days). The survival in this group of patients was ranging from 1 day to 11 years (mean 3.9 years). In the analyzed group, the two- and five-year survival rates were assessed and survival during observation was analyzed.

In all operated patients, a neoplasm originating from the mesenchymal tissue was confirmed and was defined as a stroma tumor...
Influence of location and mitotic index on prognosis in patients with gastrointestinal stromal tumors (GIST). Other types of mesenchymal and lymphoid (leiomyoma, leiomyosarcoma, neurinoma, schwannoma, lymphoma, etc.) tumors were excluded.

The investigation was performed retrospectively; thus, assessments of other parameters (such as Ki-67 and genetic investigations of the tumor tissue) were impossible.

Primary tumors were located in the upper part of the gastrointestinal tract (oesophagus, stomach, duodenum), in the median part of gastrointestinal tract (small intestine) and in the lower part of gastrointestinal tract (colon and rectum).

Prior to surgical treatment, the ultrasonography and computed tomography of the abdominal cavity, endoscopy and radiological examination with contrast of the gastrointestinal tract were performed.

Based on intraoperative and postoperative investigations, tumor size, presence of metastases and the histological type of predominant cells were described. Immunohistochemical investigations were useful for differential diagnostics between tumors originating from the muscle, neural and lymphoid tissues, although the most important was the investigation of CD117 and CD34 proteins, muscle actin and S-100 protein.

The risk of atypical changes of stromal tumors was described by determining the mitotic index, which was defined as the number of mitotic divisions in 50 vision fields (x/50 hpf), where hpf refers to high power fields. The border value was assigned a value of 10 or more for the group of high malignant potential risk according to Appelman’s classification. In tumors where the mitotic index was between 2 and 9/50 hpf, the tumors were frequently described as the group of intermediate malignant potential risk. Stromal tumors with a mitotic index of 0-1/50 hpf were defined as benign tumors.

In each patient, the tumor size in centimeters was assessed, with 5 centimeters denoted as the border diameter between groups (18, 38, 39, 40). In order to precisely describe the influence of two prognostic factors (mitotic index, tumor size) according to location within the gastrointestinal tract, the patients were divided into three groups according to Franquet’s criteria (40). In the first group, patients had stromal tumors less than 5 cm in diameter, with a mitotic index less than 5/50 hpf; in the second group with the same mitotic index the tumor diameter was 5 cm or more. In the third group, the patients were independent of the tumor size, which had a mitotic index of at least 5/50 hpf (tab. 1).

The pathologic and immunohistochemical investigations were performed in the Department of Pathology in Silesian Medical University in Katowice.

The surgical treatment was assessed as the radical tumor excision in neoplastic cells in the absence of an incision line, and otherwise operation type was defined as incomplete resection.

The survival rate from tumor recognition to death was also assessed.

Results were collected in Microsoft Excel and analyzed statistically; p≤0.05 was considered to be significant.

RESULTS

Patients over 50-years-old constituted the majority of patients with tumors of the upper 71.4% (UGIT) and lower gastrointestinal tracts 83.3% (LGIT). Tumors originating from the small intestine occurred more frequently in younger patients (69.2%). The division of patients according to age and location of tumors is shown in tab. 2.

Among the 74 patients, 3 patients (4%) had tumors located in the lower part of the oesophagus, 42 patients (56.8%) in the stomach, and 4 patients (5.4%) in the duodenum. In 13 patients (17.6%), the primary tumor originated from the small intestine, while an additional 12 patients (16.2%) had tumors that originated from the large bowel.

The most frequent (51%) mitotic index within the upper part of the gastrointestinal tract

<table>
<thead>
<tr>
<th>Mitotic index (x/50 hpf)</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 5</td>
<td>&lt; 5</td>
<td>≥ 5</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Tumor size (cm)</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 5</td>
<td></td>
<td></td>
<td>tumor size is not significant</td>
</tr>
</tbody>
</table>
was 2-9/50 hpf, which is correlated to tumors of intermediate malignant potential risk.

In the group of patients that had a mitotic index = 10/50 hpf, there was not a high rate of tumors (16.3%). In the case of stromal tumors originating from the small intestine, colon and rectum, the most frequent mitotic index was = 10/50 hpf (53.8% oraz 50%), which is a proof of the predominance of malignant tumors in the midgut and hindgut.

According to the tumor size, tumors having a diameter of 5 cm or less (76.1%) are most frequently located in the upper part of the gastrointestinal tract.

In patients with stromal tumors of the small intestine, the mean size was 9.2 cm, while 38.5% of tumors have a diameter more than 5 cm. In tumors originating from the large bowel, the mean tumor size was 6.6 cm, and the number of tumors in both groups (<5 cm and >5 cm) was equal. The tumor size originating from stromal cells is presented in tab. 4.

Analysis of the mitotic index and the tumor size together show that in the upper part of the gastrointestinal tract small neoplasms (< 5 cm) with low mitotic index (< 5/50 hpf) mainly occur. The lower location of the stromal tumor is associated with the larger size and higher mitotic index. In the group of patients with large neoplasms (>5 cm), with mitotic index = 5/50 hpf, the stromal tumor was primarily located in the colon and rectum (66.7%). The influence of the mitotic index and the tumor size together, according to location of the tumor in the gastrointestinal tract, is presented in tab. 5.

According to predominant cells in the GIST, spindle cells were the most frequent in the foregut (73.5%), midgut (76.9%) and hindgut

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**Table 2. Stromal tumor GIST: the division of patients according to the age and location**

<table>
<thead>
<tr>
<th>Age of patients</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>UGIT</td>
</tr>
<tr>
<td>≤ 50 years</td>
<td>14</td>
</tr>
<tr>
<td>(28.57%)</td>
<td>69.23%</td>
</tr>
<tr>
<td>&gt; 50 years</td>
<td>35</td>
</tr>
<tr>
<td>(71.43%)</td>
<td>30.77%</td>
</tr>
<tr>
<td>Together</td>
<td>49</td>
</tr>
</tbody>
</table>

Results of the chi² test:
chi²=9.469   p=0.009
Conclusion: there is statistical significance between the age and location of the tumor

**Table 3. Location of the tumor in the gastrointestinal tract and mitotic index**

<table>
<thead>
<tr>
<th>Mitotic index</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>UGIT</td>
</tr>
<tr>
<td>IM=0-1</td>
<td>13</td>
</tr>
<tr>
<td>IM=2-9</td>
<td>24</td>
</tr>
<tr>
<td>IM &gt; 9</td>
<td>6</td>
</tr>
<tr>
<td>Together</td>
<td>43</td>
</tr>
</tbody>
</table>

Chi² Pearson test=16.99996   p=0.00193
Conclusion: there is a significant dependency between mitotic index and the location within the gastrointestinal tract
Influence of location and mitotic index on prognosis in patients with gastrointestinal stromal tumors

In our patients, (50%) in tumors located in the colon and rectum, polymorphic and mixed (spindle and epithelial) cells and foci of necrosis were observed.

Among the 74 operated patients, long-term postoperative control was performed in 65 patients (87.3%).

Based on data obtained from patients and their families, the rate of 2- and 5-year survival was linked (tab. 6 and 7).

There is statistical significance between location of the mesenchymal tumor within the gastrointestinal tract and 2-year survival, although there was no statistical significance between the location of GIST in the gastrointestinal tract and 5-year survival. Among patients with 2-year survival after surgical treatment, the highest rate constituted patients with the stromal tumor located in the oesophagus, stomach or duodenum (34 patients; 79%), and the lowest rate of 2-year survival was noted in patients with the tumor originating from the small intestine (7 patients; 63.6%) and colon and rectum (4 patients; 36.3%).

Five-year survival rates were the highest in patients with stromal neoplasm of the foregut (37.2%), the midgut (36.3%), and the hindgut (27.7%).

Table 4. Stromal tumors GISTs – the tumor size /cm/ (n = 74)

<table>
<thead>
<tr>
<th>Tumor size</th>
<th>UGIT n = 49</th>
<th>MGIT n = 13</th>
<th>LGIT n = 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean tumor size</td>
<td>3.9 cm</td>
<td>9.2 cm</td>
<td>6.6 cm</td>
</tr>
<tr>
<td>≥5 cm</td>
<td>37/49 (75.5%)</td>
<td>8/13 (61.5%)</td>
<td>6/12 (50%)</td>
</tr>
<tr>
<td>Mean tumor size</td>
<td>2.3 cm</td>
<td>3.3 cm</td>
<td>1.8 cm</td>
</tr>
<tr>
<td>&gt;5 cm</td>
<td>12/49 (24.5%)</td>
<td>5/13 (38.5%)</td>
<td>6/12 (50%)</td>
</tr>
<tr>
<td>Mean tumor size</td>
<td>9.1 cm</td>
<td>18.6 cm</td>
<td>11.4 cm</td>
</tr>
</tbody>
</table>

ANOVA range Kruskal-Wallis
Kruskal-Wallis test H (2, N=65)=4.484664 p =0.1062
Conclusion: There is no statistical dependency between location in the gastrointestinal tract and the tumor size

Table 5. Stromal tumors (GIST): division according to mitotic index and the tumor size together, and location within the gastrointestinal tract (n = 74)

<table>
<thead>
<tr>
<th>&lt; 5/50 hpf</th>
<th>&lt; 5 cm</th>
<th>≥ 5 cm</th>
<th>≥ 5/50 hpf</th>
</tr>
</thead>
<tbody>
<tr>
<td>UGIT n = 49</td>
<td>25/49 (51%)</td>
<td>6/49 (12.3%)</td>
<td>18/49 (36.7%)</td>
</tr>
<tr>
<td>MGIT n = 13</td>
<td>5/13 (38.5%)</td>
<td>1/13 (7.7%)</td>
<td>7/13 (53.8%)</td>
</tr>
<tr>
<td>LGIT n = 12</td>
<td>3/12 (25%)</td>
<td>1/12 (8.3%)</td>
<td>8/12 (66.7%)</td>
</tr>
</tbody>
</table>

Table 6. Two-year survival and location in the gastrointestinal tract

<table>
<thead>
<tr>
<th>Survival 2 years</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>UGIT</td>
<td>MGIT</td>
</tr>
<tr>
<td>Deaths</td>
<td>9</td>
</tr>
<tr>
<td>Survival</td>
<td>34</td>
</tr>
<tr>
<td>Together</td>
<td>43</td>
</tr>
<tr>
<td>chi²</td>
<td>df</td>
</tr>
<tr>
<td>Pearson chi²</td>
<td>7.694033</td>
</tr>
</tbody>
</table>
In patients who died during observation, there was a significant dependency between the tumor size (less than 5 cm and more than 5 cm) and location of the tumor within the gastrointestinal tract.

The influence of the mitotic index and the location of the tumor in the gastrointestinal tract on survival was determined by Cox proportional hazard regression test.

The mitotic index in raw values has significant statistical influence on survival (p=0.0003), and mitotic index in groups 0-1, 2-9 and more than 9/hpf does not have a significant influence on survival (p=0.1148), although a higher mitotic index reduces the chance of survival 1.5 times (beta 1.51).

The location of the stromal tumor in the gastrointestinal tract significantly influences the survival (p=0.0264). The lower location in the gastrointestinal tract is associated with shorter survival. Location of the tumor in the small intestine reduces the chance of survival 1.6 times compared to locations within the oesophagus, stomach and duodenum, and location within the large bowel reduces the chance of survival 1.6 times compared to the
Influence of location and mitotic index on prognosis in patients with gastrointestinal stromal tumors

DISCUSSION

Gastrointestinal Stromal Tumors (GISTs) were separated into group of neoplasms characterized by variable clinical outcome compactly associated with their location (41).

Seventy-four patients with stromal tumors in the abdominal cavity were treated in the Department of Gastrointestinal Surgery of Silesian Medical University in Katowice between 1989 and 2002. According to the primary location (oesophagus, stomach, duodenum, small intestine, colon, rectum), prognostic factors influencing the survival of patients operated for GIST were differentiated.

The mitotic index is the most frequently described prognostic factor (4, 10-13, 18-38, 40, 42, 43, 44).

Patients in the present study were divided into three groups according to mitotic index on histopathological investigation. Having a mitotic index between 0 and 1/50 hpf was significant for stroma tumors with low malignant potential risk. These values of mitotic index were noted in lesions originating from the small intestine (2 /13 patients; 18.1%). Stromal tumors of intermediate malignant potential risk (2 – 9/50 hpf) were observed more frequently in the oesophagus, stomach and duodenum, and they constituted 55.8% (24 patients) of lesions of this type in the foregut. In the third group, tumors had a mitotic index greater than 10 / 50 high power fields. These tumors frequently originated from the small intestine (7 patients; 63.6%) and from the colon and rectum (6 patients; 45.4%), and less frequently from the oesophagus, stomach and duodenum (6 patients; 13.9%). In the presented material, the mean mitotic index increased with the location of the tumor in protrions of the gastrointestinal tract. For example, the mitotic index increased from the UGIT (6.4/50 hpf) to the MGI (19/50 hpf) to the LGIT (37.7/50 hpf). Hence, an association between the location of GIST in the gastrointestinal tract and the mitotic index (p=0.00193) was uncovered. Division of patients into groups according to mitotic index (I-0-1/50hpf, II-2-9/50hpf and III- 10

![Graph showing Kaplan-Meier curved line of survival](image_url)
or higher) did not alter the prognosis of patients with GIST, although the mitotic index in raw values was an independent prognostic factor.

The use of stromal tumor size as an independent prognostic factor is not precise. According to some authors, the risk of occurrence of neoplastic metastases increases when the diameter of the primary tumor is greater than 6 cm (45). Many authors think that prognosis is worse if the neoplasm has a diameter of 5 cm or more (18, 38, 39, 40, 43, 44, 45). Conversely, Fletcher believes that the smallest clinical aggression occurs in tumors with a diameter less than 2 cm (5). DeMatteo showed that a tumor with diameter greater than 10 cm significantly influenced the prognosis in a group of 200 patients with stromal tumors (the value of relative risk was 2.5) (12). Approximately 69% of patients in this group survived one year, while the 3-year survival was 44% and the 5-year survival was 35%.

In the presented material for patients with tumors having a diameter less than 5 cm, the rate of 2-year survival is 83.8% and 5-year survival is 71.6%. For patients with tumors greater than 5 cm in diameter, 56.7% of the patients survive for 2 years survival and 41.3% of patients survive for 5 years.

Intraoperative assessment of stromal tumor sizes in our patients showed that larger tumors from the small intestine had a mean diameter of 9.2 cm (ranging from 2 cm to 35 cm). If a tumor of this type was located within the upper or lower gastrointestinal tract, its mean size was 3.9 cm (ranging from 0.2 cm to 22.5 cm) or 6.6 cm (ranging from 1 cm to 25 cm), respectively.

According to the literature, tumors of this type most frequently occur within the stomach, 10 to 20% lesions of this type originate from the small intestine, and about 10% are stromal tumors originating from another location (oesophagus, colon, rectum) (4, 38, 42, 43). The frequent occurrence of stromal tumors with epithelial neoplasms of another type has been previously observed (48-51).

In our study, we observed 49 stromal tumors (66.2%) located within the foregut (oesophagus, stomach, duodenum), 13 neoplasms (17.5%) located within the midgut (small intestine), and 12 neoplasms (16.2%) located within the hindgut (large bowel). In patients with GIST originating from the hindgut, 36.3% of the patients survived 2 years and 27.2% survived 5 years. Most patients (67.3%) with stromal tumors originating from the hindgut died within two years of the operation. The best prognosis is characterized for patients with GIST in the foregut. In the literature, there are contradictory opinions on the influence of stromal tumor location on prognosis. DeMatteo and Pierie suggest that location does not influence survival (9, 10), while a study by Emory including 1,004 patients proves that the location of GIST has prognostic significance, as worse prognosis is associated with GIST originating from the small intestine and large bowel (18).

Use of radiotherapy, chemotherapy and adjuvant therapy in patients with GIST gives poor results (52, 53, 54). The method of choice is surgical resection of the tumor with margins of macroscopically unchanged tissues and removal of neoplastic metastases, but in 80% of operated patients, local recurrence, metastasis or tumors in another location occur (11, 12, 13, 52, 53, 54). Results of international clinical trials show Imanitib to be highly effective in patients with non-resectable stromal gastrointestinal tumors (30, 36, 37, 55, 56).

**CONCLUSIONS**

1. The mitotic index and location in the gastrointestinal tract are essential prognostic factors in analyzed patients with GIST.
2. In the analyzed group, lower locations of GIST and higher the mitotic indices are associated with shorter survival of patients.

**REFERENCES**

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