THE VALUE OF SURGERY FOR GASTROINTESTINAL STROMAL TUMORS

Purpose: To investigate the role and the place of the surgical management of GISTs.

Methods: It was performed a retrospective study involving the patients with GISTs surgically treated in Department of Surgery, University Hospital “Queen Joanna - ISUL” between 2005 and 2012. Several parameters were followed up - demographic characteristics of the patients, tumor features, clinical manifestation, used methods for diagnosis and treatment and achieved short- and long-term results. The data was investigated with SPSS-19.

Results: 39 patients with GISTs were included in the study. Four of them have tumors with extra-gastrointestinal localization (retroperitoneal space - in 3 cases and one patient with tumor in the mesentery of the small intestine). The distribution of GISTs in the gastrointestinal tract was established as follows: stomach (21 cases), duodenum (4 cases), small intestine (7 cases) and colon (3 cases). The most common clinical signs were abdominal pain and discomfort, weakness, dyspeptic complaints and gastrointestinal bleeding. 29 patients underwent radical operations with achieved R0 resection. Recurrence was observed in 5 patients. Achieved median, 1-, 3- and 5-year survival was respectively 52.91 months, 88%, 81% and 67%.

Conclusion: Surgical resection is the only curable method of treatment of patients with GISTs. The achievement of negative resection margins is the most important predictor of survival.

Keywords: GISTs, EGISTs, endoscopic ultrasound, retroperitoneal space

Introduction

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal neoplasms of gastrointestinal tract which constitute 80% of them and about 5% of all sarcomas (Fletcher, Berman, Corless, Gorstein et al., 2002). In Europe the estimated annual incidence is 11-14 new cases per million people but in the resent years it increases because of the better recognition and diagnosis of these tumors (Goettsch, Bos, Breekveldt-Postma, Casparie, and Herings, 2005).

GISTs can arise from all parts of the gastrointestinal tract - stomach (50-60%), small intestine (30-40%), colon/rectum (5-10%) and esophagus (5%) (Stamatakos, Douzinas, Stefanaki, Sfioleas et al., 2009). They can occur in the retroperitoneal space, mesentery and omentum (Nakagawa, Akasaka, Kanai, Takabayashi, and Miyazawa, 2005). There have been reported cases in the gallbladder, urinary bladder, pancreas and liver (Daum, Klecka, Ferda, Treska et al., 2005; Stamatakos et al., 2009; Ortiz-Hidalgo, de Leon Bojorge, and Albores-Saavedra, 2000; Park, Choi, Lee, Min et al., 2004). Tumors which occur outside of the gastrointestinal tract are known as extra-gastrointestinal stromal tumors (EGISTs) (Miettinen and Lasota, 2001).

The purpose of the study is to investigate the role and the place of the surgical management of GISTs.
Material and methods

It was performed a retrospective study involving 34 patients with GISTs surgically treated in Department of Surgery, University Hospital “Queen Joanna - ISUL” between 2005 and 2012. Several parameters were followed up - demographic characteristics of the patients, tumor features, clinical manifestation, used methods for diagnosis and treatment and achieved short- and long-term results. The data was investigated with SPSS-19. The patients were analyzed by sex, age and duration of the symptoms. The tumors were characterized by location, size and presence of lymphonodal and distant metastases. Resections were classified as: R0 radical operation (achievement of microscopic negative resection margins), R1 (macroscopic negative resection margins) and R2 (macroscopic positive resection margins). The malignancy potential was estimated with Fletcher’s classification (Fletcher et al., 2002) (Table 1).

<table>
<thead>
<tr>
<th>Malignancy risk</th>
<th>Size (Cm)</th>
<th>Mitotic (50 hmf)</th>
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<tr>
<td>Very low</td>
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<td>Any index</td>
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<td>Any size</td>
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Note: 50 hmf = 50 high magnification fields (400x)
Source: Fletcher et al., 2002.

Results

Of involved 34 patients with GISTs women were 17 and men were 17, which determined the ratio 1:1. Ages ranged from 18 to 78 with a median of 54.1 years. During follow-up of cases by year an increase of incidence and respectively operated patients with GISTs were observed (Figure 1). The figure clearly shows the progression of the number of new cases for 7-year period (2005-2011).

In 4 cases there were EGISTs - 3 patients with retroperitoneal tumor and one with GIST in the mesentery of the small intestine (ileum). The higher incidence of EGISTs in our
research was due to the concurrent major study of retroperitoneal tumors so the patients with this pathology were concentrated in the clinic. In the remaining 30 cases GIST were located in the gastrointestinal tract - stomach (18 cases), duodenum (3 cases), small intestine (6 patients) and in colon in 3 patients (Figure 2).

**FIGURE 2. DISTRIBUTION OF THE PATIENTS WITH GISTs BY THE TUMOR LOCATION**

The tumor size is an important prognostic factor which largely determines the respectability rate and the opportunity to achieve radical operation. In our study the tumor size ranged from 1.4 cm to >21 cm (Figure 3). At the time of diagnosis in 56% of patients the tumor was >5 cm and in 24% of them it was > 10 cm.

**FIGURE 3. DISTRIBUTION OF THE PATIENTS WITH GISTs ACCORDING TO THE TUMOR SIZE**

There are no specific clinical signs for GISTs. Because of this at the time of diagnosis the patients with GISTs are in advanced stages. The most common symptoms are abdominal pain, often with spastic character in the beginning, abdominal discomfort, dyspeptic complaints, weakness, palpable abdominal tumor and gastrointestinal bleeding. Described symptoms sometimes have long duration before the diagnosis of the tumor. Figure 4 shows the clinical presentation of GIST in patients involved in the study (Figure 4).

One of the most common symptoms was the bleeding from gastrointestinal tract. Despite of the fact that only 7 patients had clinically manifested hemorrhage at the time of the hospitalization, in performed more detailed investigation it was established that other 13
patients have had such symptoms in the past. This has been the reason for previous hospitalizations in other gastroenterological departments and diagnosis of the disease. Bowel disorders were observed in 9 patients. The reason for the hospitalization in 4 cases was bowel obstruction and in 5 cases the leading symptom was diarrhea. Jaundice was established in one patient and the symptoms was result from compression of the common bile duct, involvement of the descendent part of the duodenum and Vater’s papilla. In one of the cases a tumor compressed the right ureter with development of hydronephrosis was observed.

**FIGURE 4. DISTRIBUTION OF THE OBSERVED SYMPTOMS IN THE PATIENTS INVOLVED IN THE STUDY**

The diagnostic procedure for every patient included: detailed physical examination, blood tests, X-ray of the chest and conventional sonography of the abdomen. CT was performed in 19 patients (55.9%) and in 3 cases (8.8%) MRI was used. Endoscopy (gastroduodenoscopy and colonoscopy) were performed in 27 patients (79.4%). Endoscopic ultrasound was an obligatory method for diagnosis of GISTs; it was used in 14 cases (41.2%). Endoscopic resection was performed in 8 cases in Department of Gastroenterology, University Hospital “Queen Joanna - ISUL”. Only 3 of them were included in the study because of their next hospitalization in Department of Surgery, University Hospital “Queen Joanna - ISUL”. The reason for this was the presence of bleeding (for 2 patients), and in one case - histological findings for infiltration of the resection margins after performed endoscopic resection.

Radical surgical resection (R0) was achieved in 24 cases (70.6%). 6 patients underwent R1 resection. Patients with EGISTs were involved in that group because of the inability to prove microscopic negative margins. In 4 patients the tumor infiltrated the adjacent organs and tissues - omentum in 2 cases, pancreas and spleen in 1 case. In 3 patients there was involvement of the intestines and in one case an involvement of the duodenum was found. In 2 of these 4 patients R1 resection was achieved with the performance of combined resection of the affected organs. Palliative procedures (tumor reduction or bypass operations) were carried out only in 2 cases. Metastatic disease was established in 5 patients - in the liver (3 cases) and peritoneal carcinoma (2 cases). In one case the liver metastases, found during the first operation, have been removed with one course of treatment with Imatinib. The presence of metastases in lymph nodes was observed in 2 patients (5.9%) which has resulted in the performance of systematic lymphadenectomy.
Morbidity rate was 8.8% (3 patients). In all cases there was suppuration of the operative wound. Insufficiency of the duodenal stump and hemorrhage were established in one case therefore they have imposed a relaparotomy.

Recurrence after radical resection occurred only in 5 cases (14.7%). The median, 1-, 3- and 5-year survival was respectively 52.91 months, 88%, 81% and 67% (Figure 5).

**Figure 5. Achieved survival of the patients with GISTs**

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**Discussion**

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal neoplasms of the gastrointestinal tract (Stamatakos et al., 2009). Diagnosis of GISTs, especially submucous lesions with size <2cm, has significantly improved because of the development of endoscopy and endoscopic ultrasound which increases diagnostic accuracy and can help predict biological tumor activity according to its size, heterogeneity, presence of ulcerations etc. This relation has been confirmed in our study - an increase of new cases has been observed in recent years. This is probably result from improved diagnosis and routine use of the mentioned methods in our Department. Endoscopic ultrasound (EUS) is a valuable diagnostic method in the recent years because of the accuracy and can help predict biological tumor activity according to its size, heterogeneity, development of endoscopy and endoscopic ultrasound which increases diagnostic of the gastrointestinal tract (Stamatakos et al., 2009). Diagnosis of GISTs, especially submucous lesions with size <2cm, has significantly improved because of the possibility of EUS-guided fine needle aspiration or trucut needle biopsy. Mitotic index cannot be determined only on these specimens therefore it is necessary to study the entire lesion. These data clearly show that GIST must be removed. An endoscopic excision is indicated in cases with tumor smaller than 2 cm, but only if a subsequent surgical resection can be performed in patients with positive endoscopic resection margins. In our study there is one patient who has been operated because of the infiltration of the endoscopic resection margins. On the other hand, although there are many studies for various prognostic factors determining malignant potential of these neoplasms, in the literature there are many reported exceptions with presence of metastases in cases with tumor less than 5 cm and low mitotic activity (< 5 mitoses/50 HMF). That data clearly shows that the prognostic factors are not absolute.

Surgical resection remains the gold standard management of GISTs. Its goal is complete resection of the disease with achieved negative resection margins (R0). It is achieved in approximately 40% to 60% of all cases of GISTs and in over 70% of non-metastatic cases (Casali, Jost, Reichardt et al., 2008; Gutierrez, De Oliveira, Perez, Rocha-Lima et al., 2007; Hassan, You, Shyyan, Dozois et al., 2008; Liegl, Hornick, and Lazar, 2009; Roberts and
Eisenberg, 2002). Complete surgical resection is related to 48-65% 5-year survival (Parfitt, Streutker, Riddell, and Driman, 2006). Because of the short period of our study and the large number of patients with GISTs in recent years we present achieved median, 1-, 3- and 5-year survival, respectively 52.91 months, 88%, 81% and 67%, which are comparable with literature data. En bloc resection is recommended when GISTs involve adjacent organs. The avoidance of tumor rupture is essential. The rupture could result in neoplastic spread and recent relapse and/or occurrence of distant metastases which is associated with reduction in survival (Everett and Gutman, 2008; Joensuu, 2008; Ng, Pollock, Munsell, Atkinson, and Romsdahl, 1992). All resection margins have to be histologically examined because the presence of residual tumor masses is poor prognostic factor (Casali et al., 2008; Gold, Gönen, Gutierrez, Broto et al., 2009; Ng et al., 1992; Roberts and Eisenberg, 2002; Rutkowski, Nowecki, Michej, Debiec-Rychter et al., 2007).

GISTs metastasize mainly hematogenously and by contact. Nodal metastases has been observed in 4-10% of cases (De Matteo, Lewis, Leung, Muddan et al., 2000.). Our study showed 5.9% lymph node involvement because of it lymphadenectomy was performed. So far the presence of nodal metastases is not defined as a statistically significant prognostic factor. The reason for that is probably the rarity of GISTs, especially with nodal metastases, and the small number of patients for achievement of statistically significant result. Therefore, lymphadenectomy should be performed when the surgeons suspect nodal involvement.

Until 2001 the surgical resection was the only one effective treatment strategy with 50 % 5-year survival. Over 50% of cases develop metastases with subsequent median survival about 15 months. It is clear that in these cases the surgical treatment is not sufficient and is related with poor prognosis. With the introduction of Imatinib mesylate began a new era in the treatment of GIST. About 50% of patients with GIST are sensible and reversal is observed after treatment with Imatinib mesylate, and in 75-80% of cases there is no progression of the disease. 2-year survival after management with Imatinib mesylate is achieved in about 70% of cases, and for the same period stabilization without progression is observed in 50%. Many studies show that if taking of Imatinib mesylate is stopped, this leads to progression of the disease. The 50% of sensible to Imatinib mesylate patients develop resistance within 2 years. The establishment of increasing nodes in the tumor masses is a sign of resistance and progression of the disease. For now, according to the algorithms of ESMO and NCCN the use of imatinib mesylate is considered only in advanced unresectable patients, tumor recurrence or evidence of metastasis and we support that strategy for treatment.

The majority of GISTs recurs within the first 3-5 years (Tsukuda, Hirai, Miyake, Takagi et al., 2007). According to National Comprehensive Cancer Network computer tomography is recommended every 3-6 months for 3-5 years, then yearly (Stamatakos et al., 2009). Novosky et al. reported that most of the recurrence occurs during the first 2 year after resection. Because of this they recommend physical examination of the patients every 3-4 months for 2 years, then every 6 months for the next 2 years, then yearly (Gupta, Tewari, and Shulka, 2008; Kim, Kang, Moon, Park et al., 2005). The authors perform chest X-ray, CT and blood test yearly. Endoscopy is performed at 6 months and 1 year after the operation, then annually for 2 years. PET, Chest CT and MRI is preferable only if abnormalities are observed (Safdar and Sher, 2007). In our Department we recommend the follow-up of the patients with physical examination, endoscopy with ultrasound or CT every 6 months for the first 3 years, then annually for 2 years and only CT yearly after the 5-year postoperative period.

**Conclusion**

Surgical resection is the only curable method of treatment of patients with GISTs. The achievement of negative resection margins is one of the most important predictors of survival. The achievement of improved postoperative results is related to precise diagnosis
and staging preoperatively, which can be performed with endoscopy and endoscopic ultrasound, and active follow-up of the patients for the first 5 years after resection because of the highest incidence of recurrence in this period.

References


