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STRATEGY OF TREATMENT OF SUBMUCOSAL GASTRIC TUMORS

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Abstract
Background: The more frequent use of endoscopic ultrasonography (EUS) leads to an increased number of diagnosed gastric submucosal tumors (G-SMT). Since until now rather little therapeutical success in respect of these tumors has been achieved, we evaluated our concept of watchful waiting and selective treatment of patients with G-SMT in an analysis of prospectively collected data.
Patients and Methods: Forty-seven consecutive patients with G-SMT treated at our institution between 1994 and 2000, were included. All patients underwent abdominal ultrasound and EUS, and in case of suspicious findings or a tumor size > 2cm EUS fine needle aspiration (EUS-FNA) was performed. Patients were operated on if a malignant tumor was suspected (tumor size > 2cm; detection of metastases) or if complications occurred (e.g. bleeding, ulceration).
Results: All 47 patients were included in this study. Typical symptoms were nausea (64%), bleeding (11%) and pain (9%). EUS showed a G-SMT averaging 6.4 (0.8 – 30) cm in size. EUS-FNA was performed in 24 patients revealing PAP III (n = 1), PAP II (n = 21) and PAP I (n = 2) scores. Surgery was performed in 33 patients, revealing gastrointestinal stromal tumors (GISTs) in 18 patients as well as several other malignant and non-malignant lesions. During follow-up (median 37 months), none of the conservatively treated patients (n = 14) developed a malignant tumor.
Conclusions: In one third of our patients surgery could be avoided with this strategy. No delayed diagnosis of a malignant tumor during follow-up was established. Small G-GMT's should be monitored conservatively if diagnostic procedures and follow-up was performed by EUS and eventually EUS-FNA.

Key words: Gastric submucosal tumor; ultrasonography; treatment

INTRODUCTION

The introduction of endoscopic ultrasonography (EUS) and endoscopic ultrasonography- guided fine-needle aspiration (EUS-FNA) improved staging and identification of GI tumors. Upper endoscopy is very effective in examining epithelial tumors and/or for the diagnosis of ulcerous lesions. However, this procedure is limited in the diagnosis of submucosal tumors. EUS, in contrast, visualizes precisely submucosal tumors of the upper gastrointestinal tract within and adjacent to the gastrointestinal wall. In addition, ultrasound-guided fine needle biopsy can be performed during the procedure of EUS in order to obtain a cytological diagnosis.

In recent years, the pathological concept of submucosal tumors of the GI tract (SMT) changed considerably. The term SMT comprises benign and malignant neoplasms detectable with certain marker antigens at histological investigation. Generally, the malignant potential is assessed by tumor size and number of mitoses. With the advent of CD34 and c-Kit as discriminating marker antigens, formerly diagnosed leiomyoma or leiomyosarcoma are now frequently reclassified more precisely as gastrointestinal stromal tumors (GIST) [1]. SMT therefore is a relatively new entity of tumors and represents non-epithelial mesenchymal neoplasms accounting for only 0.1-1 % of all GI tumors [2]. Though SMT usually occur in the stomach, they may also develop in the small intestine, large intestine, rectum and esophagus [3].

With introduction of EUS at our institution in 1994, our strategy in treatment of patients with suspicious gastric SMT has changed. In patients where EUS reveals a tumor smaller than 2 cm in maximal diameter and no signs of infiltration in neighbouring structures are detected, we monitor these tumors at frequent intervals. In tumors, which are suspicious for malignancy, i.e. tumor size > 2 cm or presence of ulcerations we constantly perform ultrasound-guided fine needle biopsy is performed as well as other diagnostic procedures such as abdominal CT. If pathological examination or imaging results are suggestive for a malignant tumor or tumor size exceeds 2 cm, the patient is referred for surgery.

PATIENTS AND METHODS

Between August 1994, and August 2000, 47 consecutive patients with gastric submucosal tumors (G-SMT) were treated at our institution and prospectively recruited and documented. All patients underwent gastroscopy. EUS was performed in patients which gastroscopy revealed the assumption of a submucosal tumor. EUS-guided fine needle biopsy was performed if tumors were > 2 cm in diameter, an infiltrating tumor was suspected or positive lymph nodes were seen.

Routinely, a prior abdominal ultrasound was performed. Tumors with less than 2 cm in maximal diameter or without complications (e.g. bleeding) were monitored at frequent intervals shorter than 12 months.

Clinical and pathological records of all patients were reviewed to determine clinical presentation and surgical treatment. Resection was considered R0 (free margins), R1 (tumor at the resection line), or R2 (partial resection) according to the UICC classification [4]. Tumor grade (G1 - 3) was determined according to the grading system for soft tissue sarcomas of Enzinger and Weiss [5]. Classifications of tumors were performed according to Fletcher and Franquemont [6, 7]. Shortly, tumors were classified as malignant when a) metastases were present at initial diagnosis, b) tumor size was > 5 cm and more than 5 mitoses/50 HPF were counted or c) tumor size > 5cm or > 5 mitoses/HPF and necrosis was present. GIST were considered benign when tumor size was < 5 cm and $\not\subset$ 5 mitoses/50 HPF. Tumors were considered to be of uncertain malignant potential when they were ≥ 5 cm or > 5 mitoses/50 HPF were seen, but were lacking the other characteristics of a malignant tumor, i.e. necrosis and metastasis.

All patients were followed up until December 31, 2003.

RESULTS

Twenty-one male and 26 female patients had a median age of 60 (range 23-84) years. Symptoms leading to upper GI-endoscopy are listed in Table 1 and included nausea (63.8%), upper GI bleeding (10.6%) and pain (8.5%) were the presenting symptoms. Patients and tumor characteristics are displayed in Table 2. Tumor size averaged 6.4 (0.8 – 30) cm. EUS-guided fine needle biopsy was performed in 24 patients in whom tumor size exceeded 2 cm or invasion of neighbouring structures was assumed. Cytological preparations were classified as PAP I in two patients (8%), as PAP II in 21 patients and as PAP III in only one (4%). Fourteen of these 24 patients underwent surgery, and the final histological examination revealed a specificity of our preoperative clinical diagnosis (malignant vs. benign) of 86%.

Table 1. Symptoms of 47 consecutive patients with a submucosal gastric tumor.

Symptom	N	%
Nausea	30	63.8
Upper GI bleeding	5	10.6
Gastric pain	4	8.5
Reflux	3	6.4
Vomiting	1	2.1
Dysphasia	1	2.1
Gastritis	1	2.1
Gastric ulcer	1	2.1
None	1	2.1

Table 2. Patient and tumor characteristics of 47 patients with a submucosal gastric tumor (n = 47).

Characteristic	Patients n	%
Age		
< 50 years	11	23.4
> 50 years	36	76.6
Sex		
Female	26	55.3
Male	21	44.7
Size		
< 5cm	30	63.8
≥ 5cm, < 10cm	9	19.2
≥ 10cm	8	17
EUS-FNA		
Yes	24	51.1
No	23	48.9
Operation		
Yes	33	70.2
No	14	29.8
Survival status		
Alive	38	80.5
Died of disease	7	14.9
Died of other causes	2	4.3

Table 3. Histology of 33 patients with a submucosal gastric tumor.

Histology	n	%
Malignant GIST	10	30
GIST with uncertain dignity	5	15
Benign GIST	3	9
Leiomyoma	5	15
Leiomyosarcoma	3	9
Mesenchymal tumor (Vimentin+, CD34+,C-kit-)	2	6
Gastric Adenocarcinoma	1	3
Paragastric abscess	1	3
Accessory spleen	1	3
Gastric cyst	1	3
Lymphangioma	1	3

In those cases with a tumor size > 2 cm or complications such as bleeding, patients were operated on in all but one case for suspicious GIST. One patient refused surgery in respect of her age (84 years) in spite of tumor size. Extent of surgery was decided according to intraoperative findings. In case of SMT of the stomach, an atypical gastric wall resection tailored accordingly was the preferred technique. Regional lymph nodes were sampled in all patients.

Pathologic examination of resected specimen revealed a broad variety of final diagnoses (Table 3). GISTs were identified in 18 patients (55 %). Ten of these GISTs were classified as malignant (all > 5 cm),

three tumors were assessed as benign, and five cases as tumors with uncertain dignity. In one patient gastric adenocarcinoma was confirmed (tumor size 2 cm), though preoperative fine-needle biopsy revealed a PAP II cytology and this patient consequently underwent gastrectomy including lymphadenectomy. In one patient each, an intramural accessory spleen, paragastric abscess, intramural cysts, and lymphangioma was found. No malignancies were found in tumors < 2 cm.

One patient with malignant GIST presented with regional lymph nodes metastases (N1, 10 %), while in all other patients lymph nodes were tumor-free (N0, 90%). One patient underwent R1 resection and refused reoperation. Intraoperatively, four patients (12%) exhibited distant metastases with peritoneal metastases in one and liver metastases in three patients.

All patients were followed until December 2002. The 14 non-operated patients were followed-up closely for a median of 37 (17 – 91) months. An average of one endoscopy/ EUS exam was performed per year; the median tumor size of initially 2.0 cm did not change in these patients. In ten patients, control EUS-FNA were performed; cytopathology revealed PAP II in all of these specimens and monitoring of the patients was continued. None of these tumors progressed or developed clinical signs, symptoms or other characteristics of malignant transformation.

Discussion

The introduction of EUS made the detection of tumors within the gastric wall possible that were previously often not discovered using conventional imaging techniques. These limits of conventional imaging techniques, especially for small tumors became obvious over the years. In addition, histological diagnosis of submucosal tumors seemed to be a challenge if patients were not operated on.

EUS has proven its diagnostic value in gastrointestinal diseases. In particular, smaller lesions are more likely to be detected using EUS [8-10]. Futagami et al. found no difference in the detection rate for G-SMT larger than 3 cm between EUS and US [8]. A further advantage of EUS lies in the possibility of fine needle aspiration (EUS-FNA) to obtain a cytopathologic diagnosis. Using EUS-FNA, Imai et al. found a rate of technically adequate specimens of over 80% and a diagnostic value of over 90%. In contrast, others found a sensitivity of only 60% (11) [9]. In our series a specificity of 86% was found with a sensitivity of 62 %. Occasionally, it was difficult to obtain sufficient material using FNA to establish valid criteria of malignancy in cytology for soft tissue tumors. Potentially, the introduction of PCR analysis applied to cytological material may improve results as c-kit expression can now be detected on EUS-FNA specimens.

In our series, 14 out of 33 operated patients underwent prior EUS-FNA. False-negative cytologies will continue to be a problem, as shown in our patient with a gastric adenocarcinoma. The decision of further treatment, consequently, should not be made based on cytology alone but on an individual basis including all criteria such as tumor size, symptoms and medical history.

The malignant potential of G-SMT increases when the tumor exceeds 30 mm in diameter, approximately 50% of G-SMT larger than 3 cm are malignant [12]. In our series, mean diameter of the malignant tumors was 7.8 cm. No patient with a tumor < 3 cm died of a malignant gastric tumor in a large Japanese series [13]. In another study, gastric ulcers were found combined with G-SMT larger than 5 cm in 39% of the investigated patients. Thirty-seven percent of these patients presented with a malignant tumor, whereas in 11% the tumor was benign [14]. Therefore, in submucosal tumors accompanied by an ulcer should be tightly monitored, if no surgery is being performed. For tumors smaller than 3 cm this finding could not be confirmed [14]. The assumption that G-SMTs most often represent GISTs and that tumor size correlates with its malignant potential suggests a strategy of observing and treating these tumors as follows: tumors < 2 cm in diameter without clinical signs of malignancy or complications are followed-up at frequent intervals (usually 12 months). All other patients are being operated on to confirm diagnosis. This strategy is strongly supported by our clinical results.

In conclusion, we propose that patients with G-SMTs smaller than 2 cm in diameter without clinical signs of malignancy as well as absent complications should be primarily treated conservatively. A frequent follow-up, though, including EUS as the method of choice should be performed in these patients to monitor the tumor's growth. The diagnostic value of FNA could not be confirmed in our series for submucosal tumors, the clinical impression is far more important. In case of alterations suspicious of malignancy, the threshold to operate these lesions should be low.

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