Digestive and Liver Disease 43 (2011) 935–939

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Progress Report

Management of gastrointestinal stromal tumours of limited size: Proposals from a French panel of physicians

Bruno Landi[a,*], Olivier Bouché[b], Rosine Guimbaud[c], Thomas Aparicio[d], Anne Berger[e], Sylvie Bonvalot[f], Bruno Buecher[g], Jean-Yves Blay[h], Christian Boustière[i], Jean-Marie Coindre[j], Jean-François Emile[k], Marc Giovannini[l], Thierry Lecomte[m], Axel Le Cesne[n], Geneviève Monges[o], Bertrand Napoléon[p], Laurent Palazzo[q], Jean-Alain Chayvialle[r]

[a] Department of Gastroenterology, Hôpital Européen Georges Pompidou, Paris, France
[b] Department of Gastroenterology, Hôpital Robert Debré, Reims, France
[c] Department of Oncology, Centre Claudius Regaud, Toulouse, France
[d] Department of Gastroenterology, Hôpital Avicenne, Bobigny, France
[e] Department of Digestive Surgery, Hôpital Européen Georges Pompidou, Paris, France
[f] Department of Surgery, Institut Gustave Roussy, Villejuif, France
[g] Department of Digestive Oncology, Institut Curie, Paris, France
[h] Department of Medicine, Centre Léon Bérard, Lyon, France
[i] Department of Gastroenterology, Hôpital Saint Joseph, Marseille, France
[j] Department of Pathology, Institut Bergonié, Bordeaux, France
[k] Department of Pathology, Hôpital Ambroise Paré, Boulogne, France
[l] Department of Digestive Oncology, Institut Paoli Calmette, Marseille, France
[m] Department of Gastroenterology, Hôpital Trousseau, Tours, France
[n] Department of Medicine, Institut Gustave Roussy, Villejuif, France
[o] Department of Pathology, Institut Paoli Calmette, Marseille, France
[p] Department of Gastroenterology, Hôpital Privé Jean Mermoz, Lyon, France
[q] Department of Endoscopy, Clinique Turin, Paris, France
[r] Department of Gastroenterology Hôpital Edouard Herriot, Lyon, France

ARTICLE INFO

Article history:
Received 21 September 2010
Accepted 12 April 2011
Available online 28 May 2011

Keywords:
Endoscopic ultrasonography
Endoscopy
Gastrointestinal stromal tumour
GIST
Ultrasound

ABSTRACT

A number of guidelines on the management of gastro-intestinal stromal tumours (GISTs) have been published, mostly based on expert consensus. However, these guidelines have generally failed to address the specific problem of GISTs of limited size (i.e. those measuring a few centimetres in diameter) with which gastroenterologists are increasingly confronted. The aim of the present work was to draw up proposals for the diagnosis and treatment of GISTs measuring less than 5 cm in diameter. For this purpose, a number of practical questions were put to a panel of French experts.

1. Introduction

Gastrointestinal stromal tumours (GISTs) are the most frequent mesenchymal digestive tract tumours [1]. They have been well characterized in both histologic and molecular terms [2]. About 65% of GISTs are located in the stomach, with 25% in the small intestine and 5–10% in the colon or rectum [1–3]. Other digestive locations are very rare. Although surgical resection remains the standard treatment for localized tumours, the drug treatments that are now available for advanced and metastatic forms of the disease have radically changed the prognosis. A number of guidelines on GIST management (based mainly on expert consensus) have been drawn up [4–6]. However, these guidelines have generally failed to address the specific problem of GISTs measuring a few centimetres in diameter and which gastroenterologists most often detect by endoscopy. A recent survey of American endosonographers revealed substantial practice variations in terms of the diagnosis, monitoring and treatment of GISTs [7].

* Corresponding author at: Service d'hépato-gastroentérologie, Hôpital Européen Gorges Pompidou, 20 rue Leblanc, F-75015 Paris, France. Tel.: +33 156 093555; fax: +33 156 093529.
E-mail address: bruno.landi@egp.aphp.fr (B. Landi).

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doi:10.1016/j.dld.2011.04.008

Table 1
The risk of aggressive behaviour after resection of a localized GIST (expert consensus from 2002).

Risk of aggressive behaviour	Size (largest dimension)	Mitotic count
Very low risk	<2 cm	<5/50 HPFs
Low risk	2–5 cm	<5/50 HPFs
Intermediate risk	<5 cm	6–10/50 HPFs
High risk	Any	>10/50 HPFs

Adapted from Ref. [11].
HPFs, high-power fields.

The aim of the present work was draw up proposals for the diagnosis and management of GISTs <5 cm in diameter, by putting a series of practical questions to a panel of experts. These experts had to have been involved in GIST management and to have published in this field. They are from different medical specialties, and members of different French scientific societies: hepatogastroenterology (SNFGE), endoscopy (SFED), endosonography (CFED), sarcoma group (GSF), surgery (SFCD), and pathology (SFP). All experts contacted filled the questionnaire. The final objective of this approach was to assess the state of clinical practice. A much more burdensome methodology would have been necessary to establish official recommendations. This did not appear to be justified for a topic within which practice is essentially based on expert opinion, rather than clinical studies with high levels of evidence.

In terms of management, gastric GISTs will be considered separately, in view of the risk of aggressive behaviour compared to other intestinal tumour sites. It is also important to bear in mind that a diagnosis of GIST is often only speculative at the time when a treatment decision is taken especially when based on imaging data alone; this point will be expanded upon below. Histological analysis is the only way to formally diagnose a GIST. It also enables the physician to specify the risk of aggressive behaviour as a function of the tumour size, site and mitotic count. Neither the issue of adjuvant treatment after surgical resection nor the management of metastatic disease will be addressed here.

2. GIST < 5 cm and concept of "small GISTs"

A diameter of less than 5 cm was chosen from the outset because this value corresponds to the threshold used in the first ever prognostic classification of the risk of aggressive behaviour for GISTs (Table 1). The incidental discovery of a GIST < 5 cm is not infrequent. In a retrospective series of 1765 gastric GISTs with diameters ranging from 0.3 to 44 cm, 46% measured less than 5 cm in diameter at the time of diagnosis [8]. Of 906 cases of GIST of the small intestine, 36% measured less than 5 cm in diameter [9]. In a study by French pathologists, 15% of the diagnosed GISTs measured less than 2 cm in diameter and 34% measured between 2 and 5 cm [10]. In clinical practice, about half of gastric GISTs and a third of small intestine GISTs measure < 5 cm in diameter at the time of diagnosis. GISTs < 5 cm are often asymptomatic but can be revealed by occult or overt bleeding, abdominal pain, or even small bowel occlusion.

There is no precise definition of a "small GIST" and the concept is clearly arbitrary. It is known that the size of a GIST correlates with its risk of aggressive behaviour, even though this is not the only prognostic criterion. A small, incidentally identified lesion does not necessarily require radical treatment, as long as the risk of aggressive behaviour is low. A lack of symptoms, incidental discovery and the absence of metastatic spread are often associated with the notion of a "small GIST", even though tumours with a diameter < 5 cm can also be symptomatic and/or metastatic.

Tumours with a diameter between 2 and 5 cm, for which the risk of aggressive behaviour after exeresis is low for low mitotic counts but potentially high for extragastric sites and high mitotic counts (Tables 1 and 2) [11,12], cannot be considered as small GISTs. According to most experts, the term "small GIST" should be restricted to GISTs < 2 cm. However, in order to mirror clinical practice as closely as possible and to be as exhaustive as possible, we decided to broaden out the present work to GISTs < 5 cm, even though it is clear that the corresponding risk of aggressive behaviour differs from that of lesions measuring < 2 cm. Hence, the term "small GIST" could be used to designate:

- the "GIST tumourlet" (also known as a "minute GIST" or a "microscopic GIST"), a recent concept for gastric tumours measuring between 1 and 10 mm in diameter and whose risk of aggressive behaviour is uncertain. These tumourlets described in histologic studies of serial sections are generally not detected in clinical practice [13,14].
- tumours < 2 cm in diameter, generally asymptomatic, for which the risk of aggressive behaviour after exeresis is virtually null when located in the stomach [12].

In clinical practice, all symptomatic GISTs (even small ones) require treatment [4–7]. The problem of deciding between resection and monitoring mainly arises for asymptomatic gastric GISTs < 2 cm or even (according to some authors) < 3 cm (the largest dimension adopted in the American Gastroenterological Association (AGA) guidelines) [6].

3. Prognosis for localized GISTs < 5 cm

It is generally acknowledged that all GISTs are potentially malignant. This notion has been recently been modified by the description of GIST tumourlets. It is now clear that although all GISTs may progress, not all will. C-KIT mutation is observed in tumours < 1 cm [14]. For resected, localized tumours, the first prognostic classification (based on the tumour size and mitotic count) was published in 2002 as part of an expert consensus approach (Table 1) [11]. Large, retrospective series have added detail to these findings and have also underlined the major influence of the tumour site on the risk of aggressive behaviour (Table 2) [12]. Other histological, immunohistochemical and especially molecular parameters are now being evaluated. Even though most relapses occur in the 5 years following surgery (and predominantly in the first two years), very late relapse is possible [5,6].

Table 2
Rates of relapse or tumour-related death in GISTs < 5 cm as a function of tumour size, site and mitotic count.

Size (largest dimension, in cm)	Mitotic count[b]	Stomach	Duodenum	Jejunum and ileum	Rectum
≤2	≤5	0	0	0	0
>2 and ≤5	≤5	1.9%	8.3%	4.3%	8.5%
≤2	>5	0	[a]	50%	54%
>2 and ≤5	>5	16%	50%	73%	52%

Adapted from Ref. [12].
[a] Too few patients for a valid assessment
[b] Miettinen evaluated the mitotic count for a total surface area of 5 mm^2 with 50 standard high-power fields, in order to limit microscope-to-microscope variability (in fact, this may correspond to only 20–25 high-power fields on recent microscope systems).

Table 2 summarizes several important findings:

- gastric GISTs have a better prognosis than GISTs in other sites. The risk of aggressive behaviour after R0 resection is null for a gastric GIST < 2 cm and very low (1.9%) for a GIST < 5 cm if the mitotic count is 5 per 5 mm^2 or less. The mitotic count is evaluated according to Miettinen's method over a total surface area of 5 mm^2 (corresponding to a 50 standard high-power fields (HPFs)), in order to limit microscope-to-microscope variations (Table 2). In fact, this may correspond to just 20–25 HPFs with the latest microscope systems.
- GISTs in the small intestine and the rectum have a significant risk of aggressive behaviour, regardless of size (as long as the mitotic count is high).
- Overall, the mitotic count is the most significant prognostic factor.

4. Practical questions put to the experts

1. Should an endoscopic biopsy be performed for all gastroduodenal or rectal lesions which might be GISTs? If so, how?

Experts' opinion

Standard endoscopic biopsies are generally not useful for diagnosis of a GIST. In daily practice, they are nevertheless performed to rule out other submucosal lesions which may affect the mucosa (lymphoma, endocrine tumours, etc.). By convention, these biopsies should be avoided in cases of suspected leiomyoma of the oesophagus because they could promote adherences to the mucosa likely to complicate thoracoscopic enucleation. Endoscopic biopsies are more likely to be valuable for the diagnosis of GIST when performed on an ulcerated lesion. However, the haemorrhagic risk in this situation is not well known and so the procedure must be performed with caution and adapted to the clinical context (notably in cases of recent overt haemorrhage or a low haematocrit).

Bite-on-bite biopsies do not enable the histologic diagnosis of GISTs which grow out of the muscularis (corresponding to the fourth hypo-echogenic endoscopic ultrasound layer). The value of bite-on-bite biopsies has only been demonstrated for submucosal tumours growing out of the third (hyper-echogenic) EUS layer (the submucosa). This procedure should therefore not be performed for tumours developing in the fourth EUS layer.

Deep biopsies via loop electrocautery excision or mucosectomy are contra-indicated in cases of suspected GISTs, in view of the significant risk of perforation for lesions developing in the muscularis. Likewise, there is expert consensus on the need to avoid endoscopic exeresis of tumours developing in the muscularis.

2. Should all potential esogastroduodenal or rectal GISTs undergo EUS-guided fine-needle aspiration if endoscopic biopsies are negative?

Experts' opinion

An endoscopic ultrasound (EUS)-guided fine needle aspiration biopsy can provide diagnostic certainty. Its yield is, however, lower for GISTs < 2 cm (see question 3). The value of this technique must be considered on a case-by-case basis, if possible in a multidisciplinary care team meeting. This biopsy is not recommended when the endoscopic ultrasound aspect suggests a GIST and when surgical resection has been decided. It is recommended in cases where there is diagnostic doubt relative to other types of tumour.

3. Is there a lesion size below which EUS-guided biopsy of the suspected GIST is not feasible or worthwhile (or is even dangerous)?

Experts' opinion

The EUS-guided biopsy of an intramural lesion does not appear to be associated with a particularly high risk of complications. There is expert consensus on the fact that (i) EUS-guided biopsy is technically not feasible for GISTs < 1 cm and (ii) GISTs > 2 cm represent the best potential indication.

EUS-guided fine needle aspiration biopsy of a GIST measuring between 1 cm and 2 cm in diameter is technically challenging and the yield is low. Most experts doubt the value of this technique in current practice. However, it can potentially be performed with a 22-G needle by a well-trained team.

4. What practical value do EUS criteria for "benignity" or "malignancy" have for suspected GISTs?

Experts' opinion

The quality of the ultrasonographic analysis is important, since not all submucosal lesions undergo a fine-needle aspiration biopsy or exeresis. The EUS criteria for "benignity" or "malignancy" described in retrospective series of GISTs (diameter, hyperechogenic spots, irregular borders and cystic zones) have limited practical value (apart from the size criterion). They do not substitute for histological findings, even though the presence of these signs can prompt the physician to suspect a GIST with a more critical histology. Moreover, these signs are rarely observed in GISTs < 3 cm.

5. Should all GISTs (even small ones) prompt the performance of contrast-enhanced abdomino-pelvic spiral CT scans with thorax imaging, as recommended in the general guidelines on GISTs?

Experts' opinion

The performance of a contrast-enhanced spiral CT scan of the abdomen, pelvis and thorax in all cases is probably excessive. In addition to the size, it is advisable to take into account the tumour site (since the risk of aggressive behaviour is higher in extragastric GISTs). Some small GISTs, notably those in the rectum, are associated with a significant risk of aggressive behaviour. In current practice, most experts feel that the performance of a contrast-enhanced spiral CT scan of the abdomen, pelvis and thorax is not recommended for suspected GISTs < 1 cm, except for those in duodenal or rectal sites (when the examination must always be performed). In cases of gastric GISTs < 2 cm without suspicious EUS signs, most experts do not consider that contrast-enhanced spiral CT scan of the abdomen, pelvis and thorax is useful.

6. Should all small extragastric GISTs be resected?

Experts' opinion

There is expert consensus on recommending the systematic resection of small extragastric submucosal tumours suspected of being GISTs. This view should be fine-tuned when the risk-benefit ratio appears to be unfavourable (old age, severe co-morbidities, poorly surgical access to the tumour site, etc.). The oesophagus represents a special case and it should be noted that most mesenchymal tumours of the oesophagus are benign leiomyomata for which the therapeutic management differs.

7. In case of small, presumed GISTs, in which cases might open surgery be preferable to laparoscopic surgery?

Experts' opinion

During surgery, it is essential to reduce the risk of tumour dissemination. Laparoscopy is a feasible option for tumours < 5 cm as long as there are no technical complications or serous invasion.

8. In cases of small rectal GISTs, which treatment should be preferred?

Experts' opinion

There is expert consensus on recommending surgical exeresis. The published results are clearly in favour of organ exeresis (anterior resection of the rectum). Here again, it is advisable to evaluate the risk-benefit ratio in very old patients or those with severe comorbidities. The value of transanal exeresis of rectal GISTs has not been clearly established.

9. Should resection or monitoring of a suspected gastric GIST < 2 cm be left to the physician's own judgement?

Experts' opinion

A monitoring strategy is only recommended by the experts as a possible option for gastric GISTs < 2 cm, after discussion of the risk-benefit ratio with the patient and as an alternative to exeresis. These patients can either undergo immediate surgery, i.e. standard treatment, or follow-up and, if the tumour grows, subsequent elective surgery. The choice between surgery and monitoring for a gastric submucosal tumour must take account of several factors, such as the patient's age, the background, the tumour site accessibility and patient's opinion. The patient must be fully informed of the two approaches' respective advantages and disadvantages.

The experts agree on the following points:

It is useful to discuss these cases in multidisciplinary care team meetings, for advice on patient management.
There is a need to perform prospective studies with follow-up for suspected GISTs < 2 cm.
It will be useful to evaluate new techniques to better predict the risk of aggressive behaviour in small (diameter < 2 cm) GISTs.

10. If observation and monitoring are decided for small presumed gastric GISTs:

10.1 Is EUS-guided fine needle aspiration biopsy essential for refining the diagnosis?

Experts' opinion

It should be borne in mind that a monitoring strategy is only approved by the experts as a possible option for the gastric GISTs < 2 cm (see question 9), after discussion of the risk-benefit ratio with the patient and as an alternative to exeresis.

According to the majority of experts, an EUS-guided biopsy is not advisable for tumours suspected to be gastric GISTs < 2 cm, notably in view of the low yield.

Some experts feel that EUS-guided fine needle aspiration biopsy is necessary in order to be certain that the tumour is indeed a GIST before undertaking (burdensome) monitoring. In fact, the tumour may sometimes be a benign lesion (leiomyoma or schwannoma, in particular). This approach should be weighed up against the gastric site and the operator's experience as it can be a delicate procedure. None of the experts recommend aspiration biopsies for gastric lesions < 1 cm in diameter.

10. 2 Which largest dimension appears to be more appropriate: 2 or 3 cm?

Experts' opinion

Well-designed prospective studies would be essential. There is consensus on the fact that monitoring is possible for suspected GISTs < 2 cm but this must be discussed on a case-by-case basis.

A size limit of 3 cm for possible monitoring of a gastric GIST (corresponding to the AGA 2006 guidelines) [3] was not endorsed by the majority of the experts. Monitoring could only be considered in the absence of suspect EUS signs and in very particular cases (old age, a background with an unfavourable risk-benefit ratio or the patient's decision).

10. 3 Which monitoring procedure(s) and schedule should be favoured?

Experts' opinion

There is expert consensus on favouring EUS monitoring as the standard approach; it is more accurate than endoscopy for monitoring any changes over time in lesion size. Endoscopy may, however, be an alternative when the patient has low compliance or tolerance to monitoring.

Although practice differs from one establishment to another, most experts agree on the following schedule: monitoring at 6 months and 18 months and then (in the absence of a significant increase in size) every 2 years.

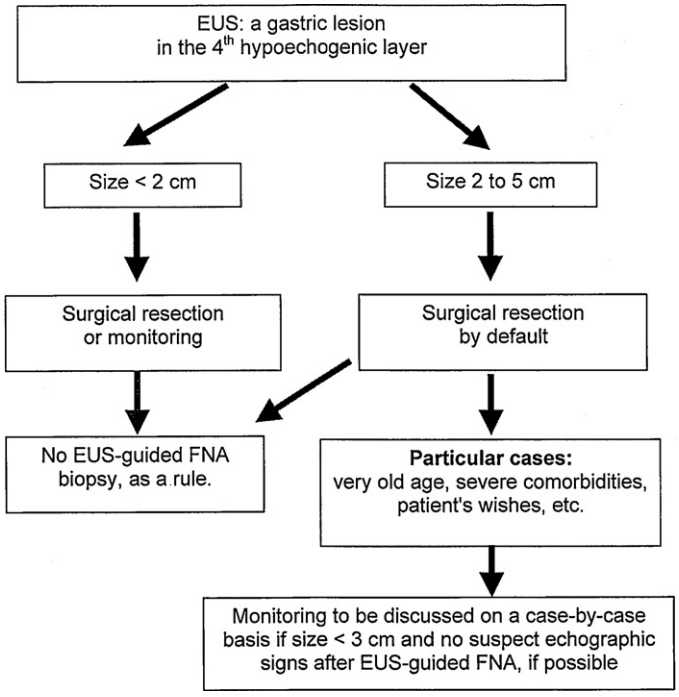

Fig. 1. Proposed treatment flowchart in cases of suspected localized gastric GISTs measuring less than 5 cm in diameter. EUS, endoscopic ultrasound.

5. Perspectives

A treatment flowchart in case of suspected, gastric GISTs measuring < 5 cm in diameter and localized is proposed in Fig. 1. The most recent prognostic classification of GISTs features three parameters: tumour size, site and mitotic count [12]. For small GISTs discovered incidentally in an endoscopic examination, the mitotic count is the most difficult prognostic parameter to specify but is probably the most important [6]. Endoscopic biopsies are rarely positive and an EUS-guided fine needle aspiration biopsy does not usually enable the physician to correctly assess the risk of aggressive behaviour of the tumour. Current progress in endoscopic techniques and histologic analysis prompts hopes of better GIST diagnosis when EUS does not provide decisive information.

Screening for KIT mutations in tissue samples from small gastric GISTs could, in the future, be of value in tumour management, given that resection is systematically indicated for small duodenal, intestinal or colorectal GISTs. Mutations in exon 11 of the KIT gene are the most frequent but vary in nature (deletions, missense mutations and duplications). It is possible that the type of mutation has an impact on the prognosis [15–17]. Mutations in the gene coding for the platelet-derived growth factor alpha receptor (PDGFRA) are quite frequent in gastric GISTs and appear to reduce the risk of aggressive behaviour [18]. In an initial approximation, a proximal deletion or bi-allelic mutation of KIT exon 11 could suggest the need for resection, whereas KIT exon 11 duplication or a mutation in the PDGFRA gene coding could favour a wait-and-see approach [15–18]. Our management approach to GISTs will certainly be refined by progress in identifying the biological basis of malignant progression. For example, a recent publication suggests that studying the expression level of various genes (particularly that of dipeptyl peptidase IV, CD26) may have value for predicting the malignancy risk for gastric tumours [19].

Even though PET scans are not recommended for the management of single-site GISTs, a Japanese series has nevertheless reported the existence of a reasonable correlation between the standardized uptake value for 18-FDG and the mitotic count [20].

This idea is worth developing, in as much as a 2 cm tumour with intense mitotic activity could probably be detected using this technique. If confirmed in multicentre studies, the expression of a metabolic signal would be a significant criterion in favour of resection rather than monitoring of gastric GISTs > 1 cm. In any case, prospective studies are absolutely required to better understand these tumours and their progression profiles when detected at an early enough stage.

Conflict of interest

None declared.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.dld.2011.04.008.

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