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A PROSPECTIVE STUDY ON ENDOSCOPIC ULTRASONOGRAPHY CRITERIA TO GUIDE MANAGEMENT IN UPPER GI SUBMUCOSAL TUMORS

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Endoscopic ultrasonography (EUS) can differentiate between impression and submucosal tumor (SMT) but it is not known whether EUS criteria can reliably guide management.

The aim of this prospective study was to assess an approach to recommend removal *versus* follow-up investigation based on clinical and EUS criteria, with respect to the predictive values to recognize malignancy *versus* benign lesions.

Material and methods. Over a 7-years time period, all patients referred for the EUS assessment of submucosal upper GI lesions were prospectively enrolled. Extraluminal impressions diagnosed with EUS were not further considered. If submucosal tumors seen with EUS were clearly symptomatic or one of several parameters (tumor size >3 cm, irregular margins, inhomogeneous echotexture and/or enlarged lymph nodes) were found, resection was recommended. The remaining cases were subjected to EUS follow-up.

Results. Of cases with 241 submucosal lesions, 65 had impressions and 176 had true submucosal lesions. Of the latter, 29 cases had non-neoplastic lesions (cysts, varices). In 59 cases, removal was deemed necessary due to clinical symptoms and suspicious findings in conventional endoscopy. These subjects underwent either surgical (originating layer, muscularis propria) or endoscopic resection (submucosal origin): 35.6% were malignant, more frequently in the surgical group (41.6% vs 20%). However, in 52.5% (n=31) of the 59 cases with no severe symptoms and true SMT, EUS suggested removal because of their additional criteria. Eighteen patients (12.2%) refused SMT removal and even regular EUS-based follow-up investigation. Clinical follow-up investigation by the family practitioner did not show frank malignancy in these cases (retransferal not registered). Follow-up investigation with EUS was recommended in 70 cases (mean follow-up period, 5 years; range, 1-7 years). The pattern remained unchanged in 67/70, and 2 of the 3 cases with changes underwent surgery for benign leiomyoma (patient refusal, n=1 with no change in the one-year follow-up MRI).

Conclusions. An EUS strategy based on defined characteristics to remove SMT with no severe symptoms and suspicious finding in the conventional endoscopy shows a good adherence to the recommended approach and has a reasonable positive predictive value for malignancy (88%). Clinical symptoms alone or with endoscopic finding are frequently too vague to decide for a reasonable SMT resection. The chosen EUS criteria are valuable to: 1) achieve the primary resection of all potentially malignant SMT and 2) avoid to overlook them as shown by the results of the follow-up investigations with no detected malignant lesion.

Key words: submucosal tumor, gastrointestinal tract, endoscopic ultrasonography, gastrointestinal stromal tumor, leiomyoma

Endoscopic ultrasonography (EUS) has been repeatedly shown to be the most accurate test in the diagnosis of submucosal tumors (SMT) (1, 2) by definition of its layer of origin (3) as well as by the correct differentiation from impressions (2, 4). In addition, the tumor type can be suspected on the basis of the originating layer (2-5). However, though the ability of EUS to further differentiate between benign and malignant tumor lesions has been discussed controversially, it appears to be possible (2, 4, 6, 7, 8).

The majority of mesenchymal stromal tumors is discovered by coincidence in asymptomatic patients and is obviously benign. The 10-30% of cases with malignant tumors are, however, associated with a poor prognosis (6, 7, 9, 10). Fifty to 60% of mesenchymal stromal tumors are GISTs. They are considered a separate tumor entity based on the originating cells (specific interstitial cells called Cajal cells) and the specific biological behavior (11, 12), e.g., GISTs may have malignant potential (1, 4, 6, 7). The knowledge about GIST appears to have changed the decision for non-operative treatment *versus* surgical intervention (1). Nevertheless, there are no general therapeutic guidelines available in the literature how to approach asymptomatic and smaller SMT.

The present study prospectively assessed an approach to recommend removal *versus* follow-up investigation based on clinical and EUS criteria, with respect to the predictive values to recognize malignancy versus benign lesions.

MATERIAL AND METHODS

Over a 7-years time period, all patients referred to EUS with an endoscopic suspicion of an upper GI SMT were enrolled in this prospective study. After exclusion of extraluminal impressions and non-neoplastic intramural lesions (e.g. cysts, varices), true SMT were analyzed according to the following parameters:

- 1) maximal size in 2 dimensions,
- 2) layer of origin,
- 3) outer contour (smooth / irregular),
- 4) echostructure (echo-poor / echo-rich / mixed),
- 5) internal echopattern (homogeneous / inhomogeneous),
- 6) detection of inner structures (cystic, tubular, solid),
- 7) deep infiltration with loss of layer structure,

- 8) enlarged locoregional lymph nodes (size, >1 cm; spheric form; loss of central echo-rich band-like reflex).

bases on clinical signs (dysphagia, bleeding, obstruction, pain, unspecific abdominal discomfort) and certain EUS features, either resection (endoscopic or surgical) or follow-up investigation was recommended. Removal was advised if EUS showed either a tumor size of >3 cm, an irregular outer contour, an inhomogeneous echopattern and/or enlarged lymph nodes (one present parameter was sufficient in decision-making for removal). In the remaining cases, EUS-based follow-up investigation was recommended. As tumor removal was concerned, endoscopic resection was attempted for lesions:

- up to 4 cm in size,
- limited to the 2nd or 3rd wall layer,
- without enlarged lymph nodes, i.e., with no evidence of lymph node involvement,
- in potentially achievable R0 resection status, and
- to find definite histologic diagnosis.

Subjects enrolled into the follow-up group were advised to undergo EUS follow-up investigations every 6 months through the first 2 years, and in yearly intervals thereafter.

Informed consent was obtained from each patient who was included in the study. The study was not submitted to an Ethical Committee since it evaluated the clinical approach, which had been chosen on the basis of best available evidence.

RESULTS

Overall, 241 patients referred for EUS because of a suspected SMT were primarily analyzed; all EUS examinations were performed by one experienced examiner (U.W.). 65 of these cases were then excluded due to the EUS diagnosis of an extraluminal impression, and 29 further cases were excluded since their intramural lesion was found to be non-neoplastic on EUS (13 varices (varices & varix-like nodes), 7 cysts, 2 abscesses, 6 duplications, 1 undefined inflammatory lesion).

Tumor resection due to clinical symptoms including suspicious findings in the conventional endoscopy (fig. 1)

Of the remaining 147 cases, tumor removal was indicated in 59 cases (23 men, 36 women;

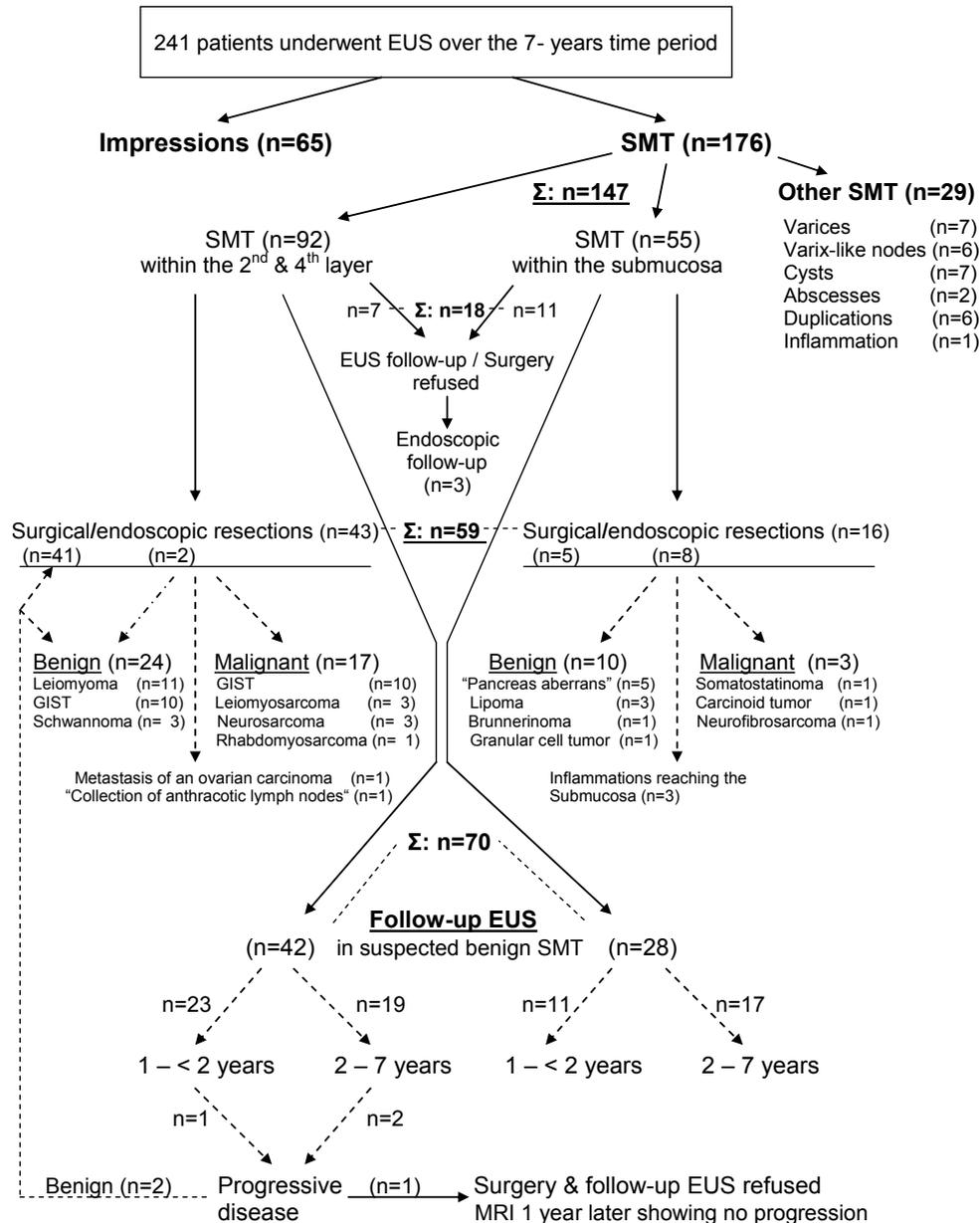


Fig. 1. Flow chart indicating differential diagnosis of SMT, case numbers, type of management, and outcome

mean age, 62 years; range, 31-89 years) on the basis of clinical symptoms (dysphagia, n=7 (11.9%); bleeding, n=28 (47.5%); obstruction, n=0; pain, n=19 (32.2%); unspecific abdominal discomfort, n=51 (86.4%)). Histopathologically, of these tumors were 21 malignant (35.6%) and 38 benign (64.4%) (tab. 1).

On the basis of EUS appearance (2nd or 3rd layer origin), removal was attempted endoscopically in 10 cases and all could be fully resected. Histopathology showed 2 malignant cases (histopathology, GIST; rate of malignancy, 20%). These two subjects were not surgically re-approached but they underwent

EUS-based follow-up investigation with no further suspicious finding.

Surgical removal was performed in 46 cases (4th layer origin, other criteria see above). Histopathology revealed 19 malignant SMT (41.3%) and 27 benign.

Of the EUS parameters, the positive and negative predictive value of tumor size >3 cm was 41% and 88%, respectively (size >4 cm, 57% and 87%, respectively); other EUS features as follows: Inhomogeneous texture, 41% and 95%, resp.; cystic lesions, 45% and 87%, respectively; inhomogeneous texture plus size >4 cm, 60% and 87%, respectively.

Table 1. Histopathological classification of resected SMT according to clinical and EUS-based criteria

	SMT of the 2 nd and 4 th layer	SMT within the submucosa
malignant (n = 21; 35,6%):	(n = 18): – GIST, n = 10 – leiomyosarcoma n = 3 – neurosarcoma n = 3 – rhabdomyosarcoma n = 1 (metastasis of an ovarian carcinoma n = 1) *	(n = 3): – somatostatinoma n = 1 – carcinoid tumor n = 1 – neurofibrosarcoma n = 1
benign (n = 38; 64,4%):	(n = 25): – leiomyoma n = 11 – GIST, n = 10 – schwannoma n = 3 ("Collection of anthracotic lymph nodes", n = 1) *	(n = 13): – "pancreas aberrans" / n = 5 – lipoma n = 3 – <i>brunnerinoma</i> , n = 1 – granular cell tumor n = 1 (inflammation reaching the submucosa n = 3) *

* no classical SMT

There were 18 cases (SMT of the 2nd and 4th layer, n=7; SMT within the submucosa, n=11), in whom removal or at least EUS follow-up investigation was recommended but not performed due to various reasons, mostly patient refusal. Finally, 3 subjects had sporadic follow-up investigations with EUS (follow-up period, 3-7 years) and did not show any change of the locally detected SMT. The remaining 15 individuals had only clinical follow-up examination (follow-up period, 3-7 years; mean, 5 years), all without evidence of frank malignancy (no retransferal registered). However, these patients were classified to be lost for EUS-based follow-up investigation, i.e., lost for further evaluation in this study with its specific conditions ("drop out", 12.2%; n=18/147).

Thus, the predictive value of clinical symptoms for malignancy was 5.43% (n=7/129) whereas the rate of malignancy was approximately 14.3% (n=21/147), which eventually needs to be slightly corrected because of a not complete data acquisition: 16.3% (n=21/129).

Management on the basis of EUS criteria (fig. 1)

Subtracting these 18 and the 59 resected patients from the total number of 147 cases, the remaining 70 patients (35 men, 35 women; mean age, 55 years; range, 20-78 years) formed the study group of asymptomatic SMT. Their lesions were located in esophagus (n=21), stomach (n=38) and duodenum (n=11).

1. Resected group

There was a group with no severe symptoms but suspicious finding in conventional upper

GI endoscopy (the majority of them reported unspecific abdominal discomfort) of 31 patients (out of the total number of patients with resection, n=59; 52.5%), who followed the EUS-based recommendation of SMT removal.

2. Group with EUS-based follow-up investigation

Of the 70 primarily asymptomatic cases, in whom EUS criteria suggested follow-up investigation only, none underwent primary resection. These patients underwent a mean of 4 follow-up EUS examinations (range, 1-8) over a follow-up period between 1 year and 7 years (mean, 5 years). Of the 70 cases with EUS follow-up, the tumor was located within the submucosa and the muscle (2nd and 4th layer in 28 and 42 cases, respectively). While no changes could be noted in patients with tumor lesions in the submucosa, such changes were detected in 3 patients of the group with suspected mesenchymal tumors of the muscle layer after 1, 2 and 2.5 years, respectively. Two lesions showed an increased size of + 1-2 cm whereas in the remaining lesion, a changed (inhomogeneous) texture was detected. All 3 SMT were located within the 4th layer of the gastric wall. Two of these patients underwent surgical intervention with the result of benign leiomyomas. The remaining one patient refused the recommended surgical approach and underwent MRI instead one year later showing no progression.

Thus, for this group, a no change situation led to the assumption of a benign SMT. Taking this as basis, the EUS approach had a negative predictive value of EUS criteria for malignancy (i.e., positive predictive value for a benign SMT) of 95.7% (n=67/70),

including only cases with EUS follow-up and 100% if all cases with any follow-up were included.

Clinical information on the follow-up of resected cases is not shown since this study is ongoing and this was not the focus of the present paper. There were, however, no major postoperative or postendoscopic complications.

DISCUSSION

By the mean of EUS, differentiation between SMT and extraluminal compressions appears to be possible in each case (2, 4). In addition, lipomas, cysts, and varices are detectable with no doubt and with no diagnostic or methodological problems because of the typical echo signalling and the location within the submucosa (2) (fig. 2, 3). In these cases, follow-up EUS is not required.

“Pancreas aberrans” usually located in the prepyloric antrum (endoscopic finding) shows a heterogeneous echo pattern and, in the majority of cases, a central, echo-rich, ligament-like structure. Based on the preferential location within the submucosa and the possible malignant transformation of this lesion in single cases as reported, endoscopic resection is recommended for histologic investigation, in particular, in patients who are symptomatic (1).

The endosonographic differentiation between malignant and benign tumors (fig. 4) (2, 4, 6, 7, 8), in particular, in stromal tumors

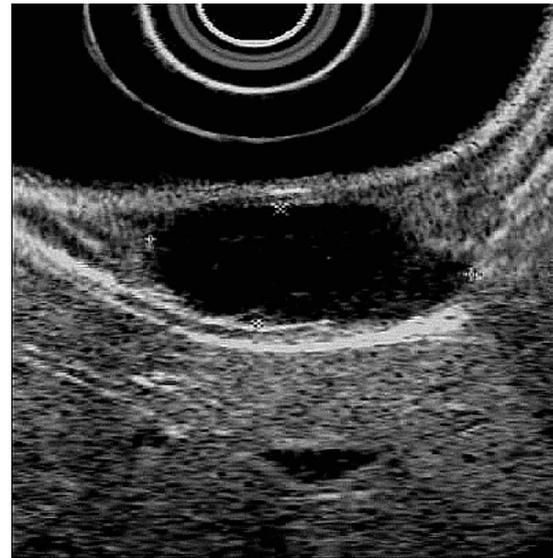


Fig. 2. Differential diagnosis of SMT: cyst of the gastric wall showing echo-free texture (“shadow of the echo”) and regular peripheral contours

(4, 7, 8, 10), is associated with a sensitivity of 71% and a specificity of 81% using a multivariate analysis of endosonographic characteristics in our study. In the literature, there is only one comparable study by Palazzo et al. (4) who has reported on a sensitivity of 41% and a specificity of 94% for the detection of cystic structures within the tumor lesion, and 77% and 55%, respectively, for the detection of a malignant tumor lesion (tumor size, >3 cm).

A high prevalence of benign tumor lesions (65%) in the group of patients who underwent

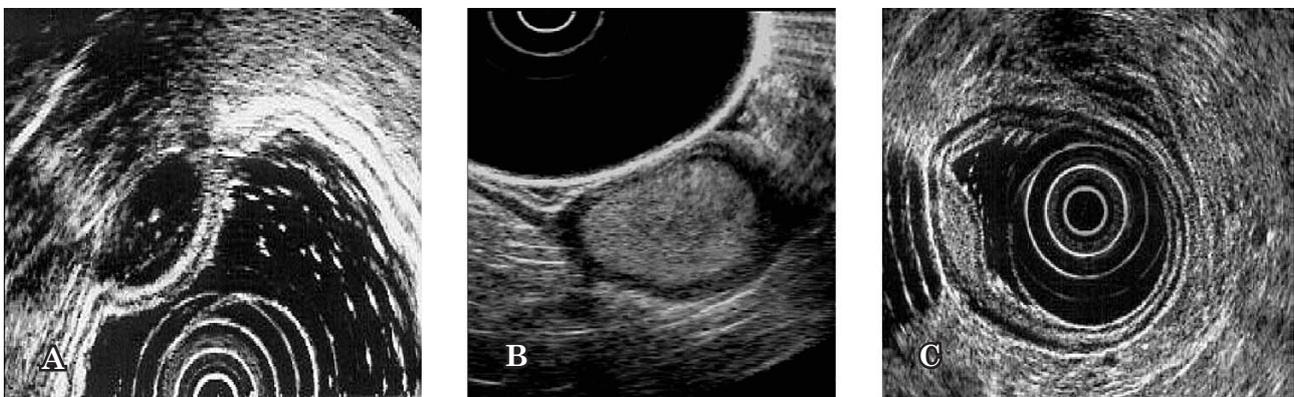


Fig. 3. Benign SMT

- A. Suspected leiomyoma within the 4th layer of the gastric wall: – homogeneous and echo-poor structure, <3 cm, regular peripheral contours;
 B. GIST within the 2nd layer (stomach): - Inhomogeneously structured, <3 cm, regular peripheral contours;
 C. Lipoma within the submucosa (stomach): – homogeneous and echo-rich structure, regular peripheral contours

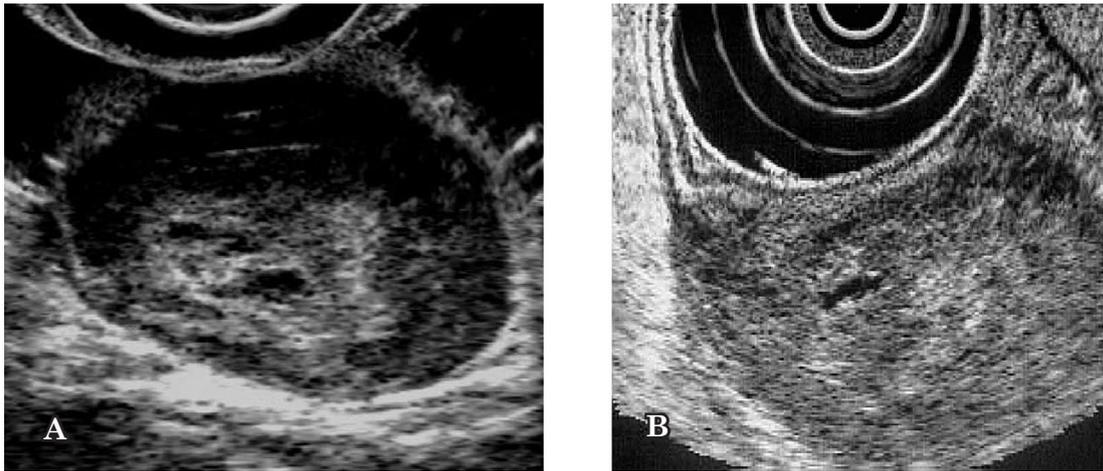


Fig. 4. Malignant SMT

A. Malignant GIST within the "Lamina muscularis propria" (stomach; size, approximately 3 cm) - inhomogeneous texture, cystic lesion, irregular peripheral contours, histologic investigation of EUS-guided FNP (biopsy) - positive CD117/CD34

B. Sarcoma within the "Lamina muscularis propria" of the gastric wall (> 3 cm): inhomogeneous texture, cystic lesions, irregular peripheral contours

surgical intervention because of suspected malignancy and the still missing detection of a malignant tumor lesion in the observation group (surgical intervention, n=2; stable finding in the remaining) indicate a favorable selection mode for a reasonable surgical approach using EUS.

In this context, follow-up EUS is a suitable diagnostic option to overcome uncertainty in asymptomatic patients with small (<3 cm), smoothly contoured, homogeneously structured SMT, which were discovered by coincidence. In case of increasing tumor size or change of texture, surgical intervention is rather indicated in each case. If the tumor lesion is >3 cm in asymptomatic patients, inhomogeneously structured, showing cystoid or tubular parts and an irregular contour with infiltrating tumor growth, surgical intervention is indicated in each case. Similar characteristics have been reported by other groups (1, 4, 7, 8, 10).

However, EUS can not differentiate between benign leiomyomas and benign GISTs (fig. 3 A,B) with potential for malignant transformation (2, 9, 14). EUS-guided FNP (9, 13, 14, 15) including immunohistologic detection of CD34 and CD117 (9, 13, 16, 17) may have an impact on a better detection rate and differentiation. If the surface markers are detectable in homogeneous, smoothly contoured tumors <3 cm, surgical approach is urgently recommended because of the indifferent biological behaviour of this type of GISTs.

Since GISTs are also found within the 2nd layer ("Lamina muscularis mucosae") (3), extended endoscopic resection is demanded, which 1) leads to the definite diagnosis, 2) avoids further endosonographic follow-up, and 3) prevents fear in patients because of possible malignant transformation. However, tumor lesions located within the 4th layer are not resectable by the mean of an endoscopic approach.

Aiming for the definite diagnosis is also recommendable using endoscopic resection in echo-poor tumor lesions located within the submucosa, since a neuroendocrine tumor needs to be included in considerations about the differential diagnosis.

In conclusion, EUS can differentiate clearly between impression from outside, cyst, and SMT within the GI tract (2, 4). Established EUS-based criteria as mentioned above are suitable to determine 1) reasonable subsequent steps of the required therapeutic management (1, 2, 18) and 2) appropriate time periods for endosonographic follow-up investigations based on a high detection rate of malignant lesions provided by EUS.

CONCLUSIONS

An EUS strategy based on certain characteristics to remove SMT with no severe symptoms and suspicious finding in the conventional endoscopy shows a good adherence to the recommended approach and has a reasonable positive predictive value for malignancy

(88%), whereas the negative predictive value – i.e. the diagnosis of a benign lesion – is quite high (100% of those with follow-up). Clinical symptoms alone or with endoscopic finding are frequently too vague to decide for a reasonable SMT resection.

The chosen EUS criteria are valuable to: 1) achieve the primary resection of all potentially malignant SMT and 2) avoid to overlook them as shown by the results of the follow-up investigations with no detected malignant lesion.

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