ORIGINAL PAPERS

# Half of the patients with subepithelial tumors present borderline or pathologic anxiety-distress and carcinophobia: a multicenter cohort study

Francesc Bas-Cutrina[1,2,3,4], Anna Casellas-Grau[5,6], Sebastià Videla[2,3,7], Carme Loras[8,9], Xavi Andújar[8,9], Francisco Luis Gil[5,10], Maica Galán[3,11], Fernando Fernández-Aranda[2,3,12,13], João Carmezim[2], Joan B. Gornals[1,2,3,14]

*[1]Endoscopy Unit. Department of Digestive Diseases. Hospital Universitari de Bellvitge. Barcelona, Spain. [2]Bellvitge Biomedical Research Institute (IDIBELL). Barcelona, Spain. [3]Department of Clinical Sciences. School of Medicine and Health Sciences. Universitat de Barcelona (UB). Barcelona, Spain. [4]Digestive Diseases Unit. Hospital General de Granollers. Granollers, Barcelona. Spain. [5]Psycho-oncology Service. Institut Català d'Oncologia (ICO). L'Hospitalet de Llobregat, Barcelona. Spain. [6]Department of Psychology. School of Education, Translation, Sports and Psychology. Universitat de Vic – Universitat Central de Catalunya (UVic-UCC). Vic, Barcelona. Spain. [7]Clinical Research Support Unit. Hospital Universitari de Bellvitge. L´Hospitalet de Llobregat, Barcelona. Spain. [8]Endoscopy Unit. Department of Digestive Diseases. Hospital Universitari Mútua de Terrassa. Terrassa, Barcelona. Spain. [9]Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBERehd). Instituto de Salud Carlos III. Madrid, Spain. [10]Tecnocampus Mataró-Maresme Foundation. Universitat Pompeu Fabra (UPF). Barcelona, Spain. [11]Department of Medical Oncology. Institut Català d'Oncologia (ICO). L'Hospitalet de Llobregat, Barcelona. Spain. [12]Eating Disorders Unit. Department of Psychiatry. Hospital Universitari de Bellvitge. L´Hospitalet de Llobregat, Barcelona. Spain. [13]Centro de Investigación Biomédica en Red de Fisiopatología de la Obesidad y Nutrición (CIBERobn). Instituto de Salud Carlos III. Madrid, Spain. [14]Faculty of Health Sciences. Universitat Oberta de Catalunya (UOC). Barcelona, Spain*

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**Correspondence:** Joan B. Gornals. Director of Endoscopy Unit. Department of Digestive Diseases. Hospital Universitari de Bellvitge - IDIBELL (Bellvitge Biomedical Research Institute). Feixa Llarga s/n. 08907 L'Hospitalet de Llobregat, Barcelona. Spain. **e-mail:** jgornals@bellvitgehospital.cat

## ABSTRACT

**Background and aims:** minor nonspecific gastrointestinal subepithelial lesions (usually defined by the term 'tumor') are usually associated with a malignant illness and cancer. The aim of this study was to assess anxiety-distress and carcinophobia in patients referred to specialized monographic outpatient clinics for evaluation and treatment of this type of lesion.

**Methods:** prospective, multicenter, cohort study. Specific self-reported questionnaires were used to report threatening life-experiences and to assess levels of distress (The Hospital Anxiety and Depression Scale) and cancer-related worries (The Cancer Worry Scale).

**Results:** forty participants were included and analyzed at baseline. Pathologic and borderline anxiety were detected in 13 % (5/40, 95 % CI: 4-27 %) and 35 % (14/40, 95 % CI: 21-52 %) of participants, respectively, whereas, cancer-related worries (moderate to very high) were observed in 48 % (19/40, 95 % CI: 32-64 %) of participants. Pathologic global distress was identified in 25 % (10/40, 95 % CI: 13-42 %) of subjects. Higher educational level (university studies), a lack of lifetime psychiatric comorbidity and a lack of family history of cancer were associated with less anxiety, global distress and carcinophobia.

*Authors' contributions: FBC, SV, and JBG conceived the project and designed the study (as steering committee). FBC and JBG registered the study. FBC, CL, XA, and JBG, as investigators at each institution, promoted the enrolment of patients. Statistical analysis: JC. Interpretation of statistical analysis: JC, SV, FBC and JBG. Revision of the manuscript for important intellectual content: JBG, SV, ACG, CL, XA, FLG, MG, FFA, and JC. Drafting of the manuscript: FBC. All authors read, revised, and approved the final manuscript.*

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**Conclusions:** almost half of the patients diagnosed with a minor nonspecific gastrointestinal subepithelial lesion presented anxiety-distress and/or carcinophobia. Specific associations with anxiety-distress reaction and fears were detected.

**Keywords:** Cancer. Cancer Worry Scale. Carcinophobia. Endoscopy. Oncology. Subepithelial tumor. Submucosal tumor. Hospital Anxiety and Depression Scale.

## BACKGROUND

An incidental subepithelial lesion (SEL) is discovered in around 1-2 % of endoscopic procedures, which requires endosonography (EUS) for further study. In more than half of these situations, EUS reveals a small-sized gastrointestinal (GI) subepithelial tumor (SET). According to current clinical practice guidelines, this nosology requires a periodic follow-up with EUS due to the potential risk, albeit a low one, of evolving to a pre-malignant tumor (1,2).

As described previously in the literature, having a 'tumor' is frequently associated with cancer and carcinophobia (3,4). A similar parallelism with GI-SETs has been found in small nonspecific pancreatic cystic lesions and pre-cancerous cervical lesions. Although several retrospective studies have evaluated the degree of patient anxiety associated with small nonspecific pancreatic cystic lesions, they share the drawback of having small sample sizes that do not allow definitive conclusions to be made (5-7). In women with pre-cancerous cervical lesions, a single-center prospective study concluded that effective information and communication are important to lessen negative sexual consequences and anxiety (8).

To date, there is no study that evaluates the degree of anxiety and carcinophobia in patients diagnosed with small-sized GI-SETs. The aim of the QUALI-BANDING-SET clinical research study (ClinicalTrials.gov identifier: NCT04316000) was to assess the degree of anxiety and cancer-related worries in patients diagnosed with a small GI-SET. Furthermore, the impact on these variables when the lesion was removed by endoscopic band ligation without resection (also known as 'banding') was also assessed (9).

## METHODS

### Study design

This was a prospective, multicenter, cohort study in patients referred to specialized monographic outpatient clinics of two tertiary hospitals for evaluation and treatment of small GI-SELs. The protocol was designed to assess anxiety-distress and cancer-related worries at baseline (previous to endoscopy), one month after and one year after the interventional endoscopic procedure. Due to the SARS-CoV-2 (COVID-19) pandemic, the study was interrupted when only 40 patients had been included. It is noteworthy that before stopping the study, the bias risk was assessed by means of The Fear of COVID-19 Scale (10). Therefore, the data presented in this manuscript correspond to the results of a cross-sectional study.

The protocol was approved by the local institutional review board (ref. approval No. 346/19) and all patients gave their written informed consent. This study was conducted in accordance with the principles of the Declaration of Helsinki, with a high level of confidentiality, in compliance with the provisions of personal data protection as required by Spanish Law (LOPD 3/2018).

### Study population

The target population were patients diagnosed with a GI-SEL, referred to the digestive endoscopy unit of two reference hospitals. The following data were gathered: gender, date of birth, date of visit, education level (primary, high school, or university), personal psychiatric history, usual mood-regulating or anxiolytic medication and personal and family history of cancer. An electronic case report form was created, based on the Research Electronic Data Capture platform (REDCap) (11).

### Self-reported instruments

Three specific self-reported instruments were used to gather information about potential stressful life events, anxiety-distress and carcinophobia:

– *The List of Threatening Experiences self-response test* (12). Twelve direct yes/no-answer questions about specific situations representing stressful life events for the person during the previous six months.

– *The Hospital Anxiety and Depression Scale (HADS)* (13). Interpretation of HADS was made following adjustments for the Spanish population (14).
Anxiety was assessed by means of the anxiety subscale of HADS (HADS-a): a score of 0-7 points was normal 8-12 borderline and 13-21 pathologic.
Depression was measured with the depression subscale of HADS (HADS-d): a score of 0-6 points was normal, 7-11 borderline and 12-21 pathologic.
Global distress (HADS-gd) was evaluated as follows: a score of 0-10 points was normal, 11-17 borderline and 18-42 pathologic.

– *The Cancer Worry Scale (CWS)* (15) was used to estimate the cancer-related worries. Each of the 6 CWS items is scored between 1 and 4. A score of 6-10 means a low level of concern, 11-15 moderate, 16-20 high and 21-24 very high.

All patients diagnosed in the study with a pathologic anxiety or depressive disorder were referred for specific psychiatric clinical care.

### Statistical analysis

All study variables were presented together using descriptive statistics according to the nature of the variable. Continuous variables were described indicating the mean, standard deviation, minimum, first quartile, median, third quartile and maximum. The categorical variables were described indicating the percentages of the different categories by column.

Prevalence of HADS and CWS categories were estimated as a measure of the proportion of subjects in the sample with the condition. Prevalence point estimation was accompanied by a 95 % confidence interval using binomial approximation. Differences in HADS and CWS in the following subgroups were explored: gender, age, educational level, personal psychiatric history, and personal and family cancer history. Effect size (Cohen's d) was estimated to quantify the differences between the above-defined subgroups. Values < 0.5 were considered as small differences, between 0.5 and < 0.8 as medium, and 0.8 or above as large (16). Data analysis was performed using the R version 4.0.3 program.

## RESULTS

### Study interruption due to COVID-19 pandemic

Forty consecutive patients were included between November 2019 and February 2020. Before stopping patient inclusion and follow-up, all were contacted by telephone in May 2020 to evaluate the COVID-19 worries with The Fear of COVID-19 Scale (10). The median score obtained was 19.9 (*SD* 7.2). This result indicates a moderate degree of fear, which could have an impact on the conclusions concerning anxiety from our study. After an *ad hoc* study team meeting, this result on fear of COVID-19 was the basis for the decision to stop the QUALI-BANDING-SET study.

### Sample characteristics

Table 1 shows the baseline characteristics of the patients included. Seventy percent were older than 65 years old, and the female to male gender ratio was 2:1. None of the participants had stressful life events in the six months prior to completing the three questionnaires.

**Table 1.** *Sample characteristics of the 40 patients diagnosed with a small-sized gastrointestinal subepithelial lesion*

| | ***n* (%) or *M (SD)*** |
|---|---|
| *Gender* | |
| Female | 26 (65) |
| Male | 14 (35) |
| *Age* | 64.3 (12.1) |
| < 65 years | 12 (30) |
| ≥ 65 years | 28 (70) |
| *Education* | |
| Primary School | 24 (60) |
| High School | 11 (27.5) |
| University | 5 (12.5) |
| *Personal psychiatric history* | |
| Anxiety disorder | 2 (5) |
| Depressive disorder | 4 (10) |
| *History of cancer* | |
| Personal | 6 (15) |
| Family | 29 (72.5) |

M: median; SD: standard deviation.

### Anxiety-distress and cancer-related worries

Pathologic anxiety (score greater than 12 on HADS-a) was detected in 13 % (5/40, 95 % CI: 4-27 %) of patients. A score of 8-12 in HADS-a, which is a borderline result, was detected in 35 % (14/40, 95 % CI: 21-52 %) of patients. Consequently, a pathological or borderline result was observed in 48 % of the subjects.

Pathologic depression (score 12-21 in HADS-d) was found in 5 % (2/40, 95 % CI: 1-17 %) and a score of 7-11 (borderline result) in 20 % (8/40, 95 % CI: 9-36 %) of patients. Pathologic global distress (HADS-gd, score of 18-42) was observed in 25 % (10/40, 95 % CI: 13-42 %) and borderline score (11-17) in 23 % (9/40, 95 % CI: 11-38 %) of patients. Thus, a pathological or borderline result was observed in 48 % of participants. Cancer-related worries were found in 48 % (19/40, 95 % CI: 32-64 %) of patients: 15 subjects with a moderate level (score 11-15), 1 a high level (16-20 points) and 3 a very high level (21-24 points).

In the subgroup analysis, higher educational level (university studies), lack of lifetime psychiatric comorbidity and lack of family history of cancer were associated with lower scores for anxiety, global distress and cancer-related worries, with medium (Cohen's d ≥ 0.5) or large (Cohen's d ≥0.8) standardized differences (Figs 1-3). Raw data are available on the Mendeley Data system (17).

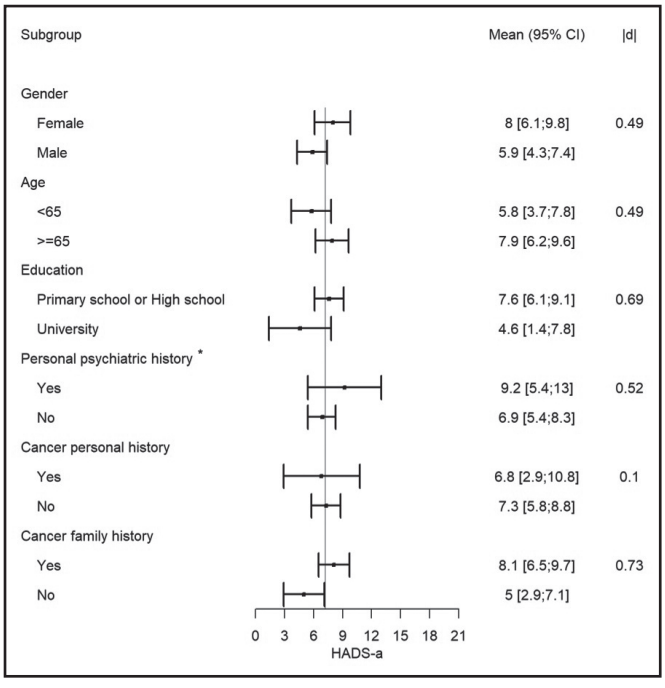


**Fig. 1.** *Hospital Anxiety and Depression Scale, anxiety subscale (HADS-a) forest plot subgroups analysis (CI: confidence interval; d: Cohen's d coefficient; HADS-a: Hospital and Anxiety Depression Scale, anxiety subscale. Vertical grey line indicates the HADS-a median score for the whole sample (= 7.2). *Anxiety or depressive disorder).*

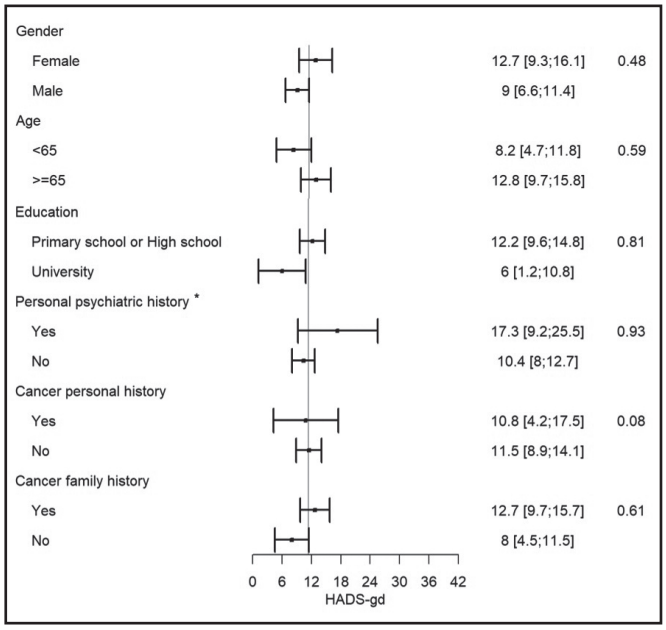


**Fig. 2.** *Hospital Anxiety and Depression Scale, global distress scale (HADS-gd) forest plot subgroups analysis (CI: confidence interval; d: Cohen's d coefficient; HADS-gd: Hospital and Anxiety Depression Scale, global distress scale. Vertical grey line indicates the HADS-gd median score for the whole sample (= 11.4). *Anxiety or depressive disorder).*

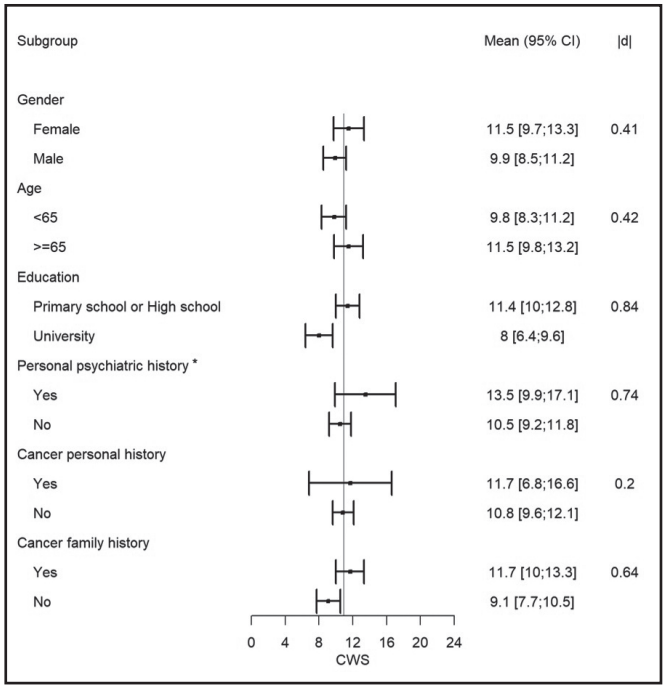


**Fig. 3.** *Cancer Worry Scale (CWS) forest plot subgroups analysis (CI: confidence interval; CWS: Cancer Worry Scale; d: Cohen's d coefficient. Vertical grey line indicates the CWS median score for the whole sample (= 11.0). *Anxiety or depressive disorder).*

## DISCUSSION

### Clinical implications

To our knowledge, this is the first time that data on anxiety and cancer-related worries has been studied in patients referred to specialized monographic outpatient clinics to evaluate and treat the small nonspecific GI-SELs. A subgroup of these lesions is defined by the term 'tumor' in medical reports. It is common for patients to associate the word tumor with cancer (3,4). Therefore, the term tumor can be uncomfortable and distressing. In addition, according to clinical practice guidelines, SELs require periodic surveillance by endoscopy due to their risk of becoming malignant (1). Even though the risk of evolving to cancer is extremely low (2), the results of our study show that a quarter of patients presented a pathologic global-distress score. 13 % of subjects had a clinical level of anxiety and 35 % a borderline result. Furthermore, 48 % had a moderate, high, or very high level of carcinophobia that should not be ignored. Similar results were found in other pathologies also defined using the word tumor as a small nonspecific pancreatic cystic lesion or a pre-cancerous cervical lesion (5-8).

A specific follow-up of this type of patient in a monographic outpatient clinic by an expert in SELs management, with the ability to transmit and explain the low possibility of malignancy in the surveillance of this type of lesion could be a measure to adopt. Likewise, the resection or extirpation of these entities, in the case of significant anxiety-distress and/or carcinophobia is also an option to consider. Especially in patients with higher risk factors, such as those observed in this study, such as patients with personal psychiatric or oncologic familiar history and a lower educational level.

In light of this scenario, we believe that not only should the organic health of the subject be considered, but also the domain of psycho-emotional well-being, which may be decisive, thereby providing a transversal approach to patient healthcare.

### Study limitations

This study has several limitations. The premature interruption of the original longitudinal study due to the COVID-19 pandemic meant that our results are based on a 'cross sectional' analysis with a small sample, which is relevant for the interpretation of our results. Nevertheless, the results presented suggest the confirmation of the working hypotheses initially raised, and the QUALI-BANDING-SET study should be completed in the future, when the bias due to the COVID effect has been reduced or disappeared.

## CONCLUSIONS

Borderline or pathologic anxiety-distress and/or carcinophobia were detected in half of the patients referred to specialized monographic outpatient clinics for evaluation and treatment of minor nonspecific GI-SELs. Proposing the removal of these growths in cases of significant anxiety-distress and/or carcinophobia is a therapeutic measure to consider.

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