Acta Biomed 2020; Vol. 91, N. 3: e2020069 DOI: 10.23750/abm.v91i3.10150

Original article

Functional dyspesia

Pellegrino Crafa[1], Marilisa Franceschi[2], Kryssia Isabel Rodriguez Castro[2], Alberto Barchi[1], Michele Russo[1], Lorella Franzoni[1], Antonio Antico[2], Gianluca Baldassarre[2], Maria Piera Panozzo[2], Francesco Di Mario[1]

[1] Department of Medicine and Surgery, University of Parma, Parma, Italy; [2] Endoscopy Unit, Department of Medicine, ULSS7 Pedemontana, Hospital AltoVicentino, Santorso (VI), Italy

Summary. Dyspepsia is a functional GI disorder consisting in a wide range of symptoms. The main diagnostic challenge has been whether to perform an EGD or an abdominal US in order not to miss organic lesions, but to avoid unnecessary and sometimes invasive tests. Pepsinogen serology has been proposed as an useful non-invasive test to explore the status of the gastric mucosa, suggesting this strategy as an adequate approach in management of dyspepsia. In a primary care setting, 266 dyspeptic patients were investigated to establish the proper diagnosis. The workup included upper GI endoscopy with biopsies, a structured questionnaire including type and severity of symptoms, serological determination of serum pepsinogens, gastrin 17 and IgG against Hp. Inclusion criteria were dyspeptic symptoms (epigastric pain, nausea and/or vomiting, post prandial fullness, early satiation) lasting more than 1 year and the association between symptoms and food ingestion.. *Helicobacter pylori* infection was present in 114 subjects, characterized by high levels of pepsinogen II and IgG against Hp. Twenty subjects were classified according with the diagnosis of chronic body atrophic gastritis. Nausea and post prandial fullness were the most frequent symptoms (48% and 41%, respectively) in the studied population, followed by epigastric pain and early satiation (37% and 26% respectively). A diagnosis of normality by serological diagnosis was found in half of patients experiencing epigastric pain and in about 60% of subjects with the three other symptoms (nausea, post prandial fullness, and early satiation). In conclusion, this experience confirms the clinical usefulness of serology in dyspepsia, contributing to correctly diagnosing CAG and H.p. infection in such patients and providing a good correlation with the clinical picture. (www.actabiomedica.it)

Key words: Dyspepsia, pepsinogens, gastrin, helicobacter pylori, gastritis, noninvasive markers

Introduction

Dyspepsia is a functional GI disorder consisting in a wide range of symptoms. The international Consensus Report "Rome III" (1) in the attempt to simplify the dyspeptic picture, focused on two groups of symptoms: 1. Meal-induced symptoms such as postprandial fullness and early satiation; 2. Epigastric pain and epigastric burning, excluding other symptoms such as nausea and vomiting. The more recent revision of functional G.I. disorders was based on Rome IV (2) consensus. The main diagnostic challenge in dyspeptic patients has always been whether to perform an EGD or an abdominal US, due to fear of missing organic problems, particularly neoplasms. It was suggested in the Maastricht IV Consensus Report that EGD with biopsy sampling should be performed in dyspeptic patients older than 45 years, in the absence of alarm symptoms (3). Since then, the possibility of avoiding EGD, with an improvement in the patient's

management as well as a remarkable economical saving, has become commonplace, leading up to the most recent Maastricht V Consensus Report (4). In this Consensus, in fact, it was claimed with a high level of evidence, that Pepsinogen serology is the most useful non-invasive test to explore the gastric mucosa status, with a possible implementation of other parameters (Gastrin 17 and antibodies against Hp.) in the management of dyspepsia (5,6), Gastrin and pepsinogens are representative biomarkers (7) influencing gastric physiology and thus reflecting the functional state of the gastric mucosa (8). Gastrin represents a powerful stimulus for gastric acid secretion and mucosal cell growth. Pepsinogen (PG) I is secreted in the mucosa of the body of the stomach. PG II is secreted not only in the corpus but also the antrum. As PGs are secreted by chief cells in the gastric mucosa, their serum levels may reflect the mass and/or turnover of those cells in the mucosa A wide literature on this subject is in favor of the issue that measure of this markers in the serum thus allows to detect gastric diseases such as atrophic gastritis, FD and modification in acid secretion (8,9). H.p. infection is claimed to have a role in the development of dyspeptic symptoms in infected patients, but only in a minority of them (Maastricht V) (4), In 1994, the International Agency on Research for Cancer (IARC) established that Helicobacter pylori (H pylori) infection represents a class I carcinogen (10). H pylori infection, in fact, results in chronic gastritis that will develop into atrophic gastritis of different severity in subgroup of infected subjects lasting their lifetime (11,12). H pylori itself is not carcinogenic but the gastritis it causes, particularly atrophic gastritis, and the subsequent hypochlorhydric stomach are carcinogenic (10, 13-18). Conversely, subjects with healthy stomach mucosa show no increase in cancer risk, as well as they are at risk to develop for peptic ulcer disease except in aspirin or NSAIDs users (19). Therefore, the differentiation between patients with healthy (no H pylori, gastritis or atrophic gastritis) and affected gastric mucosa is clinically relevant. The majority of subjects affected by atrophic gastritis are asymptomatic, however symptoms - when present - are likely dyspeptic ones.

Material and Methods

In a primary care setting, 266 (106 M, 160 F, 47.6 Mean age, 38-72 range) consecutive dyspeptic patients were investigated in order to establish the proper diagnosis The diagnostic workup included upper GI endoscopy with biopsies, a structured questionnaire including type and severity of symptoms, serological determination of serum pepsinogens, gastrin 17 and IgG against Hp. Exclusion criteria were chronic gastrointestinal diseases (cirrhosis and hepatitis, peptic ulcer disease and GERD, pancreatic and biliary diseases) , neoplasms, neurological diseases, chronic assumption of drugs except for medication against hypertension, diabetes, cardiovascular diseases, as well as chronic renal failure. Inclusion criteria were dyspeptic symptoms lasting more than 1 year, relationship between food ingestion and symptoms like epigastric pain, nausea and/or vomiting, post prandial fullness, early satiation.

All patients were addressed to a single referral center to assess diagnosis, which was established by a team of gastroenterologists, in cooperation with general practitioners. Symptoms were collected focusing on four items: epigastric pain, post-prandial fullness, nausea and/or vomiting, early satiation, by means of a structured questionnaire, including a score of severity from zero to four (corresponding to absence of symptoms, mild, moderate, or severe symptoms, respectively). When patients experienced more than one symptom, each symptom was recorded as a separate item. Epidemiological and environmental risk factors like smoking (cut off 10 cigarettes/day) this should probably be explained, for instance smoking raises gastrin levels, alcohol intake (cut off 20 g/day), obesity (B.M.I >30), drug injection, first degree familiarity for gastrointestinal diseases, concomitant disease(s) were recorded. An upper GI endoscopy was performed in all patients (after being off PPI therapy for at least 15 days) by the same endoscopy team and gastric biopsies were taken according to the Kyoto (20) protocol and classified according to OLGA (21) staging. In all patients a serological sample was obtained to measure levels of pepsinogen I and II, gastrin 17 and IgG antibodies against Hp. using Gastropanel (Elisa method: BioHit. Helsinki, Finland). Normal values are summarized as follows: Pepsinogen I: 30-160 μg/L, Pep-

sinogen: II 2-15 μg/L, Gastrin 17: 1-10 pg/L, H.p. IgG <30 i.u. A special interest was placed on the presence of autoimmune thyroiditis (Hashimoto disease) in the study population, in order to establish a possible concomitant autoimmune atrophic gastritis.

Statistical analysis was performed by using Fischer test for paired data. The statistically significance was considered as $p < 0.05$

Results

Non statistically significant differences were found in the study population with regard to sex, age, smoking habit, alcohol intake, and concomitant disease(s) in comparison with a referral sample of the same geographical area (control group) Table 1

Table 2 summarizes the serological results: diagnosis of .H.p infection in 114 subjects (55 M, 59 F, mean age 42.4 years, range 33-72 years), characterized by high levels of pepsinogen II and IgG against Hp. Twenty subjects were classified according to the diagnosis of chronic body atrophic gastritis (all histologically confirmed and scored by OLGA staging system) based on low levels of pepsinogen I and high levels Gastrin 17. One hundred thirty-two subjects showed normal values of serological markers, notably absence of H p infection, non-atrophic and atrophic gastritis. Endoscopic findings in these subjects were as follows: no peptic ulcers or neoplasms were found;, erosive gastritis was found in n=95 patients, hyperemia of gastric mucosa in n=138, hiatal hernia in n=39, biliary reflux in n=71, fundic micro-polyposis in n=29. Of note, erosive gastritis was found in 92% of Hp- infected patients.

Hyperemia of the gastric mucosa was found in 138/266 patients, including the vast majority of H.p.-infected subjects and in all patients with biliary reflux (71/266). Hiatal hernia was present in 99/266 subjects;

Table 1. Epidemiological data

	Dyspeptic patients	Control Group	p
All patients	266	305	-
Males	106	142	ns
Females	160	163	ns
Mean Age (years)	47.6	51.4	ns
Range (years)	38-72	27-69	ns
Smoking habit (%)	41	36	ns
Alcohol Intake (%)	28	26	ns
Body mass index (BMI) >30 (%)	27	24	ns

Table 2. Serological diagnosis in 266 dyspeptic patients

	Normal	H. pylori gastritis	Chronic atrophic gastritis
Patients (n°)	132	114	20
Mean Age (years)	40.8 ± 22.2	42.4 ± 12.4	58.0 ± 15.8
Thyroiditis(%)	6.1	12.3	50
PGI (ug/L)	79.4 ± 22.2	130.4 ± 11.7	15.2 ± 11.5
PGII (ug/L)	5.8 ± 2.4	14.1 ± 8.2	7.3 ± 3.6
PGI/PGII	14.5 ± 4.3	10.0 ± 3.9	2.5± 2.5
G-17 (pmol/L)	5.4 ± 13.2	12.6 ± 15.2	47.4 ± 42.9
H.p. Abs (EIU)	5.8 ± 5.9	83.9 ± 31.8	29.8 ± 32.8

in 29 out of 39 the hernia was less than 1 cm in length. In 29 patients micropolyposis was detected, all in the body except 2 located in the antrum. No one of such patients were on PPI treatment at the moment of diagnosis, but history therapy with PPI was present in 85% of the cases in the past 3 years. Histologically, they all corresponded to fundic gland ectasia except for two hyperplastic polyps of the antrum.

The distribution of symptoms and the severity score is reported in Table 3, as well as the relationship with both serological and endoscopic diagnosis.

Nausea and post prandial fullness were the more frequent symptoms (48% and 41%, respectively) in the study population, followed by epigastric pain and early satiation (37% and 26% respectively).

The majority of symptoms (epigastric pain, nausea, post prandial fullness) was present in the female population, with no difference between sexes for early satiation. Smoking habit was associated with epigastric pain and post prandial fullness (being present in 64% and 63% of smokers, respectively). Half of the studied population showed a relationship between alcohol intake and symptoms, except early satiation.

H.P. infection was found in 52% of subjects experiencing epigastric pain and in 43% of those showing post prandial fullness. The endoscopic findings of erosive gastritis, strictly related to H.p. infection, was associated with both epigastric pain and post prandial fullness, nearly in all case*s*. A diagnosis of normality by serological diagnosis was found in half of patients experiencing epigastric pain and in about 60% of subjects with the three other symptoms (nausea, post prandial fullness, early satiation). The finding of hiatal hernia was present in a strict minority of dyspeptic patient ranging from 9% to 15%, according to different symptoms.

Discussion

The use of serology as a non-invasive test is useful to clarify the role of different factors: H.p. infection, atrophic gastritis, and gastric acid secretion, and allows the establishment of diagnosis of functional dyspepsia.The combination of serum pepsinogens, gastrin-17 and H.p. IgG (Gastropanel test) is a non-invasive tool

Table 3 - (A-B) Relationship between symptoms epidemiological data and diagnosis

A

	Epidemiological data				
Symptoms	Males (%)	Females (%)	Smoking habit (%)	Alcohol intake (%)	H.p +ve (%)
Epigastric pain	37	29	64	49	52
Nausea and/or vomiting	48	60	51	53	39
Post prandial fullness	41	49	63	54	43
Early satiation	26	24	43	32	36

B

	Serology diagnosis			Endoscopic diagnosis	
Symptoms	Hp+ve Gastritis (%)	CAG (%)	Normal (%)	Hiatal Hernia (%)	Erosive gastritis (%)
Epigastric pain	52	1	47	15	47
Nausea and/or vomiting	39	3	58	11	35
Post prandial fullness	43	4	53	9	39
Early satiation	36	2	62	14	32

for the diagnosis of upper G.I. diseases. In fact, this test was designed to provide information of both morphology and function of the stomach (22, 23). Syrianen (24) in 2016 published a systematic review on the properties of Gastropanel in providing a non-invasive diagnosis of upper G.I. diseases based on 27 studies, including 8654 patients. By using the combination of these 4-biomarkers it is possible to obtain information about all the areas of stomach, and not only restricted to either antrum or body only (22, 23, 25). PG I detects AGC with 70.2% sensitivity and 93.9% specificity, whereas G-17 detects AGA with 53.8% sensitivity and 84.1% specificity. A comprehensive review was made in 2017 by Zagari (26) et a. based on 20 studies including 4241 subjects for the diagnosis of atrophic gastritis, compared to histology. The sensitivity was 74.7% and the specificity was 95.6%. With a mean prevalence of atrophic gastritis of 27%, the negative predictive value resulted of 91%. Following the first proposal of Samloff (27) in 1982 to use Pepsinogen I as a "serological biopsy" for gastric mucosa, a body of evidence populated the scientific literature thereafter (28). In 1986 Chawla investigated pepsinogen levels in patients with dyspepsia. Aggarwal (29) in 1994 determined serum pepsinogen (SP) levels in 100 patients with upper G.I lesions, and in a group of 100 healthy volunteers, showing that Pepsinogen I levels were significantly elevated in patients with duodenal ulcer (DU). Age and sex of patients and controls did not influence SP levels. In 2005, Germanà. et al (9) investigated in Italy the clinical usefulness of serum Pepsinogens, Gastrin 17, H.p. IgG in the management of dyspeptic patients in primary care, concluding that the high negative predictive value and the accuracy of the test supported the proposal of daily use in the clinical practice. Song (30) performed a study of the prevalence of atrophic gastritis in Sweden between 1990 and 2009 by using serum pepsinogens. Overall, 305/5284 subjects resulted positive for ACG, based on their level of pepsinogen I. In 2009 Reshetnikov (31) investigated dyspeptic symptoms in the adult population of Novosibirsk, Siberia, analyzing prevalence and risk factors such as H pylori infection and level of pepsinogen I, in a study comprising 1040 subjects. In 2009, Iijima (32) assessed the clinical usefulness of serology to single out patients with gastric atrophy from subjects with a healthy stomach. This biomarker, in fact, correctly classified patients into groups with "healthy" or "affected" stomach mucosa with 94% accuracy, 95% sensitivity and 93% specificity, respectively. In 2012, Tahara (33) examined serum pepsinogen in functional dyspepsia, in a sample of 75 subjects with dyspeptic symptoms and 42 asymptomatic healthy subjects.

Although serum pepsinogen (PG) is considered as a marker of gastric atrophy, it also reflects gastric acid secretion, which closely influences dyspeptic symptoms. We investigated serum PG levels and PGI/PGII ratios in dyspeptic patients, in relation to various subtypes of symptoms including Rome IV classification.

The results suggest that subjects with higher PGI level, and PG I/II ratio are more likely to develop dyspeptic symptoms. In 2019, Kawamura (34) investigated the characteristics and predictive factors of Helicobacter pylori-associated functional dyspepsia in Japanese patients.PGI levels were significantly lower in the HP-associated FD group (42.6 ± 21.4 pg/mL) than in the HP-non-associated FD group (70.4 ± 52.6 pg/mL; $p = 0.02$).

In 2013 a large population-based study was performed in Kazakhstan (35) on a cohort of 835 symptomatic and asymptomatic subjects by using a combination of serological markers (Pepsinogens, Gastrin 17, H.p. IgG) focusing on the detection of atrophic gastritis and H.p infection. The author concluded that the serological approach was capable of detecting the subjects at risk for GC (HP or AG), being a cost-effective means in diagnostic workup.

In conclusion, in recent literature and rising number of studies are pointed out to establish a clinical relationship between present or past H.p. infection and dyspeptic symptoms, as well as the real frequency of dyspepsia after H.p. eradication. The search of a precancerous condition like chronic atrophic gastritis in dyspeptic population allow to several studies performed in different geographical areas, clearly establishing that, serology could be suggested in subjects with upper G.I. complaints, without alarm symptoms (anemia, weight loss, etc..) leading to a complete non-invasive assessment of both function and morphology of the stomach, and providing a comprehensive picture for dyspeptic symptoms in individual patients.

Conflict of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

References

1. Tack J, Talley NJ, Camilleri M, Holtmann G, Hu P, Malagelada JR, Stanghellini V. Functional Gastroduodenal Disorders Gastroenterology. 2006 Apr;130(5):1466-79
2. Stanghellini V., Chan F.K., Hasler W. L et al. Gastroduodenal Disorders. Gastroenterology 2016 May;150 (6):1380-92.
3. Malfertheiner P., Megraud F., O'Morain C. et al. Current concepts in the management of Helicobacter pylori infection: the Maastricht III Consensus Report. Gut. 2007 Jun; 56(6):772-81.
4. Malfertheiner P., Megraud F., O'Morain C. et al. Management of Helicobacter pylori infection—the Maastricht V/ Florence consensus report. Gut 2017 66: 6-30.
5. Tack J., Talley J.N., Camilleri M. et al. Functional gastroduodenal disorders. Gastroenterology 2006; 130.5: 1466-1479.
6. Igarashi M., Nagano J., Tsuda A., et al. Correlation between the Serum Pepsinogen I Level and the Symptom Degree in Proton Pump Inhibitor-Users Administered with a Probiotic. Pharmaceuticals (Basel). 2014 Jun 25;7(7):754-64.
7. Monkemuller K., Neumann H., Nocon M. et al. Serum gastrin and pepsinogens do not correlate with the different grades of severity of gastro-oesophageal reflux disease: A matched case-control study. Aliment. Pharmacol. Ther. 2008, 28, 491–496.
8. Väänänen H, Vauhkonen M, Helske T, et al. Nonendoscopic diagnosis of atrophic gastritis with a blood test. Correlation between gastric histology and serum levels of gastrin-17 and pepsinogen I: a multicentre study. Eur J Gastroenterol Hepatol, 2003 15: 885-891.
9. Germanà, B., Di Mario, F., Cavallaro L.G. et al. Clinical usefulness of serum pepsinogens I and II, gastrin-17 and anti-Helicobacter pylori antibodies in the management dyspeptic patients in primary care. Dig. Liver Dis. 2005, 37, 501–508.
10. IARC monographs on the evaluation of carcinogenic risks to humans. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Schistosomes, liver flukes and Helicobacter pylori. Lyon: International Agency for Research on Cancer, 1994; 61: 218-220
11. Valle J, Kekki M, Sipponen P, Ihamaki T, Siurala M. Longterm course and consequences of Helicobacter pylori gastritis. Results of a 32-year follow-up study. Scand J Gastroenterol 1996; 31: 546-550
12. Maaroos HI, Vorobjova T, Sipponen P, et al. An 18-year follow-up study of chronic gastritis and Helicobacter pylori association of CagA positivity with development of atrophy and activity of gastritis. Scand J Gastroenterol 1999; 34: 864-869
13. Sipponen P, Kekki M, Haapakoski J, Ihamaki T, Siurala M. Gastric cancer risk in chronic atrophic gastritis: statistical calculations of cross-sectional data. Int J Cancer 1985; 35:173-177
14. Uemura N, Okamoto S, Yamamoto S, et al. Helicobacter pylori infection and the development of gastric cancer. N Engl J Med 2001; 345: 784-789
15. Correa P, Haenszel W, Cuello Cet al. Gastric precancerous process in a high-risk population: cohort follow-up. Cancer Res 1990; 50: 4737-4740
16. Filipe MI, Munoz N, Matko I, et al. Intestinal metaplasia types and the risk of gastric cancer: a cohort study in Slovenia. Int J Cancer 1994; 57: 324-329
17. Ohata H, Kitauchi S, Yoshimura N, et al. Progression of chronic atrophic gastritis associated with Helicobacter pylori infection increases risk of gastric cancer. Int J Cancer 2004; 109: 138-143
18. Wong BC, Lam SK, Wong WM, et al. Helicobacter pylori to prevent gastric cancer in high risk region of China: a randomized control trial. Jama 2004; 291: 187-194
19. Sipponen P, Seppala K, Aarynen M, Helske T, Kettunen P. Chronic gastritis and gastroduodenal ulcer: a case control study on risk of coexisting duodenal or gastric ulcer in patients with gastritis. Gut 1989; 30: 922-929
20. Sugano K, Tack J, Kuipers EJ, et al. Kyoto global consensus report on Helicobacter pylori gastritis. Gut. 2015 Sep;64(9):1353-67.
21. Rugge M, 1 , Meggio A., Pennelli G., et al. Gastritis Staging in Clinical Practice: The OLGA Staging System Gut 2007;56:631-636
22. Oksanen A, Sipponen P, Miettinen A, Sarna S and Rautelin H. Evaluation of bood tests to normal gastric mucosa. Scand J Gastroenterol, 2000 35: 791-795.
23. Syrjänen KJ, Sipponen P, Härkönen M, Peetsalu A and Korpela S. Accuracy of Gastropanel testing in detection of atrophic gastritis. Eur J Gastroenterol Hepatol, 2015 27: 102-104.
24. Syrjänen K. A Panel of Serum Biomarkers (Gastropanel®) in Non-invasive Diagnosis of Atrophic Gastritis. Systematic Review and Meta-analysis. Anticancer Res. 2016 Oct;36(10):5133-5144.
25. Agréus L, Kuipers EJ, Kupcinskas L, et al. Rationale in diagnosis and screening of atrophic gastritis with stomach-specific plasma biomarkers. Scand J Gastroenterol, 2012 47: 136-147.
26. Zagari RM1, Rabitti S1, Greenwood DC2, Eusebi LH1, Vestito A3, Bazzoli F1. Systematic review with meta-analysis: diagnostic performance of the combination of pepsinogen, gastrin-17 and anti-Helicobacter pylori antibodies serum assays for the diagnosis of atrophic gastritis. Aliment Pharmacol Ther. 2017 Oct;46(7):657-667
27. Samloff IM, Varis K, Ihamaki T, Siurala M and Rotter JI. Relationships among serum pepsinogen I, serum pepsinogen II, and gastric mucosal histology. A study in relatives of patients with pernicious anemia. Gastroenterol, 1982 83: 204-209.

28. Chawla YK, Irshad M, Chawla TC, Nundy S, Tandon BN. Urinary uropepsinogen in patients with dyspepsia. J Assoc Physicians India. 1986 Dec;34(12):851-2.
29. Aggarwal SP1, Walia DJ, Chawla LS. Serum pepsinogen levels in patients with gastro-duodenal lesions. J Assoc Physicians India. 1994 Sep;42(9):713-4
30. Song H1, Held M2, Sandin S3,et al. Increase in the Prevalence of Atrophic Gastritis Among Adults Age 35 to 44 Years Old in Northern Sweden Between 1990 and 2009. Clin Gastroenterol Hepatol. [Epub 2015 Apr 6] 2015 Sep;13(9):1592-600.e1
31. Reshetnikov OV, Kurilovich SA, Bobak M, Maliutina SK, Pylenkova ED. Gastrointestinal symptoms in adult population of Novosibirsk city: prevalence and risk factors Ter Arkh. 2009;81(2):11-6.
32. Iijima K1, Abe Y, Kikuchi R, et al..Serum biomarker tests are useful in delineating between patients with gastric atrophy and normal, healthy stomach World J Gastroenterol 2009 February 21; 15(7): 853-859
33. Tahara T, Shibata T, Okubo M, et al. Examination of serum pepsinogen in functional dyspepsia. Hepatogastroenterology. 2012 Nov-Dec;59(120):2516-22.
34. Kawamura Y1, Funaki Y2, Yoshimine T1, et al. Characteristics and Predictive Factor of Helicobacter pylori-Associated Functional Dyspepsia in Japanese Patients. Digestion. 2019;100(4):277-285.
35. Benberin V, Bektayeva R, Karabayeva R et al.Prevalence of H. pylori infection and atrophic gastritis among asymptomatic and dyspeptic adults in Kazakhstan. A Hospital-Based screening with a panel of serum biomarkers. Anticancer Res, 2013 33: 4595-4602

Received: 5 July 2020
Accepted: 6 July 2020
Correspondence:
Pellegrino Crafa
Department of Medicine and Surgery,
University of Parma, Parma, Italy
E-mail: pellegrino.crafa@unipr.it