Prevalence of Neuroendocrine Tumors in the Gastrointestinal and Hepatobiliary Systems

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Abstract

Background: Carcinoid tumors are the most common neuroendocrine tumors. In recent years, these tumors have had an increase in incidence, which is probably due to a higher number of them being incidentally found as a result of the rise of preventive medicine.

Objectives: This study aimed to analyze a series of digestive carcinoid tumors detected by conventional endoscopy and/or echoendoscopy to evaluate the prevalence of those located in the colon and rectum, and subsequently make a comparison with data available in the literature.

Methods: In this retrospective, multicenter study (two centers), the clinical records of 100 white patients with more than 100 digestive carcinoid tumors (some multiple) diagnosed from 1994 to 2018 were reviewed.

Results: The mean age of presentation was 52 years and 57% of the patients were men. The mean tumor size was 10 mm. The localization of the tumors was: stomach 43% (n = 43); duodenum 5% (n = 5); intestine 8% (n = 8); appendix 14% (n = 14); colon 4% (n = 4); rectum 19% (n = 19); pancreas 3% (n = 3); liver 2% (n = 2); gallbladder 1% (n = 1); primary tumor of unknown origin 1% (n = 1). Most multifocal tumors were in the stomach (20%; n = 20), followed by the duodenum (1%; n = 1) and intestine (1%; n = 1). Metastases and carcinoid syndrome were observed in 6% and 5% of the cases, respectively. General survival at the closure of the study was 80%.

Conclusions: Age and sex were similar to those described in the literature, while the colon and rectum represented 23% of all carcinoid tumors. There was a predominance of gastroduodenal and rectal carcinoid tumors, probably because the series analyzed was essentially endoscopic. In comparison with the literature, less cases of metastases or carcinoid syndrome were recorded and survival was greater, perhaps due to earlier diagnosis and treatment.

Keywords: Carcinoid Tumors, Neuroendocrine Tumor, Carcinoid Syndrome, Colon, Rectum, Gastrointestinal System, Hepatobiliary System

1. Background

Neuroendocrine (NET) or carcinoid (CT) tumors of the digestive tract were first described in 1907 by Oberndorfer (1) before being detailed further by Sanders in 1964 (2). MacDonald, in 1956, demonstrated the presence of CT in 0.02% of surgical cases and in 1% of autopsies (3).

In recent years, an increase in the incidence of carcinoid tumors has been observed, rising from 0.32/100000 inhabitants per year in Europe in the only community-based study published in 1986 (4) to 2.0/100000 inhabitants per year for men and 2.4/100000 inhabitants per year for women in a study conducted in Sweden between 1983 - 1998 (5). On the other hand, in a study also performed in Sweden over 12 years on surgical and autopsy material, the frequency found to be 8.4/100000 per year (6). The only similar study was conducted in Spain and published in 1994, indicating an incidence of 0.7/100000 inhabitants per year for all TCs (0.125% in autopsies) (7).

In the United States, studies published in 1975 and 1997 figure the incidence at 1 - 2 cases/100000 per year (8, 9), whereas those published in 2008 (10) and 2003 (11) reported incidences of 4.4 and 4.48 per 100000 per year, respectively.

The incidence of NETs is double in the African-American population compared with white patients (12). The distribution by sex is very even, although malignant
carcinoids are somewhat more common among women. NETs can present at any age, although they predominate in the sixth decade of life.

In early studies on NETs, a predominance of digestive tumors over bronchopulmonary tumors was observed (67.5% versus 25.3%) (11); whereas in recent studies, this proportion has almost reversed, with an incidence of around 20% versus 72%, respectively (13).

For the diagnosis of gastrointestinal and duodenal CTs, endoscopic ultrasonography (EUS) is a sensitive method with results superior to those obtained by conventional endoscopy, mainly in the detection of small tumors (2-3 mm) that are located in the intestinal lumen (14, 15), and featuring an accuracy of 90% for the location and staging of colorectal carcinoids (16).

2. Objectives

The objective of this retrospective and multicenter study was to review a series of digestive neuroendocrine tumors (carcinoids) collected from 1994 to 2018 and evaluate the prevalence of NETs of the colon and rectum. The diagnosis obtained by EUS and/or conventional endoscopy was analyzed, as well as the incidence, location, size, treatment, and survival of the patients. The data obtained were compared against other published studies, analyzing the changes observed throughout this period.

3. Methods

The clinical records of 100 white patients dated between 1994 - 2018 were reviewed, including more than 100 digestive carcinoid tumors diagnosed by imaging methods such as endoscopy, endoscopic ultrasound (EUS), computed axial tomography (CT) and octreoscan.

The procedures and treatments performed included biopsy, polypectomy, mucosectomy, transanal endoscopic microsurgery (TEM), appendectomy, surgical resection, somatostatin analogs, and chemotherapy. None of the patients were treated with growth factor inhibitors.

Demographic data such as race, age, and sex were collected. Variables related to the endoscopic characteristics of the tumors, including size and morphology, were collected as relevant data. The lesion locations, clinical manifestations, treatment, and survival rate were also recorded.

Statistical analysis was carried out using the statistical package of SPSS V. 11.5 for Windows.

4. Results

A total of 100 patients were studied. The average age of presentation was 52 years (interval: 13 - 83 years). By sex, 57% of the CTs occurred in men.

In the series investigated, several multifocal tumors (in the same organ) were found, in addition to a multicentric tumor in a patient with multiple endocrine neoplasia type 1 (MEN-1) including gastric CTs and a retroperitoneal CT.

The location of the tumors was: stomach 43% (n = 43), duodenum 5% (n = 5), intestine 8% (n = 8), appendix 14% (n = 14), colon 4% (n = 4), rectum 19% (n = 19), pancreas 3% (n = 3), liver 2% (n = 2), gallbladder 1.0% (n = 1) and primary tumor of unknown origin 1% (n = 1). Most multifocal tumors were in the stomach (20%; n = 20), followed distantly by the duodenum (1%; n = 1) and intestine (1%; n = 1).

Colorectal tumors represented 23% of all neuroendocrine tumors of this series. Of them, 22 were CTs (22/23, 95.7%) of the colon, with most being G1 (Ki-67 < 2%), and only one was a CT of the rectum (1/23, 4.3%).

Regarding multicentric tumors, a case of MEN-1 (n = 1: 1%) was detected with duodenal gastrinomas, gastric CTs, and a retroperitoneal CT; the patient was treated with somatostatin analogs (17).

The average size of the lesions was 10 mm, with an interval of 2 to 35 mm.

Treatments and procedures were performed based on the characteristics of the tumors. These included biopsy and polypectomy (n = 48; 48%), mucosectomy (n = 6; 6%), transanal endoscopic microsurgery (TEM) (n = 3; 3%), appendectomy (n = 14; 14%), surgical resection (n = 24; 24%), somatostatin analogues (n = 3; 3%) and chemotherapy (n = 2; 2%).

Of the 100 patients in the series, 52 (52%) had gastroduodenal or colorectal CTs and underwent endoscopic treatment. Sixteen patients (n = 16, 16%) with 21 CTs, in whom distant disease had been ruled out using computerized tomography and octreoscan, underwent endoscopic resection assisted by endoscopic ultrasound. Among the patients, 63% (n = 63) presented with hypergastrinemia.

The percentage of metastases was 6% (n = 6); while carcinoid syndrome was seen in 5% (n = 5) of all cases. Among the latter group, four patients had a typical carcinoid syndrome while one was atypical.

Survival at the time of the completion of the study was 80% (n = 80).

5. Discussion

In recent years, an increase in the frequency and incidence of CTs has been observed (18), which also seems to be reflected in our series. The prevalence of digestive, gastrointestinal (19, 20) and rectal CTs is increasing compared with 25 years ago when figures were around 0.4/100000 per year (4, 21). Currently, the incidence of CTs is probably over 4 cases/100000 inhabitants per year, while in the USA...
of bronchopulmonary CTS was 1.57/100000 in 2003 (22). The total prevalence of CTS is higher than 5 cases/100000 per year, with a preponderance of those located in the digestive system (10, 23), specifically in the intestine (24, 25). However, the prevalence and incidence of rectal (26, 27) and gastric (28-30) CTS continues to rise. In our series, the age and sex of white patients were similar to those described in the literature. The most frequent location was the stomach, followed by the rectocolon.

Given that our series is based mainly on endoscopy and endoscopic ultrasound (EUS), the incidence of gastroduodenal and rectocolonic CTS may be biased due to missing some appendicular (detected in cases of appendicitis) or intestinal (identified in cases of subocclusion) CTS, whose frequencies are higher in surgical or clinical surgical series (31, 32) (Table 1). Polish authors (27) analyzed more than 50000 colonoscopies in a colorectal cancer screening program, finding 25 carcinoids (prevalence: 0.05%) in 24 patients with a mean age of 54 years, with the maximum tumor size being 10 mm (mean: 6 mm).

Some of the factors that determine the clinical course and the results of patients with gastrointestinal CTS include the following: site of origin, size of the primary tumor, and the anatomic extension of the disease (34).

Esophageal CTS are located in the esophagus and represent 0.1% of all cases (13). Gastric CTS comprise less than 1% of gastric neoplasms and represent 2%–4% of all CTS (8, 9), although their frequency has increased to almost 12%. Tumors located in the biliary system, papilla and pancreas are anecdotal cases (Table 2) (35). Over 70% of cases (35-40) are associated with chronic atrophic gastritis type A (GCA type A) or pernicious anemia and are type 1 gastric CTS presenting with hypergastrinemia. CTS are usually less than 1 cm, and are multifocal in 50% of cases. Hypergastrinemia plays a significant role (36, 37), for which chronic treatment with somatostatin is available. Between 5%–10% of the cases correspond with type 2 gastric CTS, which are associated with Zollinger-Ellison syndrome (SZE) in the context of a NEM-1 with genetic character. The treatment and prognosis of these cases are similar to those associated with GCA type A. Between 15%–25% of cases are sporadic and greater than 1-2 cm, corresponding with type 3 gastric CTS, with a rate of metastasis of more than 50% (when Ki-67 > 2%). These cases have also been associated with an atypical carcinoid syndrome caused by histamine release. Sizes of gastric CTS above 2 cm are usually associated with fatal prognosis (38).

In the present series (Tables 1 and 3), the percentage of gastric CTS was 43%; none of these tumors exceeded 20 mm, and most were treated endoscopically.

Duodenal CTS are usually small (< 1 cm) and are seated in the bulb (39). In the most extensive series (40) featuring 24 cases, 89% were less than 2 cm, 85% were limited to the mucosa and submucosa, and 100% survival was reported at almost at four years. Rectal CTS should be treated like carcinomas of the rectum if they are 2 cm or more in diameter or if they demonstrate muscularis propria invasion independent of tumor size (44). However, some studies have pointed out that staging according to European Neuroendocrine Tumor Society (ENETS)/North American Neuroendocrine Tumor Society (NANETS) guidelines should be used in the treatment algorithm rather than size alone (45).

Intestinal CTS represent 1% of digestive tract cancers, with an incidence of 0.7 and 0.6 per 100000 in men and women, respectively (46). These tumors are usually located in the ileum and be multifocal or multicentric; they tend to metastasize to the ganglions and liver (If these tumors are placed in the right colon, they will be more metastasis to the other organs), and lead to a typical carcinoid syndrome (flushing and watery diarrhea) due to serotonin (5-HI AA), substance P, and other mediators in 5%–7% of cases. Intestinal CTS can cause hemorrhage, mesenteric fibrosis, and occlusion that requires intestinal resection. In our series, of the intestinal tumors diagnosed (8%), two were single and one was multifocal (found in surgery by subocclusion) without hepatic metastasis, showing an excellent response to surgery. Malignant carcinoids have a 5-year survival of 65% (35). In a recent study of 3911 intestinal carcinoids over 30 years (20), mean 5-year survival was 63%. Specifically, this survival was 74% for localized CTS, 72% for those with regional metastases, and 43% for those with distant metastases. This registry states that intestinal CTS are the most frequent (21% of total digestive CTS), and that they are seen more in women and black patients.

Appendicular CTS are diagnosed in the fourth or fifth decade of life (35, 47) and in young patients through post-appendectomy biopsies obtained due to acute appendicitis (33), with greater frequency in women (33). Among the CTS of the digestive system, the appendicular CTS are the most frequent with percentages of 44% (8), 60% (3), 66% (7), 78% (31) and 73% (43) in different studies. In our series, the value was lower (14%) because it was not a surgical series. The size of the tumor is the most significant predictive factor of the prognosis. Among appendicular CTS, about 95% are < 2 cm, for which appendectomy alone is sufficient. One-third of appendicular CTS > 2 cm present with metastases, meaning that a right colectomy should be performed (43, 44). Survival at five years is 94% when the disease is localized to the appendix (9), 85% when regional metastases exist, and 34% when there is distant metastasis, including liver metastases that can cause carcinoid syndrome.

CTs of the colon and rectum are rare and large, representing less than 1% of all tumors of the colon, with less than 5% causing carcinoid syndrome. Its survival to 5 years
Table 1. Carcinoid Tumors: Historical Series and Current Endoscopic Series

<table>
<thead>
<tr>
<th>Sample size</th>
<th>Surgical (31)</th>
<th>Clinical/Surgical (32)</th>
<th>Endoscopic (31)</th>
<th>Current</th>
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<tr>
<td></td>
<td>14</td>
<td>11</td>
<td>66</td>
<td>41</td>
</tr>
<tr>
<td>Carcinoid syndrome</td>
<td>2 (14.3)</td>
<td>1 (9.1)</td>
<td>5 (7.6)</td>
<td>2 (4.9)</td>
</tr>
<tr>
<td>Digestive system</td>
<td>14 (100)</td>
<td>10 (90.9)</td>
<td>66 (100)</td>
<td>40 (97.6)</td>
</tr>
<tr>
<td>Stomach</td>
<td>-</td>
<td>1 (10)</td>
<td>-</td>
<td>14 (35)</td>
</tr>
<tr>
<td>Duodenum</td>
<td>1 (7.1)</td>
<td>1 (10)</td>
<td>-</td>
<td>3 (7.5)</td>
</tr>
<tr>
<td>Intestine</td>
<td>2 (14.3)</td>
<td>3 (30)</td>
<td>-</td>
<td>3 (7.5)</td>
</tr>
<tr>
<td>Appendix</td>
<td>11 (78.6)</td>
<td>4 (40)</td>
<td>25 (37.9)</td>
<td>5 (12.5)</td>
</tr>
<tr>
<td>Colon</td>
<td>-</td>
<td>1 (10)</td>
<td>-</td>
<td>1 (2.5)</td>
</tr>
<tr>
<td>Rectum</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>12 (30)</td>
</tr>
<tr>
<td>Other</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Pancreas</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Liver</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Gallbladder</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Unknown</td>
<td>1 (1.0)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are expressed as No. (%).

Table 2. Distribution of CTs by Location in Different Series

<table>
<thead>
<tr>
<th>Author</th>
<th>Sanders (2)</th>
<th>Godwin (8)</th>
<th>Modlin (9)</th>
<th>Modlin and Sandor (11)</th>
<th>Soga (38)</th>
<th>Younes et al. (11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases</td>
<td>2569</td>
<td>2837</td>
<td>5468</td>
<td>13715</td>
<td>11842</td>
<td>10000</td>
</tr>
</tbody>
</table>

Localization of tumors in percentage (%)

<table>
<thead>
<tr>
<th>Thorax</th>
<th>Digestive System</th>
<th>Esophagus</th>
<th>Stomach</th>
<th>Bilir</th>
<th>Appendix</th>
<th>Duodenum</th>
<th>Intestine</th>
<th>Colon</th>
<th>Rectum</th>
<th>Other</th>
<th>Unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>10.2</td>
<td>32.7</td>
<td>0</td>
<td>2.2</td>
<td>0.1</td>
<td>45</td>
<td>43.9</td>
<td>7.6</td>
<td>2.5</td>
<td>11</td>
<td>11.4</td>
<td>0.1</td>
</tr>
<tr>
<td>25</td>
<td>67</td>
<td>1.1</td>
<td>3.8</td>
<td>0.3</td>
<td>45</td>
<td>3.8</td>
<td>1.8</td>
<td>&lt; 3</td>
<td>3</td>
<td></td>
<td>3.6</td>
</tr>
<tr>
<td>35.8</td>
<td>64.2</td>
<td>0.1</td>
<td>8.7</td>
<td>9.6</td>
<td>2.5</td>
<td>8.2</td>
<td>2.1</td>
<td>&lt; 3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>71.6</td>
<td>20.2</td>
<td>11.4</td>
<td>11.3</td>
<td>8.3</td>
<td>2.5</td>
<td>18.2</td>
<td>2.1</td>
<td>12</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>49.1</td>
<td>20.2</td>
<td>11.4</td>
<td>11.3</td>
<td>8.3</td>
<td>2.5</td>
<td>18.2</td>
<td>2.1</td>
<td>12</td>
<td></td>
<td></td>
<td></td>
</tr>
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<td>20.2</td>
<td>11.4</td>
<td>11.3</td>
<td>8.3</td>
<td>2.5</td>
<td>18.2</td>
<td>2.1</td>
<td>12</td>
<td></td>
<td></td>
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<tr>
<td>49.1</td>
<td>20.2</td>
<td>11.4</td>
<td>11.3</td>
<td>8.3</td>
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<td>18.2</td>
<td>2.1</td>
<td>12</td>
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</tr>
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</table>

is 70% when localized (9), 44% for regional metastasis, and 20% for distant metastases. In the present series, the percentage of CTs of the colon and rectum was 23% of all the gastrointestinal tumors (colon 4% (n = 4) and rectum 18.9% (n = 19)). Of the four diagnosed colonic CTs (4%), only one (25%) was found to measure 30 mm, having no metastasis (Table 1). In the series investigated by McMullen M. et al., it was reported that among 530 patients with gastrointestinal NETs of the stomach, small intestine, colon, and rectum diagnosed between 1990 and 2005, 7% (n = 37) were located in the colon and 11% (n = 60) were in the rectum (35). Cesar et al. reviewed 174 patients treated for NET between 1996 and 2010, and reported that, similar to our finding, 34 (19%) of the tumors were localized in the colon (n = 12, 6.9%) and rectum (n = 22, 12.6%) (36).

Rectal CTs represent 1.8% of rectal neoplasms (8) and up...
Table 3. Series and Reviews of Gastric CTs

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>N</th>
<th>Gender, %</th>
<th>Age, y</th>
<th>Size, mm</th>
<th>Multiples, %</th>
<th>H, %</th>
<th>Metastases, %</th>
<th>CS, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sanders (2), 1964</td>
<td>86</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>28</td>
<td>-</td>
</tr>
<tr>
<td>Modlin et al. (18), 1995</td>
<td>16</td>
<td>F(50)</td>
<td>66</td>
<td>-</td>
<td>-</td>
<td>50</td>
<td>63a</td>
<td>-</td>
</tr>
<tr>
<td>Modlin et al. (19), 1973-1999</td>
<td>562</td>
<td>-</td>
<td>62</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Varas Lorenzo et al. (33), 1994-2009</td>
<td>13</td>
<td>F(38)</td>
<td>50</td>
<td>7.9</td>
<td>69</td>
<td>61</td>
<td>7.7</td>
<td>0</td>
</tr>
<tr>
<td>Aguirre et al. (41), 1996-2009</td>
<td>14</td>
<td>F(50)</td>
<td>39</td>
<td>-</td>
<td>64</td>
<td>-</td>
<td>7.1</td>
<td>-</td>
</tr>
<tr>
<td>Yuksel (42), 1996-2007</td>
<td>21</td>
<td>F(76)</td>
<td>52</td>
<td>2.4</td>
<td>33</td>
<td>-</td>
<td>9.5</td>
<td>9.5</td>
</tr>
<tr>
<td>Varas Lorenzo et al. (43), 1994-2012</td>
<td>24</td>
<td>F(42)</td>
<td>50</td>
<td>8.3</td>
<td>46</td>
<td>62</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Current series, 1994-2018</td>
<td>43</td>
<td>F(43)</td>
<td>52</td>
<td>10</td>
<td>-</td>
<td>63</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

Abbreviations: F: female; GCA: atrophic chronic type A gastritis; H, hypergastrinemia; N, number of sample; SC, carcinoid syndrome.
aCases with chronic atrophic gastritis type A.

To 15% - 20% of gastrointestinal CTs (37, 38), being more frequent in the sixth decade of life (9). Approximately 50% are asymptomatic and are found in routine colonoscopies (in the USA). The most frequent symptom is anorectal discomfort (37). In the USA, the 5-year survival is 81, 47 and 18% for localized tumors, regional metastasis, and distant metastases, respectively (9), while mean 5-year survival has been reported at 85% in Japan (37).

Tumors smaller than 1 cm are treated with local excision because they are diagnosed at a developing stage (38). Tumors greater than 2 cm are surgically treated with low anterior resection or abdominoperineal resection (depending on the height of their location in the rectum) since they present with metastasis in 83% of cases and 88% feature infiltration of the muscularis propria (39). The management and treatment of tumors between 1 - 2 cm are controversial, although most benefit from local therapy (polypectomy versus bands) (40, 44, 45). The majority of our cases (18/95, 18.9%) were treated with polypectomy, mucosectomy, and TEM.

The survival of patients with rectal and gastric CTs has increased by more than 20% according to the latest reviews, probably due to earlier diagnosis (via endoscopy, biopsies, endoscopic ultrasound, computerized tomography and octreoscan), more early-stage treatments, and the use of analogs. Somatostatin has probably also been an advance in the treatment of CTs, especially gastric type 1 and 2 (26, 30, 46). The mean tumor size, mean age of onset, and percentage of metastasis and carcinoid syndrome have been reported to have decreased in the most recent studies (33, 43, 47). These data would support the hypothesis that screening procedures for more common pathologies, such as the colon or gastric chamber, have favored the detection of this type of tumors in its more initial stages and, therefore, give a better prognosis for the patient. However, as mentioned in recent articles (41), the understanding of these tumors is incomplete and continues to evolve (48). In our series, survival at the end of the study was 80%.

5.1. Conclusions

It is possible that the overall incidence of the CTs has increased compared with the historical series, and that the proportion of gastroduodenal (many multifocal) and rectal carcinoids has also increased, probably due to the use of screening endoscopy and because early studies were based primarily on surgical cases.

Early detection means that the average tumor size is lower than that of the historical series, which affects the treatment modality, as observed in the present series, where the majority of gastroduodenal and rectal CTs were treated endoscopically. As a result of this increase in early detection, and due to the innovation of novel treatments, a decrease in metastases and carcinoid syndrome has been observed, which has slightly increased the survival of patients with CTs.

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Footnotes

Authors' Contribution: Study concept and design, analysis and interpretation of data, and study supervision: Modesto J Varas Lorenzo; acquisition of data: Modesto J Varas Lorenzo, Fernando Munoz Agel, and Ramon Abad Belando; drafting of the manuscript and critical revision of the manuscript for important intellectual content: Modesto J Varas Lorenzo and Elena Sanchez-Vizcaino Mengual; statistical analysis: Modesto J Varas Lorenzo, Elena
Sanchez-Vizcaino Mengual, and Fernando Munoz Agel; administrative, technical, and material support: Modesto J Varas Lorenzo, Fernando Munoz Agel, amon Abad Belando, and Elena Sanchez-Vizcaino Mengual.

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