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Research Article

Small Bowel Adenocarcinoma. Resection Has A Favorable Prognosis?

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1. Abstract

Purpose: Tumors of the small bowel representing 3% of all gastrointestinal malignancies (33% adenocarcinomas). We performed a retrospective study of the adenocarcinomas of the small bowel in 18 years.

Methods: Analyzed variables: age, sex, risk factors, reason and date of first consultation, urgent or ambulatory diagnosis, imaging, tumor markers and stage at diagnosis, surgery, type of surgery and postsurgical complications, adjuvant treatment, disease progression and metastatic disease, cause of death and the overall survival.

Results: 21 patients were studied. They were diagnosed as complications in 55%. For the diagnostic were use the CT scan (91%) and endoscopy (81%). Tumor markers were increased to 50% in advanced stages. 76.2% of the patients underwent a surgical intervention and 10% received adjuvant treatment. The overall survival at 5 years was of 60% in the early stages and of 10% in patients with advanced stages.

Conclusion: The tumor marker increased at diagnosis can suggest an advanced stage. The 5 years overall survival rate was 10%, so it is necessary to progress in the radiological techniques, which will allow an earlier diagnosis.

2. Keywords: Adenocarcinoma; Small bowel; Survival

3. Introduction

Small bowel neoplasms, despite the increase in their prevalence in recent years, are infrequent tumors[1]. They represent 3% of all neoplasms of the gastrointestinal tract (GIT) and 0.5% of all cancers in the United States [2,3].

Regarding the malignant tumors, adenocarcinomas are the second most frequent tumors (33%) behind carcinoid tumors (44%). The most infrequent tumors found are the stromal tumors (17%), and lymphoma (8%) [4]. Although the adenocarcinoma of the small intestine is the second tumor in frequency, there are very few new cases in the world, including Spain [1].

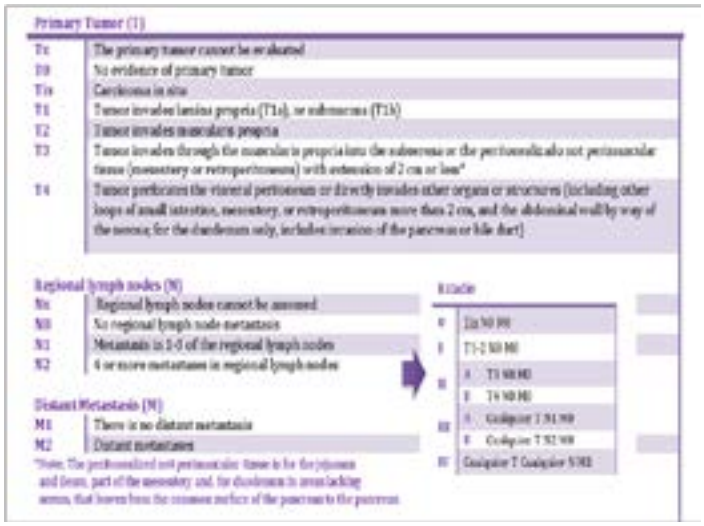
The objective of this study is to present our experience in the diagnosis and treatment of adenocarcinoma of the small intestine in La Paz University Hospital, Madrid.

4. Methods

We performed a descriptive and retrospective study of the adenocarcinomas of the small intestine from January 1998 until July 2016 (18 years), in La Paz University Hospital, Madrid. An adenocarcinomas review is performed in the Coding Service database and confirmed in the Pathology Department. The clinical, laboratory, and radiological data was obtained from the electronic and paper medical records carried out by the General Surgery and Medical Oncology Departments. The inclusion criteria were patients with adenocarcinoma of the small intestine histologically-confirmed by PC (Primary Care) in those records. We excluded patients with a diagnosis of tumors of the ampulla of Vater originated in the duodenal epithelium, Pancreatic or bile that delimit the papilla, periampullary tumors and patients with incomplete medical records for the study.

After employing the exclusion criteria, there were studied 21 patients with the diagnosis of adenocarcinoma, made through the examination of biopsies and surgical specimen with identification of the degree of differentiation, level of infiltration, nodal and surgical margins affectation. The staging of tumors was performed according to the latest edition published in 2010 [5] of the TNM system of the American Joint Committee on Cancer (AJCC) and the International Union against Cancer (UICC), see **Table 1**.

Table 1: Staging of adenocarcinoma of the small intestine.



*According to the TNM system of the AJCC and the UICC.

The variables analyzed were: age, sex, risk factors, reason and date of first consultation and date of diagnosis at admission or in an outpatient, diagnostic tests, tumor markers at the time of diagnosis, stage at diagnosis, as well as the conduction or not of surgery, type of surgery and postsurgical complications, the adjuvant treatment, the progression of the disease and distant metastases presented, and, finally, the date and cause of death and the overall survival (OS).

5. StatisticAnalysis

The qualitative variables were described from the absolute frequency and percentages. The quantitative variables from the median value accompanied by the interquartile range (RI).The comparisons between qualitative variables were performed using the Chi Square test of hypothesis or Fisher's exact test. The comparative analysis of the quantitative variables by groups was performed using the nonparametric Mann-Whitney U test. The survival curves were estimated by the Kaplan-Meier method. For the comparison of the survival curves for groups it was used the Log-Rank test. In the particular case of the variables that describes the stage of the disease, they were grouped in categories I and II (early), on the one hand, and III and IV (advanced) on the other hand, and the survival curves were analyzed and compared.

6. Results

We studied 21 patients diagnosed with small bowel adenocarcinoma. The descriptive characteristics are summarized in **Table 2**, **3** and **4**.

Table 2. Epidemiological characteristics of patients with small bowel adenocarcinoma.

Variables analyzed	N (21)	%
Median age, years (IR)	79,32 (IR 13,2)	
Sex		
Woman	13	62
Man	8	38
Risk factors		
Present	3	14
Out	18	86
Location		
Duodenum	13	62
Jejunum	3	14
Íleum	5	24

he TNM system of the AJCC and the UICC.

Abbreviations: Intercuartilic Rank (IR).

Table 3. Clinicopathological characteristics, diagnostic and staging of patients with small bowel adenocarcinoma.

Variables analyzed	N (21)	%
Reason for consultation		
Bleeding	6	30
Abdominal pain	5	25
Intestinal obstruction	3	15
Jaundice	3	15
Incidental finding	1	5
Other	2	10
Diagnostic		
Urgent	11	55
Ambulatory	9	45
Diagnostic test		
CT	19	91
Endoscopy	17	81
Intestinal transit	11	52
PET-CT	1	5
US-endoscopy	1	5
Tumor markers		
Negative	13	62
Positive	8	38
CEA	3	14
CA 19.9	5	24
Other (AFP, CA 125)	3	14
Disease stage at diagnosis		
I	3	16
II	4	21
III	4	21
IV	8	42

Tabla 4. Treatment and evolution characteristics of patients with small bowel adenocarcinoma.

Variables analyzed	N (21)	%
Surgery of the primary tumor		
Si	16	76
Whipple	4	29
Local Resection	10	71
No	5	24
Postsurgical complications	6	46
Adjuvant treatment		
Yes	2	10
No	18	90
Progression of the disease (M1)	9	43
Lymph node	5	56
Liver	4	44
Peritoneal	3	33
Pulmonary	3	33
Exitus (during follow-up)	16	76
Disease progression	7	50
Postsurgical complications	5	34
Natural causes or others	2	14

7. Epidemiological Characteristics, Risk Factors and Tumor Location

The age range was 45-87 years, 79.32 (RI 66, 12-92,52) being the median age of presentation, being predominantly female (62%).

There were found risk factors for adenocarcinoma of the small intestine in 3 cases (14%). In one of them the person had celiac disease, another neoplasm of cecum operated 3 years before and a patient with rectal neoplasm operated 6 years ago.

The rate of adenocarcinoma was higher in the duodenum (62%), followed by the ileum and jejunum, which represent 24% and 14%, respectively.

8. Diagnostic

The most frequent reason for consultation was bleeding (30%), either as lower gastrointestinal hemorrhage (LGIH), melena or fecal occult blood test (FOBT). 25% of the patients had abdominal pain being the second reason for consultation followed by intestinal obstruction and jaundice, which represent 15% of the consultations. In a 5% of the cases, there was an incidental finding. 55% of the patients were diagnosed in the emergency room because of a complication of this disease, and the remaining 45% were diagnosed on an outpatient basis. The average duration of delay from the first consultation until the definitive diagnosis of neoplasm of the small intestine in patients whose diagnosis was made in the emergency room was 8.0 days (RI: 7.0), while in the diagnosis on an outpatient basis, the average delay time was 139.0 (RI: 294.5): RI. Thus, the delay time was significantly higher in the studied patients on an outpatient basis ($Z=-3,269$, $p<0.001$).

The most used additional tests for the diagnosis and the study of extension were: Computed Axial Tomography (CT) in 19 patients (91%), endoscopy in 17 patients (81%) and intestinal transit in 11 patients (EGD, 52%), The PET-CT and the Eco-endoscopy, as an extension study, it was only performed in one patient (5%).

Diagnostic testing and extension allowed to classify tumors according to the TNM system of the AJCC and the UICC, monitoring 8 patients who were diagnosed at stage IV (42%), 4 patients at stage III and 4 other patients at stage II (21%, in both stages), and three patients at stage I (16%). The staging of a patient was not studied.

It was examined whether there was a relationship between the diagnosis of the disease in the emergency and the stage of the disease at more advanced diagnosis, and there was no evidence found in the association ($p=0.88$). In both patients diagnosed in the emergency area and those studied in a different way, stages III and IV were the most frequently found (6 patients in each case).

9. Tumor markers

Tumor markers in the diagnosis were found in 8 patients (38%): High CA 19.9 in 5 patients (24%) followed by the high CEA, in 3 patients (14%). Other markers also found are the alpha-fetoprotein (AFP) and the CA 125.

We analyze the relationship between presenting positive tumor markers (CEA, CA 19.9, CA 125 and AFP) and presenting a more advanced stage of disease at diagnosis too. It was noted that in the early stages of the disease (I and II) all tumor markers were negative and in advanced stages (III and IV), 50% had positive markers. In stage III (17%) and in stage IV (83%) they had positive markers. However, there is no evidence to correlate the stage of disease with the positivity or not of the tumor marker (p=0.08). On the other hand, 37% of patients with stage IV presented positive CEA, while none of the patients with early stages presented positivity for this marker. We did not find evidence of association between this marker and the stage of the disease (p=0.18).

10. Treatment

Surgery of the primary tumor was performed in most patients, performing local resection instead of Whipple operation in most patients (10 patients with local resection, 4 Whipple patients, 2 patients missing). Out of these, 6 patients (46%) had surgical complications, being the most frequent postoperative pancreatitis, followed by respiratory failure and dehiscence of the anastomosis. We observed that 50% of patients undergoing Whipple had complications, compared to 38% of patients undergoing local resection, without finding statistically important differences (p=1) when we analyze if the type of surgery performed associated a greater number of postsurgical complications. Adjuvant treatment after surgery was exceptional.

11. Proggression of the disease and Survival

With regard to the progression of the disease, regardless of the treatment, a 43% had distant metastases, lymph node involvement being the most frequent, followed by the liver affection, peritonealand pulmonary metastasis.

During the follow-up, 16 patients died (76%). The progression of the disease was the cause in half of the cases, followed by surgical complications. Only 2 patients died from natural or non-disease causes. We do not know the cause of the death of two patients.

Performing or not the surgery of the primary tumor is associated to less progression of the disease noticing that in the 16 patients who underwent surgery, 38% presented progression of the disease, while 63% did not present progression of the disease; in the 5 patients that did not undergo surgery, we observed that 3 patients presented progression of the disease (60%) and 2 patients (40%) did not present it. These differences are not statistically significant (p=0.61).

Analyzing overall survival we found that 15 died and 5 were still alive at the end of the study. We note that after 6,2 months (186 days, is: 86.09) from the diagnosis, 50% of the patients die. The OS at 5 years is close to 20%.

After categorizing the patients in the early stages (I and II) and advanced (III and IV), it was noted that in patients with early tumors 43 % died, while patients with advanced tumors 91% died. For the group of early tumors it could not be performed the estimation of the median survival because less than half of those patients died, considering this category a predictive factor of good prognosis. However, for advanced tumors, the median time of survival is 186.0 days (105.7) There is no evidence to affirm that both survival rates are significantly different (log-rank test Chi square: 3.32 p=0,068). The OS at 5 years is 60% in patients with early-stage and of 10% in patients with advanced stages. There was no evidence to affirm that the survival differed by location (log-rank test Chi square: 2.91 p=0,234), or by the type of surgery performed (log-rank test Chi square: 0.23 p=0,626). However, if we were able to observe that the patients with adenocarcinoma in the duodenum, who underwent Whipple's surgery, had a median survival markedly lower than the rest of locations (33 days, is 108.25).

12. Discussion

Adenocarcinomas of the small intestine are infrequent tumors within the gastrointestinal tract. The increase of its incidence is uncertain, without being able to rule out the possibility that this is due to the advance in diagnostic techniques.

In this research we studied 21 adenocarcinomas of the small intestine diagnosed for 18 years in La Paz University Hospital, Madrid. This number is lower than in other series because of the established exclusion criteria, discarding the ampullary tumors and periampullary tumors. This neoplasms being able to include diseases of different etiology and, therefore, with different epidemiological, clinicopathological and survival characteristics. We believe that this limited sample has prevented us from assessing the differences between the different variables

analyzed.

The average age at diagnosis of adenocarcinoma of the small bowel is from 67 to 68 years [1,6]. There is a slight predominance in men, with a man-woman relationship (M-W) of 1.5:1[1]. In our study, the average age at diagnosis was higher (75,5 years) and had a greater prevalence in the female sex with an M-W of 1:1.62.

The etiology of most cancers of the small intestine is unknown, although there have been several risk factors and predisposing conditions. Patients with adenocarcinoma of the small intestine have a higher incidence of malignancies involving the colon, rectum, the ampulla of Vater, the endometrium and ovary[7-9]. It is associated with a number of hereditary syndromes, including Hereditary Non-Polyposis Colorectal Cancer (HNPCC), Familial Adenomatous Polyposis (FAP) and Peutz-Jeghers syndrome. As risk factors for its development, there have been described the inflammatory bowel disease, particularly Crohn's disease [10], and the celiac disease[11]. In our study, we found 3 patients (14%) with risk factors, in two of the cases the personal history of colorrectal cancer and celiac disease in the other case.

The predominant symptoms in literature are abdominal pain (44-90%), followed by loss of weight (22-44%), nausea, vomiting (17-64%), and intestinal bleeding (23-41%). Rarer causes of presentation are the obstruction and bowel perforation [11-13]. In our study, the main reason for consultation was intestinal bleeding (30%), followed by abdominal pain (25%).The symptoms are vague and non-specifics, specifying very large differential diagnoses that require a high index of suspicion in order to conduct a study. This can be a significant delay from onset of symptoms to the diagnosis, finding average delays reported in literature of 30 weeks[14]. In our study, the average time of delay was similar, of 103.1 days (26 weeks). As a result of this delay, at the time of diagnosis patients present an advanced disease, with nodal or metastatic disease (stage III and IV)[11].In our study, 42% had a stage IV diagnosis and 21% a stage III. As the prognosis is closely linked to the spread of the disease, early detection and treatment can contribute to a favorable outcome[15,16].

There is an increased incidence of adenocarcinomas in the duodenum, followed by the jejunum and ileum, how Dabaja BS et al. and Halfdanarson TR et al. [17,18] reported an incidence in the duodenum of 52-57%. In our study, the duodenum was the most frequent location (62%) followed by the ileum (24%) and in the last place the jejunum (14%).

The best diagnostic method when there is suspected a tumor of the small intestine, has not been established, therefore, various tests are made, choosing one or the other depending on the clinical manifestations of the patient and their availability. The options are radiological and endoscopic. Within the endoscopic tests in the case of proximal tumor, endoscopy is useful. If the tumor is more distal, it would be necessary the endoscopy-capsule (avoiding its use in subacute obstruction boxes) or enteroscopy (whose realization is not always technically possible and requires experienced teams)[19]. In our hospital, 81% (17 of 21 patients) of the patients underwent an endoscopy, while none of them underwent endoscopic capsule or enteroscopy. Regarding the radiological tests, as an initial test in the study, may be performed an abdominal x-ray, although this test has low diagnostic value and it is only useful to rule out possible tumor complications such as intestinal obstruction. The transit intestinal has a low sensitivity (S) and specificity (E), 50 and 60%, respectively [20], the enteroclysis being considered superior (introduction of double contrast through a nasogastric tube). In the study of Bessette JR et al. The sensitivity of this compared to conventional transit intestinal was of 90 to 33%[20]. The CT scan allows you to detect lesions in 70-80% of cases, as well as to make an extension study to assess the lymph node involvement, and metastatic disease[21.22]. There are two new techniques that appear promising, these are the CT enterography and MR enterography. These tests combine the use of oral contrast with CT and MR for the relaxation of the abdominal wall, allowing the best characterization of lesions of the walls of the GIT. The positive and negative predictive values are very high, so that its implementation at the present time could allow an earlier diagnosis[23-26]. The PET-CT, as in the case of colorectal tumors, that it is mainly used as a complement to other forms of image, is used to locate sites of recurrence of the disease. In our study, the most commonly used radiological test was the CT (91%), followed by the transit intestinal (52%) and PET-CT (5%). Enteroclysis or CT

enterography or MR enterography were not performed on any patient.

The role of tumor markers in this pathology is uncertain. The most studied marker is the CEA, noticing a rise in blood in 44% of patients with locally advanced or metastatic adenocarcinoma (Stage III and IV)[27]. Similar data we have obtained in our study, finding CEA positive only in patients with advanced stages of the disease, being positive in 38% of patients with metastatic disease (stage IV).No patient with early stages presented positive tumor markers, which may suggest that if in the initial study of a patient with adenocarcinoma of the small intestine we get tumor markers, mainly the CEA, probably they are already in an advanced stage of the disease and so, with a worse prognosis. In our study, we also found the tumor marker CA 19.9 positive only in advanced stages of the disease (24% of stages III and IV).

The curative treatment of locoregional disease continues to be the radical surgical resection with or without adjuvant chemotherapy. Pancreaticoduodenectomy is considered the standard treatment for adenocarcinomas of the 1st and 2nd duodenal portion. In the lesions in 3º and 4º duodenal portions a segmental resection with free surgical margins should be made, since the pancreatoduodenectomy has not shown benefits in survival compared to the segmental resection, and the first has a higher morbidity and mortality[29-34]**.** Tumors located in the proximal jejunum or ileum should be treated through a large intestinal resection, and the terminal ileum with right hemicolectomy. In all the cases they should have a regional lymphadenectomy (minimum 6 lymph nodes), as the nodal involvement is the main prognostic factor in these tumors. There is a lack of data about the benefits of adjuvant therapy (chemotherapy, radiation therapy, or both) after resection of adenocarcinoma of the small intestine, and their role is still to be defined. A Cochrane review in 2007 concluded that there were no appropriate tests to analyze[35]. It is proposed the use of chemoradiation therapy, according to the results obtained with the colorectal tumors, in patients with node-positive margins and/or primary T4. With regard to the advanced disease, the use of systemic chemotherapy is proposed with similar schemes in colorectal cancer, with few prospective studies carried out. In our study, 76% were submitted to surgical intervention by performing a Whipple surgery in 29% of the cases and local resection in the rest. With regard to the progression of the disease, 43% of the patients, regardless of treatment, mainly with nodal, hepatic and peritoneal metastasis. 10% of the patients received adjuvant chemotherapy.

Small bowel tumors have a worse prognosis in colorectal tumors, possibly due to the delay in diagnosis, absence of screening measures and lesser degree of histological differentiation. The rate of overall survival at 5 years is correlated with the tumor stage: 50% to 60% for stage I, from 39% to 55% for stage II, 10% to 40% for the stage III, and 3 to5% for the stage IV[36,37]. In our study, given the limited sample, we were unable to calculate the rate of survival by stage, but we noticed a markedly lower survival rate in advanced tumor (III and IV), 5-year OS of 10%, which in early tumors (I and II), 5-year OS is of 60%.

13. Conclusions

The elevated level of CEA at the time of diagnosis can suggest an advanced stage of the disease, the OS in these tumors at 5 years is around 10%, so it is necessary to progress in the radiological techniques with the incorporation of the TC and MR enterography which will allow an earlier diagnosis of these tumors. However, we must not forget that the diagnosis of these tumors requires a high index of suspicion, so that its existence must be included in the differential diagnosis of abdominal pain.

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