American Journal of
Biomedical Science & Research

www.biomedgrid.com
ISSN: 2642-1747

Case Report

Main Determinants Impacting the Survival of Malignant Tumors of the Small Intestine

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To Cite This Article: *Imane Ouafki*. Main Determinants Impacting the Survival of Malignant Tumors of the Small Intestine. Am J Biomed Sci & Res. 2024 21(1) AJBSR.MS.ID.002808,* DOI: 10.34297/AJBSR.2024.21.002808

Received: January 02, 2024; **Published:** January 11, 2024

Abstract

Introduction: Malignant neoplasms of the small intestine constitute an extremely rare entity. Their insidious nature as well as their almost asymptomatic evolution are responsible for a late diagnosis, sometimes following a hemorrhagic or occlusive complication. Reason why these tumors are often accompanied by a poor prognosis. This article made it possible to analyze the main determinants impacting the survival of these patients in order to evaluate the effectiveness of the therapeutic means deployed in their treatment.

Materials and Methods: This is a retrospective cohort study, having collected patients with a malignant tumor of the small intestine, treated in the medical oncology department, of the Hassan II University Hospital Center in Fez, from January 2016 to January 2020. A description of patient characteristics was carried out before analyzing the 2-year overall survival (OS) according to the different risk factors reported in the literature.

Results: We included 43 patients. The average age was 57 years, with a female predominance. A history of smoking was common to 34.8% of patients. The ileal localisation was the most found (58.1%). Adenocarcinoma (ADK) was the most common histological type (42%). The disease was diagnosed at an advanced stage in 58.1% of cases. Optimal surgery was performed in more than half of patients (53.4%). Chemotherapy was administered to 88.3% of patients. The median OS at 2 years was 23.8 months (95% CI: 18.6-28.9), representing a survival rate estimated at 25.6%. We observed a significantly short survival in patients over 50 years old (11.6 months; 95% CI: 7.6-15.5; p=0.002), with a performance status (PS) greater than 1(11.5 months; 95% CI: 6.4-16.5; p=0.017), hypertensive patients (6.5 months; 95% CI: 5.26-7.8; p=0.019), in the case of duodenal location of the primary tumor (8.6 months; 95% CI: 1.8-15.4; p=0.041), for neuroendocrine carcinomas (NEC) (8.6 months; 95% CI:2.3-15.0; p= 0.026) and in stages IV (8.6 months; 95% CI: 7.4-9.8; p=0.000). For the other factors studied: male sex, history of smoking, alcoholism, celiac disease and neurofibromatosis, , we found a numerical drop in survival but without statistically significant benefit. While there was no impact on survival in diabetic patients, with a history of Crohn's disease and breast cancer. However, in multivariate analysis, the factors that were found to be prognostic for survival were advanced age, impaired PS, duodenal location of the primary tumor, the metastatic stage of the disease compared to localized stages and sarcomatous histology unlike ADK which had better survival.

Conclusion: This study confirms, in our context, the results of the literature. Although we have not been able to prove the significant association with survival of all the factors already validated. This is probably justified by the lack of statistical power relating to the retrospective design of the study and the low representativeness of the workforce.

Keywords: Determinants, Survival, Tumors, Malignant, Intestine, Small

Introduction

Malignant tumors of the small intestine are very rare and represent 2 to 6% of all cancers of the gastrointestinal tract [1,2]. The histological types found in the small intestine are adenocarcinomas (ADK) which are the most common, sarcomas, neuroendocrine carcinomas (NEC), gastrointestinal stromal tumors (GIST) and lymphomas [3]. These patients often have a poor prognosis, insofar as median overall survival (OS) is of the order of 19 months, with a 5-year OS around 30% [4]. Indeed, the 5-year survival rates do not exceed 28% for ADK, are 30% for lymphomas and 60% for NEC [5]. The symptoms can be chronic or intermittent, but most tumors of the small intestine are clinically silent for a long time. Nearly half of tumors are found incidentally, during surgery or exploration visualizing the intestine. As a result, patients can remain asymptomatic until the final stages of the disease or during an indicated intervention for acute intestinal obstruction [6]. The heterogeneity of these tumors as well as the limited number of cases have meant that all currently available data are based on small studies or retrospective series [6]. Due to the low incidence of small intestinal neoplasms, it is not easy to recruit a sufficient number of patients for a study. To better understand this question, we collected patients with small intestine cancers treated in our medical oncology department. The main objective of this work is to analyze the determinants impacting the survival of these patients in order to evaluate the effectiveness of the therapeutic means used in their treatment as well as their prognosis.

Materials and Methods

This is a retrospective cohort study, including patients with a malignant tumor of the small intestine, treated in the medical oncology department, of the Hassan II University Hospital Center in Fez, on a period spread from January 2016 to January 2020. The inclusion criteria were: age over 18 years; histologically confirmed cancer of the small intestine; localized or metastatic. The exclusion criteria were lymphoma histology and non-consent of the patient. Eligible patients were searched from the "HOSIX" information system database, by selecting patients treated for a malignant tumor of the small intestine. The non-opposition of patients to the use of data concerning them was verified before the analysis by verbal consent. The agreement of the regional ethics committee was obtained. The data are entered using Excel software, then analyzed using SPSS software version 20. The significance level was set at $p<0.05$ for all statistical tests with a 95% confidence interval (95% CI). The descriptive analysis focused on the age distribution which was transformed into a binary qualitative variable (<50 years and >50 years), sex, performance status (PS), history, tumor locations, histological types noted, stage of the disease, metastatic sites found. We have also described the medico-surgical therapeutic modalities including: surgery ,monitoring and chemotherapy. We also detailed the different chemotherapy protocols. The 2-year survival which is the main objective of the study, was estimated from the date of diagnosis for a 2-year follow-up. The estimation of survival and 95% CI were determined using the Kaplan-Meier method. Comparison between patient groups was performed using the log-rank test for the factors studied. Cox regression analysis was used to calculate respective hazard ratios and 95% CIs. In multivariate analysis, Cox regression was used to test the independence of significant factors in univariate analysis. The significance level was set at $p<0.05$ for all statistical tests.

Results

Among the 43 patients who met the eligibility criteria, the average age was 57 years (35-86) of which 74.4% were over 50 years old. The male/female sex ratio was 0.95. The PS was 1 in 72.1% of patients. A history of smoking was noted in 34.8% of patients. Other pathological histories were hypertension, diabetes, Crohn's disease, celiac disease, neurofibromatosis and breast cancer. Ileal location was reported in 58.1% of cases. ADK was found in 42% of cases (Figure 1). The disease was diagnosed at an advanced stage in 58.1% of patients (Table 1). Optimal surgery was performed in 53.4% of cases. Monitoring after surgical treatment was decided in 11.6% of patients and 88.3% had received chemotherapy. The CAPOX regimen (Capecitabine + Oxaliplatin) was administered in 44.1% of patients (Table 2). The median 2-year overall survival (OS) was 23.8 months (95% CI 18.6-28.9) with a survival rate estimated at 25.6%. In univariate analysis, among those under 50 years old the 2-year survival rate was 63.6% compared to 12.5% among the oldest (p=0.002). Patients with a PS of 1 had a median survival of 24 months compared to 11.5 months in those with a PS of 2 (p=0.017). The 2-year survival rate was 37.9% for non-smokers and 0% in those with a history of smoking (p=0.068). Hypertensive patients had a survival rate of 0% compared to 27.5% for the others (p=0.019). Duodenal location was accompanied by a median survival of 8.6 months compared to 24 months for ileal and jejunal tumors (p=0.041). Survival rates in ADK, GIST, NEC, sarcomas and poorly differentiated carcinomas (PDC) were respectively 33.3%; 75.0%; 6.7%; 0.0% and 33.3%. Stages IV had a median survival of 8.6 months compared to 24 months for stages II and III (p=0.000) (Table 3) (Figure 2). In multivariate analysis, the factors significantly associated with survival were age (p=0.000), PS (p=0.030), duodenal location of the primary tumor (p=0.001), stage of the disease (p= 0.000), sarcomas (p=0.004) and ADK (p=0.010) (Table 4).

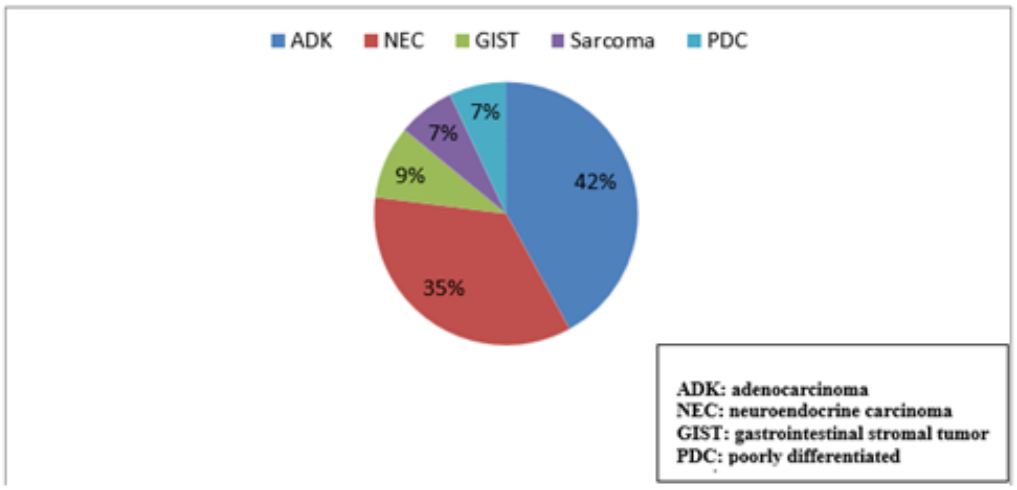

Figure 1: Distribution of histological types found in the 43 patients followed for malignant tumors of the small intestine, medical oncology department, Hassan II University Hospital, Fez, Morocco, January 2016-January 2020.

Table 1: Characteristics of patients followed for malignant tumors of the small intestine, medical oncology department, Hassan II University Hospital, Fez, Morocco, January 2016-January 2020.

	Patients (n=43)	Percentage %
Age (years)		
<50	11	25,6
>50	32	74,4
Sex		
Men	21	48,8
Women	22	51,2
PS		
1	31	72,1
2	12	27,9
History		
Tobacco	15	34,8
Alcohol	6	13,9
Hypertension	3	6,9
Diabetes	3	6,9
Crohn's disease	2	4,6
Celiac disease	1	2,3
Neurofibromatosis	1	2,3
Breast cancer	1	2,3
No history	19	44,1
Tumor locations		
Ileon	25	58,1
Jejunum	9	20,9
Duodenum	9	20,9
Stage		
II	6	14,0
III	12	27,9
IV	25	58,1
Metastatic sites		
Liver	18	41,8

Lung	10	23,2
Peritoneum	2	4,6
Bone	5	11,6
Nodes	3	6,9
Brain	1	2,3

Table 2: Therapeutic modalities of patients followed for malignant tumors of the small intestine, medical oncology department, Hassan II University Hospital, Fez, Morocco, January 2016-January 2020.

n =43		
	Patients	**Percentage (%)**
Surgery	23	53,4
Monitoring after surgery	5	11,6
Chemotherapy	38	88,3
Adjuvant	13	30,2
Palliative	25	58,1
Chemotherapy regimens		
CAPOX	19	44,1
FOLFOX	7	16,2
EP	3	6,9
Imatinib	3	6,9
Doxorubicin	3	6,9
Lanreotide	7	16,2
Everolimus	2	4,6
Zoledronic Acid	2	4,6

Note*: CAPOX capecitabine plus oxaliplatin;FOLFOX fluorouracil/leucovorin plus oxaliplatin ;EP etoposide plus platin (cisplatin or carboplatin).

Table 3: Analysis of 2-year survival according to the different risk factors found in patients followed for malignant tumors of the small intestine, medical oncology department, Hassan II University Hospital, Fez, Morocco, January 2016-January 2020.

n=43				
	Median 2-year survival in months (95%CI)	**Average 2-year survival in months (95%CI)**	**P**	**2-year survival rate**
2- year Overall Survival	23,8[18,6-28,9]	16,7[14,2-19,1]	-	25,6%
Age (years)				
<50	-	22,6[19,5-25,6]	0,002	63,6%
>50	11,6[7,6-15,5]	14,6[11,8-17,5]		12,5%
Sex				
Men	14,3[0,0-29,0]	15,8[12,3-19,3]	0,145	9,5%
Women	24,0[14,6-33,3]	17,5[13,9-21,0]		40,9%
PS				
1	24,0[23,8-24,1]	18,4[15,5-21,3]	0,017	32,3%
2	11,5[6,4-16,5]	12,1[8,5-15,8]		8,3%
Tobacco				
0	24,0[23,8-24,1]	17,5[14,5-20,5]	0,068	37,9%
1	11,6[1,1-22,1]	14,8[10,5-19,1]		0,0%
Alcohol				
0	23,8[18,4-29,1]	16,7[14,1-19,3]	0,970	28,2%
1	8,6[0,0-24,1]	16,2[7,4-25,1]		0,0%

Hypertension				
0	24,0[22,5-25,4]	17,3[14,8-19,9]	0,019	27,5%
1	6,5[5,26-7,8]	7,9[4,3-11,5]		0,0%
Diabetes				
0	21,4[15,9-26,8]	16,6[14,1-19,1]	0,765	25,0%
1	24,0[0,0-52,9]	17,9[4,3-31,6]		33,3%
Crohn's disease				
0	-	-	0,089	22,0%
1	-	-		100,0%
Celiac disease				
0	23,8[17,3-30,2]	16,7[14,2-19,2]	0,618	26,2%
1	15,7	15,7		0,0%
Neurofibromatosis				
0	23,8[18,7-28,9]	16,9[14,4-19,4]	0,318	26,2%
1	8,6	8,6		0,0%
Breast cancer				
0	-	-	0,239	23,8%
1	-	-		100,0%
Tumor Locations				
Ileon	24,0[14,5-33,4]	16,2[12,9-19,5]	0,713	32,0%
Duodenum	8,6[1,8-15,4]	11,7[6,8-16,7]	0,041	11,1%
Jejunum	24,0[23,8-24,1]	22,8[20,9-24,7]	0,237	22,2%
Histological types				
ADK	24,0[21,3-26,6]	18,7[15,1-22,4]	0,133	33,3%
GIST	_	20,8[15,5-26,1]	0,097	75,0%
NEC	8,6[2,3-15,0]	13,7[9,3-18,2]	0,026	6,7%
Sarcoma	11,5[3,1-19,9]	13,8[3,7-24,0]	0,158	0,0%
PDC	15,7[4,4-27,0]	16,1[9,0-23,2]	0,939	33,3%
Stage				
II	24,0	24,0		75,0%
III	24,1	23,1[20,7-25,5]	0,000	33,3%
IV	8,6[7,4-9,8]	11,8[9,0-14,7]		0,0%

Note*: 95%CI 95% confidence interval; p significance level set at p<0.05; PS performance status; ADK adenocarcinoma; NEC neuroendocrine carcinoma; GIST gastrointestinal stromal tumor; PDC poorly differentiated carcinoma.

Table 4: Multivariate analysis of risk factors associated with survival in patients followed for malignant tumors of the small intestine, medical oncology department, Hassan II University Hospital, Fez, Morocco, January 2016-January 2020 (n=43).

	HR	95%CI	P
Age	0,031	0,006-0,168	0,000
PS	3,159	1,116-8,941	0,030
Duodenum	0,113	0,030-0,419	0,001
Sarcoma	15,535	2,424-99,544	0,004
ADK	4,807	1,452-15,909	0,010
Stage II	-	-	0,000

Stage III	0,024	0,004-0,143	0,000
Stage IV	33,758	6,344-179,625	0,000

Note*: HR hasard ratio; 95%CI 95% confidence interval; p significance level set at p<0.05; PS performance status; ADK adenocarcinoma.

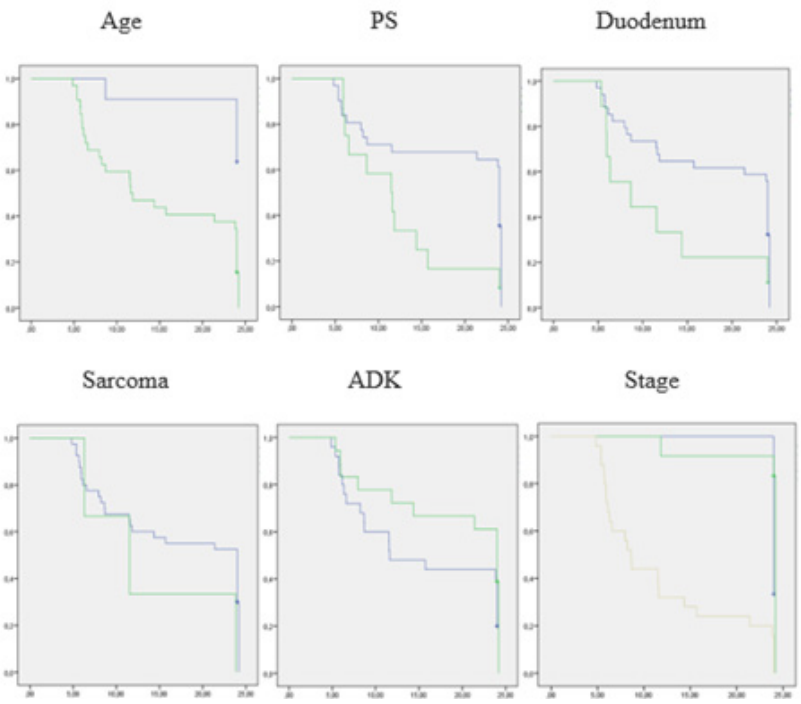

Figure 2: Kaplan Meier curves of factors associated with 2-year survival, in the 43 patients followed for malignant tumors of the small intestine, medical oncology department, Hassan II University Hospital, Fez, Morocco, January 2016-January 2020.

Discussion

Our patients were younger (mean age = 57 years) compared to the average age at diagnosis of 65.2 years found in the literature [7]. Both sexes are affected, approximately equally [7], which is what we found in our series.Several risk factors have been incriminated in the genesis of small bowel cancers, the family history comes first. Indeed, hereditary syndromes namely: Familial Adenomatous Polyposis (FAP), Lynch and Peutz-Jeghers syndrome have been shown to be involved [8,9]. Other situations may be linked to the occurrence of these tumors such as alcoholism and smoking; rich diet in red meat, fat, salt and sugar [10,11]; Crohn's disease, celiac disease [12] and HIV(human immunodeficiency virus) infection [8,9].

Furthermore, we find in the literature certain factors associated with a poor prognosis, notably: advanced age, impaired PS, male gender, black race, duodenal location of the primary tumor and poor tumor differentiation [13-15]. Our data were consistent with the literature to the extent that 34.8% of patients had a history of smoking and 13.9% were alcoholics. The patients also had a history of Crohn's disease, celiac disease, hypertension, diabetes, neurofibromatosis and breast cancer. In a retrospective study of 1260 cases of malignant tumors of the small intestine, there were 25.4% duodenal tumors; 15.3% jejunal tumors and in 29.7% of patients ileal involvement [7]. The duodenal location was reported in 20.9% of our cases, a little less than the literature; the tumor was jejunal in 20.9% of patients, discreetly surpassing the literature, while the ileal location was more important, found in 58.1 % of patients. ADK is the most common histological type representing 40% of malignant tumors [16]. In our series ADK represented 42% of cases which is in agreement with the literature. NEC occupy second place with 35 % of cases [17], this value corresponds exactly to that of our series. GIST and sarcomas are found in less than 10% of cases [18]. In our series, GIST and sarcomas represented 9% and 7% respectively. Radical surgery based on R0 resection and lymph node dissection constitutes the gold standard for localized tumors. For metastatic stages, surgery is reserved for the management of acute complications, in the face of severe digestive hemorrhage, obstruction or perforation [19]. Curative surgical resection was performed in 53.4% of our patients.Systemic chemotherapy is the prerogative of locally advanced or metastatic tumors based on retrospective studies having demonstrated its significant benefit in terms of progression free survival (PFS) and OS. However, the benefit of chemotherapy in these situations has still not been validated by randomized phase III studies [19,20]. As a result, chemotherapy was administered in 88.3% of our patients. Associations based on Fluorouracil/Leucovorin plus Oxaliplatin (FOLFOX) and Capecitabine plus Oxaliplatin (CAPOX)

have proven their effectiveness through several prospective phase II and retrospective studies [21,23]. In accordance with the literature, we used the CAPOX and FOLFOX regimens in 44 .1% and 16.2% of ADK respectively. The treatment of metastatic NEC is initially based on the management of the symptoms of carcinoid syndrome with somatostatin analogues such as Octreotide [24] and Lanreotide [25]. In the event of progression of metastatic disease, treatment with Everolimus is indicated [26]. The Cisplatin plus Etoposide combination resulted in high response rates between 42% and 67% with a median survival of 15 to 19 months, across several studies, for poorly differentiated NEC [27]. Therefore, Lanreotide was administered in 16.2% of our patients with symptomatic metastatic NECs. Poorly differentiated NECs received the combination of Cisplatin plus Etoposide. Everolimus was administered in 4.6% of patients who progressed on first-line metastatic treatment. Imatinib is the reference targeted therapy for GIST whether in adjuvant setting to surgery, in locally advanced or metastatic situations based on phase III trials [28,29]. In our series, we had 6.9% of patients treated adjuvantly with Imatinib. Doxorubicin is considered as an active agent on soft tissue sarcomas having shown response rates of 15% to 35% [30]. In this light, cases of metastatic sarcomas have been treated with doxorubicin as monotherapy. The use of bone modulating agents, in cases of bone metastases, makes it possible to reduce the occurrence of skeletal events (pathological fractures, malignant hypercalcemia, spinal cord compression). There are two classes: bisphosphonates, of which Zoledronic Acid is the mainstay, and Denosumab [31]. Consequently, our patients with bone metastases benefited from the addition of Zoledronic Acid to their chemotherapy or targeted therapy protocol. The 2 year median OS was 23.8 months (95% CI 18.6-28.9) with an estimated survival rate of 25.6%. Through phase II studies, we noted an OS of between 15 and 20 months in patients treated with chemotherapy based on FOLFOX or CAPOX [21-23], which is a little lower than our observation .The univariate analysis of the data from our series showed us that the 2-year survival was significantly lower in patients aged over 50 compared to younger patients (12.5% and 63.6%;p=0.002),those with a PS above 1 compared to patients who were in good performance status (8.3% and 32.3%; p=0.017) and in hypertensives unlike the others (0.0% and 27.5 %;p=0.019).For male patients, smokers, alcoholics, with a history of celiac disease and neurofibromatosis, we found a numerical drop in survival but not statistically significant. On the other hand, no impact on survival has been reported in patients with a history of diabetes, Crohn's disease or breast cancer (Table 3). The median survival was 24 months in the case of ileal (95% CI 14.5-33.4; p=0.713) and jejunal (95% CI 23.8-24.1; p=0.237) tumor localization while it was of 8.6 months (95% CI 1.8-15.4; p=0.041) in the case of duodenal tumor. We found that ADK, GIST and PDC had a better survival rate (75%; p= 0.133), (33.3%; p=0.097) and (33.3%; p=0.939) respectively, compared to other histological types (Table 3). In fact, the survival rate of GISTs treated with Imatinib is close to the 92% [29] and does not exceed 28% for ADK [5]. The survival rates of stages II (75%) and III (33.3%) are significantly better (p=0.000) compared to that of stages IV (0%). Indeed, in the literature, the survival rate goes from 60% for stages I to 3-5% for stage IV[14,32,33]. In multivariate analysis, age and PS remained closely linked significantly to survival (HR=0.031; 95% CI 0.006-0.168; p=0.000) and (HR=3.159; 95% CI 1.116-8.941; p=0.030) respectively. Also duodenal localization was accompanied by lower survival compared to other locations (HR=0.113; 95% CI 0.030-0.419; p=0.001). Sarcomatous histology was associated with very short survival compared to ADK (HR=15.535; 95% CI 2.424-99.544; p= 0.004) and (HR=4.807; 95% CI 1.452-15.909; p=0.010) respectively. Furthermore, we found that stages IV significantly increased the risk of death (HR=33.758; 95% CI 6.344-179.625; p=0.000), compared to stages II and III (HR =0.024; 95% CI 0.004-0.143; p=0.000) .However, there was no statistically significant association between survival and the rest of the risk factors recognized in the literature, namely male gender, alcoholism and smoking, diabetes, hypertension, hereditary syndromes, Crohn's and celiac diseases. This could be justified by the small number of our series and the retrospective study design.

Conclusion

This work, which is the first in our institution, confirms the involvement and impact of the factors studied on the survival of patients with malignant tumors of the small intestine. This is advanced age, PS>1, male gender, alcohol and smoking, diabetes, hypertension, hereditary syndromes, Crohn's and celiac diseases, histological type and metastatic stage of the tumor. These factors are accompanied by a rate of lower survival reported in prospective phase II and retrospective studies. However, it is essential to validate these results by prospective phase III studies before retaining them as certain prognostic factors. Hence the importance of early diagnosis of these tumors in order to be able to correct their prognosis through optimal surgeries at localized stages, associated or not with adjuvant chemotherapy.

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