

# MALIGNANCY RISK PREDICTION FOR PRIMARY JEJUNUM-ILEAL TUMORS

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**ABSTRACT** - This work is aimed at identifying factors associated with primary jejunum-ileal tumors malignancy, defining a prediction model with sensitivity, specificity and accuracy to distinguish malign from benign neoplasms. These tumors are rare, have highly unspecific presentation and, frequently, are diagnosed late. We reviewed the charts of 42 patients with primary jejunum-ileal tumors treated in the Department of General Surgery of Rio de Janeiro State University Hospital, Rio de Janeiro, RJ, Brazil, from 1969 to 1998. We performed bivariate analyses, based on  $\chi^2$  test, searching associations between tumors malignancy and demographic and clinical variables. Then logistic regression was employed to consider the independent effect of variables previously identified on malignancy risk. The malign tumors included 11 adenocarcinomas, 7 leiomyosarcomas, 5 carcinoids and 4 lymphomas; the benign tumors included 10 leiomyomas, 2 hamartomas, and single cases of adenoma, multiple neurilemoma and choristoma. The bivariate analyses indicated the association between malignancy and palpable abdominal mass ( $P = 0.003$ ), period from signs and symptoms onset to diagnosis ( $P = 0.016$ ), anemia ( $P = 0.020$ ), anorexia ( $P = 0.003$ ), abdominal pain ( $P = 0.031$ ), weight loss ( $P = 0.001$ ), nausea and vomit ( $P = 0.094$ ), and intestinal obstruction ( $P = 0.066$ ); no association with patients demographic characteristics were found. In the final logistic regression model, weight loss, anemia and intestinal obstruction were statistically associated with the dependent variable of interest. Based only on three variables – weight loss, anemia and intestinal obstruction – the model defined was able to predict primary jejunum-ileal tumors malignancy with sensitivity of 85.2%, specificity of 80.0%, and accuracy of 83.3%.

**HEADINGS** – Jejunal neoplasms. Ileal neoplasms. Risk factors.

## INTRODUCTION

The jejunum-ileal segment accounts for 70-80% and 80-90% of the gastrointestinal tract length and surface area, respectively. Primary small bowel neoplasms constitute 1-5% of all tumors and less than 2% of the malign lesions located at the digestive tube, with a population incidence of

1.6/100,000<sup>(2, 10)</sup>. Concerning the relative rarity of small bowel tumors, compared with esophagus, stomach and colon tumors, many possible explanations have been speculated: (1) fluid content; (2) rapid intestinal transit; (3) alkaline pH; (4) lower bacterial population than in colon and difference in bacterial metabolism; (5) high concentration of immunoglobulin A, particularly in the ileum; (6) possible cytogenetic

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factors; (7) rapid proliferation and replacement of mucosa; and (8) stem-cells with more efficient apoptosis than in colon for removal of genetically modified cells<sup>(1, 4, 7, 14, 16)</sup>.

Taking into account that the onset of a small bowel tumor may be associated with some degree of immunodeficiency, these patients would be more likely to present a second primary tumor. This really occurs in 17-20% of the cases, while the frequency of multiple primary tumors among patients with other types of cancer varies from 3-6%<sup>(3, 7)</sup>.

Jejunum-ileal tumors are generally only suspected under extreme circumstances such as the presence of palpable abdominal mass, intestinal obstruction, digestive hemorrhage or intestinal perforation. Due to their rarity and unspecific signs and symptoms, diagnosis is often late, what makes cure chances lower in the case of malign neoplasms, leading treatment to produce merely palliative effects. The prediction of tumor malignancy before surgery enable us to design more adequate therapeutic strategies for these patients.

This work evaluated the primary jejunum-ileal tumors casuistic of the Department of General Surgery of Rio de Janeiro State University Hospital. Moreover, it is aimed at identifying factors associated with the malignancy of these lesions, establishing a predictive model able to distinguish malign from benign neoplasias with expressive accuracy, sensitivity and specificity.

## METHODS

### Casuistic

We reviewed the charts of 42 patients with primary jejunum-ileal tumors operated in the Department of General Surgery of Rio de Janeiro State University Hospital, Rio de Janeiro, RJ, Brazil, from 1969 to 1998.

Among these patients, 27 had malign and 15 benign tumors. The malign tumors included 11 adenocarcinomas, 7 leiomyosarcomas, 5 carcinoids and 4 lymphomas; the benign, 10 leiomyomas, 2 hamartomas, and single cases of adenoma, multiple neurilemoma and choristoma.

The patients age varied between 2 and 88 years (mean of  $52.6 \pm 22.0$ ) and between 10 months and 78 years (mean of  $49.9 \pm 21.7$ ), for patients with malign and benign tumors, respectively. Half of the patients were males, despite the predominance of females among those with malign neoplasms. Only eight patients (19.0%) looked for medical care up to 30 days after the onset of symptomatology and 17 (40.5%) between 1-6 months. Seven tumors (16.7%) were found incidentally in patients without significant complaints, with surgery indications motivated by other diseases: four leiomyomas, two carcinoids and one hamartoma.

The most frequent symptom was abdominal pain (83.3%), which was present in all symptomatic patients, followed by anemia (61.9%) and nausea/vomit (54.8%); weight loss, anorexia and palpable abdo-

minal mass were found almost exclusively with malign tumors. Constipation and diarrhea were observed, respectively in 23.8% and 14.3% of the patients; low digestive hemorrhage (28.6%) occurred only with melena, having no cases of hematemesis. Tumors close to Treitz ligament were responsible for complaints of post-prandial plenitude in six patients (14.3%); fever occurred in three patients — two with intestinal perforations blocked with epiplo (leiomyoma and neurilemoma), and one leiomyosarcoma with a large tumoral necrosis area.

Twenty-four patients were operated electively, and other 18 under an urgency regimen. Among those submitted to elective surgery, the main diagnostic method employed was small bowel contrasted radiological exam, while for urgent cases, the only available exams were abdominal simple radiography and ultrasonography. Correct pre-surgical diagnoses were made for 13 (30.9%) patients, being the small bowel contrasted radiological exam, individually or associated with other exams, important for nine of them.

Thirteen patients presented diagnosis of intestinal obstruction. Among them, 11 were related to malign tumors (three adenocarcinomas, three lymphomas, three carcinoids and two leiomyosarcomas), and two to benign (one leiomyoma and one choristoma).

Moreover, we should underline that there were no cases of celiac disease, Crohn's disease, neither any type of immunodeficiency, among the patients in this casuistic.

### STATISTICAL METHODS

We performed bivariate analyses based on  $\chi^2$ -test in order to identify associations between the tumoral type (malign versus benign) and demographic (age and sex) and clinical variables. These, specifically, were expressed in terms of categorical variables indicating the tumor site (jejunum vs. ileum), the surgery type (elective vs. urgency), the symptomatology period prior to diagnosis, the presence (vs. absence) of intestinal obstruction, as well as the presence (vs. absence) of signs and symptoms such as palpable abdominal mass, digestive hemorrhage, intestinal rhythm alteration, anemia, anorexia, weight loss, abdominal pain and nausea/vomit.

We also employed regression logistic modeling to consider the independent effect of variables previously identified on jejunum-ileal tumors malignancy risk<sup>(6)</sup>.

The analyses were performed with the statistical package SAS<sup>(12)</sup>.

## RESULTS

Table 1 presents the results of contingency tables relating the variable designating the tumoral type (malign vs. benign) to demographic and clinical variables.

There is no evidence in the sense of rejecting the null hypotheses of no associations between type and the demographic variables con-

**TABLE 1** – Bivariate analyses relating malign and benign primary jejunum-ileal tumors with clinical and demographic variables

Variable	Malign		Benign		$\chi^2$	Prob
	n	%	n	%		
Age (years)					0.104	0.7747
0-49	13	48.2	8	53.3		
$\geq 50$	14	51.8	7	46.7		
Sex					2.593	0.107
Male	11	40.7	10	66.7		
Female	16	59.3	5	33.3		
Palpable abdominal mass					8.575	0.003
Presence	14	51.9	1	6.7		
Absence	13	48.1	14	93.3		
Digestive hemorrhage					2.052	0.152
Presence	17	63.0	6	40.0		
Absence	10	37.0	9	60.0		
Local					0.201	0.654
Jejunum	18	66.7	11	73.3		
Ileum	9	33.3	4	26.7		
Surgery					0.864	0.353
Elective	14	51.8	10	66.7		
Urgent	13	48.2	5	33.3		
Intestinal rhythm alteration					0.543	0.461
Presence	14	51.8	6	40.0		
Absence	13	48.2	9	60.0		
Symptomatology					10.368	0.016
0-30 days	3	11.1	5	33.3		
1-6 months	13	48.2	4	26.7		
7-12 months	9	33.3	1	6.7		
Incidental findings	2	7.4	5	33.3		
Anemia					5.401	0.020
Presence	19	70.4	5	33.3		
Absence	8	29.6	10	66.7		
Anorexia					8.575	0.003
Presence	14	51.9	1	6.7		
Absence	13	48.1	14	93.3		
Abdominal pain					4.667	0.031
Presence	25	92.6	10	66.7		
Absence	2	7.4	5	33.3		
Loss of weight					14.263	0.001
Presence	20	74.1	2	13.3		
Absence	7	25.9	13	86.7		
Nausea and vomit					2.800	0.094
Presence	18	66.7	6	40.0		
Absence	9	33.3	9	60.0		
Intestinal obstruction					3.389	0.066
Presence	11	40.7	2	13.3		
Absence	16	59.3	13	86.7		

sidered (age and sex). Even in the case of the variable sex, for which the relative distribution of males and females seems to be different for patients with malign and benign tumors, suggesting higher risk of malignancy for females, the  $\chi^2$ -test is not statistically significant.

There is no association between tumoral type and tumor site, surgery type, digestive hemorrhage and intestinal rhythm alteration.

On the other hand, results indicate strong association between malignancy and the presence of palpable abdominal mass, anemia, anorexia, abdominal pain and weight loss, as well as symptomatology period prior to diagnosis.

Observed in 37.5% of all patients, the presence of palpable abdominal mass characterized 51.9% of malign tumor cases and only 6.7% of benign cases.

Concerning the period since first symptoms to diagnosis, we underline the predominance of incidental findings and the presence of symptoms for less than 30 days in the benign tumor group, against greater symptomatology periods in the malign tumor group.

The presence of anemia was registered in 70.4% of the patients with malign tumors and 33.3% of those with benign tumors. Anorexia and weight loss also occurred in the majority of patients with malign tumors — 51.9% and 74.1%, being less frequent among those with benign tumors — 6.7% and 13.3%, respectively.

Finally, results do not provide evidence at the 5%, but do so at the 10% level of significance, in the sense of rejecting the individual

hypotheses of no association of nausea/vomit and intestinal obstruction with tumor malignancy (vs. benignity). In both cases, the probability of occurrence seems to be higher for patients with malign tumors.

Table 2 shows the results of the final logistic regression model for prediction of jejunum-ileal tumors malignancy risk. This model was obtained from consideration of diverse signs and symptoms that were statistically associated with the event of interest, up to 10% level of significance, in the bivariate analyses.

Only weight loss, anemia and intestinal obstruction kept independent effects on the malignancy risk when clinical variables were controlled simultaneously. The odds of tumors being malign (instead of benign) among patients with weight loss were approximately 32 times as much as the odds among patients without weight loss. The odds ratio of malignancy (vs. benignity) considering patients with and without anemia, was 6.8. Finally, the odds of tumors being malign (vs. benign) for patients with intestinal obstruction were 8.3 times as much as those related to patients without intestinal obstruction.

In Table 2, we still should stress the following aspects: (1) the large confidence intervals defined for the odds ratios, maybe reflecting the small size of the sample studied; (2) the borderline statistical significance of anemia and intestinal obstruction; and (3) the model

**TABLE 2** – Logistic regression model explaining the risk of primary jejunum-ileal tumors being malign

Variable	Coefficient estimate	Standard error	Pr > $\chi^2$	Odds ratio
Intercept	-2.456	0.983	0.013	
Weight loss	3.461	1.081	0.001	31.853
Anemia	1.920	0.992	0.053	6.822
Intestinal obstruction	2.119	1.117	0.058	8.320

Log-likelihood ratio = 24.864 with 3 degrees of freedom ( $P = 0.0001$ )

Concordant = 88.4%; Discordant = 5.4%; Tied = 6.2%

**TABLE 3** – Predicted probabilities of malignancy for different combinations of explanatory variable values

Weight loss	Anemia	Intestinal obstruction	Benign	Malign	(MALIGN)
0	0	0	7	1	0.0790
0	1	0	4	2	0.3693
0	0	1	1	1	0.4166
1	0	0	2	3	0.7322
0	1	1	1	3	0.8297
1	1	0	0	10	0.9491
1	0	1	0	3	0.9579
1	1	1	0	4	0.9936

For a probability cut-off of 0.5: sensitivity = 85.2%; specificity = 80.0%

fitness statistics, indicating a concordance of 88.4% between observed and predict values of the dependent variable.

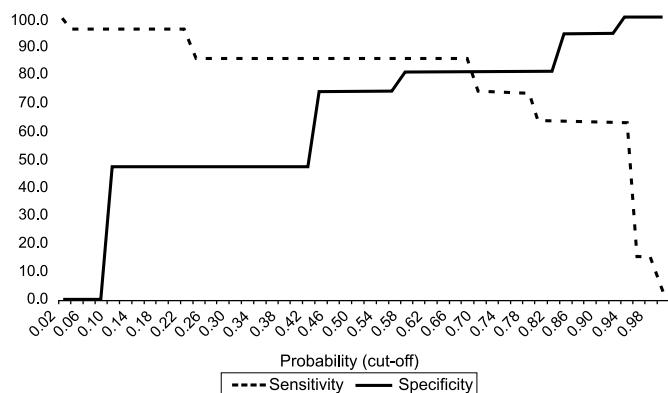
It is also important to underline that the validity of modeling data related to jejunum and ileal tumors separately was compromised by the sample size. Controlling for tumor location in addition to weight loss, anemia and intestinal obstruction, however, leads intestinal obstruction to lose statistical significance, without adding significantly to model fitness. Intestinal obstruction is more likely to occur among those patients with ileal tumors, what may explain this result.

Table 3 presents the different possible combinations of the three explanatory variable values, and, in each case, the number of benign and malign tumors observed, as well as the probability of tumors malignancy according to the logistic regression model. This probability varies from 7.9% and 99.4% for patients with none or all considered clinical characteristics, respectively.

Figure 1 shows the sensitivity and specificity of the model obtained, considering various cut-off probabilities for discrimination of benign from malign tumors. Between the probabilities 0.58 and 0.68, approximately, it is indicated a sensitivity of 85.2% and a specificity of 80.0%.

### DISCUSSION

Primary jejunum-ileal tumors are among the rarest tumors in the digestive tube, but they should always be in mind, mainly for those patients older than 40 years with unexplained recurrent abdominal



**FIGURE 1** – Sensitivity and specificity of primary jejunum-ileal malignancy risk predictive model

pain, obstructive intestinal symptoms, as well as anemia and gastrointestinal hemorrhage<sup>(9)</sup>.

Only when we make an early diagnosis we are able to provide a better prognosis to these patients. MAGLINTE et al.<sup>(8)</sup> claim that the time lost before definitive diagnosis is due more to imprecise request of complementary exams, because of incorrect evaluation of clinical characteristics, than to delay of patients in looking for medical care. We had 13 pre-surgical diagnoses, which is in accordance to different authors that indicate percentages varying between 21 to 70%<sup>(11, 13)</sup>.

Malign tumors often produce more exuberant clinical manifestations than benign tumors. However, because of the unspecific signals and symptoms observed, the mean time required for diagnosis was close to 6 months, a fact that is corroborated by the literature<sup>(8, 9)</sup>. Lesions that lead to digestive hemorrhage occur more frequently in the proximal small bowel segment, what is likely to be explained by the larger diameter of jejunum, allowing for tumoral growth with posterior ulceration and hemorrhage. Distal lesions obstruct the ileal lumen before the occurrence of such alterations.

In accordance to other authors, abdominal pain, weight loss, anemia and nausea/vomit represented the signals and symptoms more commonly observed in our patients with malign tumors<sup>(9, 10, 11)</sup>. Among these patients, 51.9% had palpable abdominal mass. Additionally, in a group of 13 (30.9%) patients with intestinal obstruction, 11 were associated with malign tumors, confirming the delay in diagnosing these lesions. These findings conducted mostly to a purely palliative treatment.

This study takes into account statistical techniques largely applied in the medical field to identify demographic factors, signals and symptoms, as well as diagnosis data predictive of clinical outcomes<sup>(5, 15)</sup>.

The proposition of a model involving only three variables — weight loss, anemia and intestinal obstruction — makes possible the risk prediction for primary jejunum-ileal tumors with high sensitivity (85.2%), specificity (80.0%) and accuracy (83.3%). Its implications include an earlier diagnosis and a better therapeutic planning for these patients.

The casuistic here considered embodies only 42 patients treated in the Department of General Surgery of the Rio de Janeiro State University Hospital. Even being clinical situations frequently generalizable, we underline the importance of validating our results in other settings, with larger samples.

Marques RG, Portela MC. Predição do risco de malignidade em tumores jejuno-ileais primários. *Arq Gastroenterol* 2000;37(3):174-179.

**RESUMO** - O objetivo deste trabalho é identificar fatores associados à malignidade de tumores jejuno-ileais primários – tumores raros, com quadro clínico inespecífico e com diagnóstico freqüentemente tardio – estabelecendo um modelo de predição capaz de distinguir neoplasias malignas de benignas com acurácia, sensibilidade e especificidade expressivas. Foram revistos os prontuários de 42 pacientes com diagnóstico de tumor jejuno-ileal primário (27 malignos e 15 benignos) operados no Serviço de Cirurgia Geral do Hospital Universitário Pedro Ernesto da Universidade do Estado do Rio de Janeiro, Rio de Janeiro, RJ, entre 1969 e 1998. Realizaram-se análises bivariadas, com base no teste- $\chi^2$ , buscando associações entre malignidade (vs benignidade) desses tumores com variáveis demográficas e clínicas. Regressão logística foi, então, utilizada para a consideração do efeito independente de variáveis previamente identificadas sobre o risco de malignidade. Os tumores malignos compreenderam 11 adenocarcinomas, 7 leiomiossarcomas, 5 carcinóides e 4 linfomas; os benignos, 10 leiomiomas, 2 hamartomas e casos isolados de adenoma, neurilemoma múltiplo e coristoma. As análises bivariadas indicaram associação entre malignidade e massa abdominal palpável ( $P = 0,003$ ), tempo de sintomatologia prévio ao diagnóstico ( $P = 0,016$ ), anemia ( $P = 0,020$ ), anorexia ( $P = 0,003$ ), dor abdominal ( $P = 0,031$ ), emagrecimento ( $P = 0,001$ ), náuseas/vômitos ( $P = 0,094$ ) e obstrução intestinal ( $P = 0,066$ ); não foi encontrada qualquer associação com as características demográficas (sexo e idade) dos pacientes. No modelo final de regressão logística, emagrecimento, anemia e obstrução intestinal mostraram-se estatisticamente associados com a variável dependente de interesse. Levando-se em consideração somente três variáveis — emagrecimento, anemia e obstrução intestinal — foi possível prever a malignidade de tumores jejuno-ileais primários com sensibilidade de 85,2%, especificidade de 80,0% e acurácia de 83,3%.

**DESCRITORES** - Neoplasias do jejunum. Neoplasias do íleo. Fatores de risco.

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