

Colon carcinoma staging by endoscopic ultrasonography miniprobos

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ABSTRACT

Background and Objectives: Due to the increasing use of endoscopic techniques for colon cancer resection, pretreatment locoregional staging may gain critical interest. The use of endoscopic ultrasonography (EUS) miniprobos in this context has been seldom reported. Our aim was to determine the accuracy of EUS miniprobos for colon cancer staging. **Materials and Methods:** Forty patients with colon cancer (2 in the cecum, 9 in the ascending colon, 5 in the transverse colon, 5 in the descending colon, and 19 in the sigmoid colon) were submitted to staging using 12 MHz EUS miniprobos. EUS and the anatomopathological results were compared with regard to the T and N stages. It was assessed if the location, longitudinal extension, or circumferential extension of the tumor had any influence on the accuracy in EUS staging. **Results:** Tumor staging was feasible in 39 (98%) patients except in one case with a stenosing tumor (out of 6). Globally, T stage was accurately determined in 88% of the cases. In the assessment of the presence or absence of lymph node metastasis, miniprobos presented an accuracy of 82% with a sensitivity of 67%. These results were neither affected by the location nor by the longitudinal or circumferential extension of the tumor. **Conclusions:** EUS miniprobos may play an important role in assessing T and N stages in colon cancer and may represent an incentive to the research of new therapeutic areas for this disease.

Key words: Colon cancer, endoscopic ultrasonography (EUS), locoregional staging, miniprobos

INTRODUCTION

The conduction of endoluminal ultrasonography (US) in the lower digestive tract was initially restricted to the rectum and anus and was exclusively performed with rigid probes. The current availability of echoendoscopes and endoscopic ultrasonography (EUS) miniprobos allow us to perform US from the anus to the cecum.

The main advantage of EUS miniprobos is the possibility of introducing them into the conventional endoscopes instrumentation channel, allowing them to be used in upper gastrointestinal (GI) endoscopy, colonoscopy, or endoscopic retrograde cholangiopancreatography.

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Therefore, there is a possibility to obtain additional ultrasonographic information during an endoscopic procedure without the need to switch devices and subsequently reduce the number of endoscopic procedures with clinical and economic advantages.^[1]

By providing this unique possibility to use colonoscopes and simultaneously conduct endoluminal US, and also by allowing the obtainment of high resolution images, miniprobes open new perspectives for colon EUS.^[2-5] However, studies to assess the clinical impact of EUS in this segment are necessary.

In what concerns the colon, there are no established indications for the conduction of EUS,^[6,7] with the likely exception of subepithelial lesions assessment previously diagnosed by colonoscopy. Hard progression of echoendoscopes throughout the colon and their high cost of acquisition are the main motives that seem to cause this lack of indication.

Although EUS indications in colon disease are currently reduced, recent technical and clinical developments may change this scenario in the near future and this may result in the need to reassess the current indications.

We can consider different approaches in the therapeutics of colon cancer, with the possibility of its endoscopic^[8,9] or laparoscopic resection^[10,11] and conduction of neoadjuvant chemotherapy^[12,13] Therefore, its locoregional staging is essential.

However, some factors have been preventing EUS from achieving the same relevance in colon cancer staging as in gastroesophageal and rectal cancers. If the treatment is uniform, its value in clinical practice may be very reduced by resorting to conventional surgery regardless of its staging.

EUS miniprobes may overcome the previously described difficulties for conventional echoendoscopes and are an important tool for local staging of colon carcinoma. The aim of this study was to determine the feasibility and accuracy of EUS miniprobes for colon cancer staging.

MATERIALS AND METHODS

Ethics

The study was approved by the Ethics Committee for Health of our institution and the procedures were in accordance with the Helsinki Declaration.

Study design

Patient selection

Patients with colon cancer were consecutively included in the present analysis. All patients gave their informed consent in writing. Patients younger than 18 years old, pregnant women or patients with mental disorders or inability to give informed consent were excluded.

Technical information

EUS miniprobe procedure

A 12-MHz EUS miniprobe with a 2.5 mm diameter (Olympus UM-2R[®], Japan Shinjuku Monolith, 2-3-1 Nishi-Shinjuku, Shinjuku-ku, Tokyo 163-0914, Japan) was used in all cases. Patients were subjected to colonoscopy under propofol sedation after oral intake of 4 L polyethylene glycol (Klean-Prep[®]). The colonoscope was positioned at the distal end of the tumor and the colon lumen was filled with water in order to submerge the entire lesion; sometimes, it was necessary to change the patient's position for this to be achieved. Subsequently, the miniprobe was introduced through the colonoscope instrumentation channel and advanced to the tumor to proceed with its assessment [Figure 1]. Peri-intestinal space, at a distance of around 10 cm upstream and downstream of the lesion, was also assessed for the identification of eventual adenopathies. Carcinoma was considered stenosing when it did not allow the colonoscope to pass throughout the lesion. It was also determined if the miniprobe did or did not assess all its extension.

EUS sizing and staging

A single operator determined the extent of invasion of the wall (T stage) by the carcinoma, which was defined in accordance with TNM staging^[14] as: T1m— involvement limited to the mucosa; T1sm— involvement of the submucosa, with interface preserved with the *muscularis propria*; T2— invasion of the *muscularis propria*, without surpassing it; T3— tumor surpasses *muscularis*

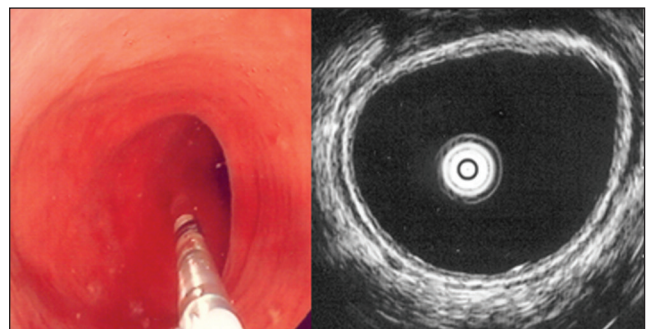


Figure 1. Colon lumen filled with water, miniprobe, and respective ultrasonographic image

propria, with involvement of the subserosa or the peri-intestinal tissue without invasion of the peritoneal cavity; T4—involvement of the peritoneal cavity or of other surrounding structures or organs by the carcinoma. A peri-intestinal node was considered to be metastatic (N1) in case of identification of a round or oval structure, with well-defined edges and hypoechoic echostructure in comparison with peri-intestinal fat regardless of its size.

The longitudinal extension, in centimeters, and circumferential extension of the carcinoma were also determined. The latter was subdivided into six groups, depending on the extent of involvement of the intestinal wall circumference: <1/3; 1/3; >1/3 < 2/3; 2/3; >2/3 <1; and 1 (whole circumference).

Gold standard

All patients were subjected to endoscopic resection (*n* = 1) or surgery (*n* = 39) in the 4 weeks after staging. Pathology results were considered as reference test.

Statistical analysis

EUS staging was compared with anatomopathological results and accuracy (global, sensitivity, and specificity) was determined. Moreover, tumor location and circumferential and longitudinal extension effects on these results was assessed. In the analysis of association between tumor location and its circumferential or circular extension and T and N staging by EUS, Pearson’s chi-square and Spearman correlation test were respectively used.

The relation between the number of metastasized nodes in the surgical sample and the probability to identify them by the EUS miniprobe was assessed by the receiver operating characteristic (ROC) curve.

A type I error of 0.05 was considered in the statistical analysis.

The software used in the analysis was IBM SPSS Statistics 21.

RESULTS

Forty patients were assessed; out of these, 19 (47.5%) were females with age ranging between 40 years and 90 years. The mean age was 70.3 ± 10.5 years.

Location of tumors: cecum-2 (5%), ascending colon-9 (22.5%), transverse colon-5 (12.5%), descending colon-5 (22.5%), and sigmoid colon-19 (47.5%).

There were no complications with the patients (regarding the tests conducted).

Assessed parameters

Tumor stenosis

From the 40 (100%) tumors assessed, 6 (15%) were stenosing and did not allow the colonoscope to pass but only in 1 (2.5%) of the cases the miniprobe was not able to assess the whole extension of the tumor.

Longitudinal and circumferential extensions of the tumors

Longitudinal and circumferential extensions of the tumors were determined with the miniprobe. Longitudinal extension ranged between 1.5 cm and 8 cm, with a median value of 3.5 cm. Circumferential extension may be observed in Table 1. We also point out that in 16 (40%) cases, carcinomas involved the entire wall circumference.

T staging

Correlation between EUS miniprobe (uT) and anatomopathological (pT) T staging may be observed in Table 2.

Given the Kappa coefficient value (0.78), we observed that T staging by EUS miniprobe was concordant with anatomopathological staging.

EUS accuracy for pT1m, pT1sm, and pT3 stages was 100%. In pT2 stage, overstaging occurred in four (33.3%) cases. The only pT4 carcinoma case observed was infrastaged as uT3 and therefore, accuracy for this stage was null. Globally, EUS total accuracy for T stage was 87.5%.

Table 1. Circumferential extension of the tumors (wall involvement)

	<1/3	1/3	>1/3 < 2/3	2/3	>2/3 <1	1	Total
<i>n</i> (%)	10 (25)	3 (7.5)	3 (7.5)	4 (10)	4 (10)	16 (40)	40 (100)

Table 2. Correlation between T staging by EUS miniprobe (uT) and anatomopathological (pT)

	Total <i>n</i> (%)	uT1m <i>n</i> (%)	uT1sm <i>n</i> (%)	uT2 <i>n</i> (%)	uT3 <i>n</i> (%)	uT4 <i>n</i> (%)	Acuity (%)
pT1m	3 (7.5)	3 (7.5)					100
pT1sm	3 (7.5)		3 (7.5)	8 (20)	4 (10)		100
pT2	12 (30)	3 (7.5)		8 (20)	21 (52.5)	0	66.6
pT3	21 (52.5)		3 (7.5)		1 (2.5)	0	100
pT4	1 (2.5)				26 (65)		0
Total	40 (100)						87.5

N staging

The correlation between EUS miniprobe (uN) and anatomopathological (pN) N staging was possible in 39 patients since an endoscopic resection was conducted in one case [Table 3].

Given the Kappa coefficient value (0.65), we observed that N staging by EUS miniprobe was concordant with anatomopathological staging.

EUS sensitiveness for the identification of metastasized nodes was 66.7%; specificity was 100%; positive predictive value was 100%; negative predictive value was 72%; and global accuracy was 82.1%.

Relation between tumor location and staging accuracy by EUS miniprobe

Given the low number of tumors in some intestine segments, to study this relation we grouped them in three locations: cecum and ascending colon (*n* = 11; 27.5%), transverse colon (*n* = 5; 12.5%), and descending and sigmoid colons (*n* = 24; 60%).

No relation was observed between the tumor location and uT stage (*P* = 0.07) or the uN stage (*P* = 0.81).

Relation between tumor longitudinal or circumferential extension and staging accuracy by EUS miniprobe

Neither the tumor’s longitudinal extension nor its circumferential extension influenced EUS miniprobe accuracy in T stage (*P* values of 0.52 and 0.43, respectively), and N stage (*P* values 0.49 and 0.41, respectively).

Relation between the number of metastasized nodes and the probability of identifying them by EUS miniprobe

It was observed that the higher the number of metastasized nodes in the major surgical sample, the higher the probability of echoendoscopic identification (ROC curve — Area under the curve 0.83; standard error = 0.07; *P* < 0.001).

Table 3. Correlation between N staging by EUS miniprobe (uN) and anatomopathological (pN)

	Total <i>n</i> (%)	uN0 <i>n</i> (%)	uN1 <i>n</i> (%)
pN0	18 (46.2)	18 (46.2)	0
pN1	21 (53.8)	7 (17.9)	14 (35.9)
Total	39 (100)	25 (64.1)	14 (35.9)

DISCUSSION

EUS has a well-established role in staging of the esophagus, stomach, pancreas, and rectum carcinomas.^[15-18] This does not occur in colon carcinoma, for which EUS staging does not constitute, at the present time, an indication in clinical practice. However, as previously mentioned, recent and progressive developments of minimally invasive surgical techniques and new modalities of adjuvant therapy are creating the need to conduct colon carcinoma staging with maximum accuracy, a situation in which EUS may play a fundamental role.

We staged 40 patients with colon carcinoma with EUS miniprobe in order to assess its accuracy and to identify if its use for this indication was feasible, namely, by the possibility of overcoming several difficulties associated with echoendoscopes.

There are few works in the literature to compare our results with. This problem has been increased by the different used methodologies in the existing works, among which we highlight the simultaneous assessment of colon and rectum carcinomas and adenomatous polyps in the same work, the use of different frequencies in miniprobes, miniprobes with and without balloon, and the different criteria to define metastasized nodes.^[19-22]

Among the different parameters assessed, one of the most important was the tumor stenosis. This was not so much for its frequency — Present in 6 (15%) cases — As for its existence, with the exception of 1 case (2.5%), that was not an impediment for staging using miniprobe. This finding means that with miniprobes, it is almost always possible to overcome one of the main obstacles in the use of echocolonoscopes in staging colon tumors: tumor stenosis. These results are in accordance with three works published, in which authors drew conclusions on the increased value of miniprobes in assessing colon stenosing malignancies.^[22-24] However, only in one of these works it is possible to observe a reference to the percentage of stenosing tumors in which the miniprobe assessment was not possible, the result of which was close to ours, 3.3% (in a total of 35 rectum carcinomas and 26 colon carcinomas, which were assessed together).^[24]

Concordance between staging by EUS miniprobe and anatomopathological staging, for both T and N stages,

was significant, as it was possible to observe by the respective statistical analysis [Kappa coefficients of 0.78 ($P < 0.001$) and 0.65 ($P < 0.001$), respectively].

In what concerns T stage, our global accuracy was 87.5%. In the literature, we observed values ranging from a minimum of 76%^[25] to a maximum of 94%^[19] with intermediate values of 82%^[21] 85%^[22,24] 87%^[20] 89%^[23] and 92%^[26]. We observed that globally, accuracy in the different works was similar, except in the one conducted by Yoshida *et al.*^[25] whose accuracy was the lowest-76%.

In the assessment of the different stages, we observed an accuracy of 100% in pT1m, pT1sm, and pT3 stages; from the 12 (30%) patients with pT2 stage, we overstaged 4 (33.3%) patients as uT3 (accuracy of 66.6%); the only (2.5%) carcinoma which stage was pT4 was infrastaged as uT3.

Information available in the literature with which our accuracy results in the different T stages may be compared is scarce and needs to be cautiously analyzed, not only because of the previously mentioned methodological constraints but also because T1 stage was not subdivided into T1m and T1sm. We currently consider that this subdivision is important because the therapeutic approach of malignancies located in the mucosa and submucosa is not consensual. Some opine that only tumors located in the mucosa (T1m) shall be resected by endoscopy because in the eventuality of submucosa involvement, this therapy is not adequate in most situations, given the potential risk of node metastization.^[27,28] On the contrary, others admit that if the carcinoma involves the most superficial third of the submucosa, this therapy can also be used, given the low risk of node metastization.^[29,30]

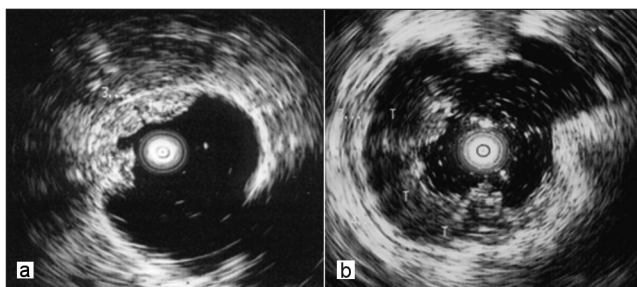


Figure 2. uT1 carcinomas. (a) Carcinoma (T) limited to the mucosa (uT1m), with preservation of interface with submucosa, layer 3. (b) Carcinoma (T) that involves submucosa, layer 3 (uT1sm)

Since we obtained 100% of accuracy in T1m and T1sm stages, we may consider this same value in stage T1 [Figure 2]. In the literature, there are three works with this exact accuracy^[19,22,24] and two works with lower accuracy, 88%^[23] and 71%.^[21] This last work was the one with the least number of patients included in this stage, i.e., seven, and this fact may influence the result.

In what concerns stage T2 [Figure 3], our results were similar to the ones of Akahoshi *et al.*,^[23] who obtained an accuracy of 64% from the 11 studied patients. Three works obtained higher accuracy values: 80% (10 patients),^[19] 78% (10 patients),^[24] and 75% (8 patients).^[22] One work had a lower accuracy, i.e., 50% but only four patients were assessed at this stage.^[21] In this stage, our error resulted from the overstaging of the other four cases as uT3, which also happened in the study of Stergiou *et al.*^[19] In the other works, the authors presented a 50% overstaging and 50% infrastaging.^[21,22,24]

In T3 stadium, accuracy was high in all works. In our case, it was 100% and in the others it was 96%^[21] 95%^[23] 90%^[24] 88%^[22] and 83%^[19]. It should be mentioned that it was in this stage that the highest number of patients was included, whether by us or in the works quoted, except the one in which a lower accuracy was observed with an assessment of only six patients.^[19]

Stage T4 registered the highest differences in accuracy, but this was also the stage with the lowest number of patients, Therefore, the only patient studied in this stage was infra-staged and, consequently, accuracy was null [Figure 4]. Among the five works that we mentioned in the previous paragraph, it was certainly also the

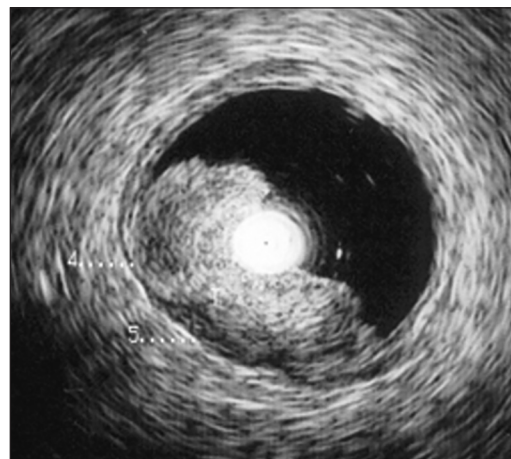


Figure 3. uT2 Carcinoma. Invasion of *muscularis propria*, layer 4, with preservation of layer 5, serosa

reduced number of patients that dictated results of 0% accuracy (two patients included, two infrastaged), 100% accuracy (one patient included), 40% accuracy (five patients included, three infrastaged), 50% accuracy (two patients included, one infrastaged) and 100% accuracy (one patient included).

We registered overstaging situations at the level of T2 stage and of infrastaging in T4 stage, as previously mentioned. We think that the overstaging situations were due to the peritumoral inflammatory changes, which were interpreted as subserosa or periintestinal tissue neoplastic infiltration. The carcinoma that was observed to be T4 due to pancreas involvement and that was infrastaged as uT3, a large mass in which ultrasounds limited penetration (12 MHz) was not sufficient for an in-depth assessment. These main causes of error are also pointed out by other authors.^[19,22,23]

Globally, our results are in accordance with the main works in the literature with which we have been establishing comparisons: high accuracy for stage T1 and T3 and the lowest for stage T4.

Concordance between staging by EUS miniprobe and anatomopathological staging for N stage, being lower than for T stage, was also significant (Kappa coefficient equal to 0.65; $P < 0.001$) [Figure 5]. Global accuracy was 82.1%, with a sensitivity to identify metastasized nodes of 66.7% and a specificity of 100%; positive predictive value was 100% and negative predictive value was 72%.

The comparison of results in the N stage available in the literature shall be made with many reservations,

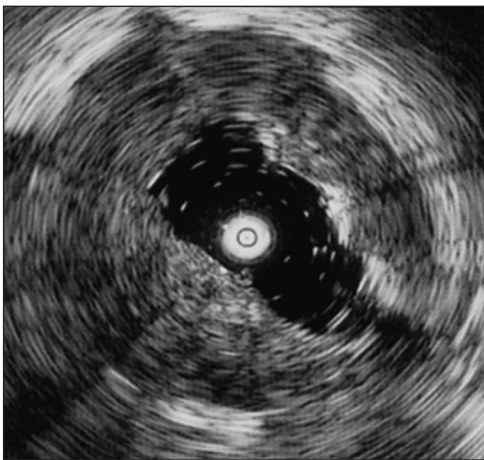


Figure 4. pT4 carcinoma, caused by pancreas invasion, infrastaged as uT3. Large tumor mass that prevented the assessment by US miniprobe in all its depth

given the existence of methodological differences between the different works in what concerns the used frequency, definition of the metastasized node, number of patients included, and presentation of joint results with the colon and rectum. Global accuracy ranges from 66% to 84%, sensibility from 56% to 95%, specificity from 64% to 90%, positive predictive value from 56% to 84%, and negative predictive value from 58% to 90%.^[19-24,26]

Although we consider our results to be very reasonable, in comparison with the ones available in the literature, global accuracy for N staging (82.1%) was lower than for T staging (87.5%). This observation was also made by other authors. This situation was predictable at the beginning since we worked with a high frequency (12 MHz). Other authors share this opinion.^[22,24] However, in the work of Hamada *et al.*^[31] a miniprobe with a frequency of 15 MHz was used and the global accuracy for N staging, in 30 patients, was not only superior to the one from T staging (87% and 82%, respectively) but also higher than the one obtained by the works that used a frequency of 12 MHz. Our results are consistent with the ones from other authors^[19-21,26,31] and allow us to declare that with EUS miniprobes, it is possible to obtain a good accuracy in colon carcinoma N staging, which contradicts some skepticism from three other studies,^[22-24] in which the highest value of registered accuracy was 67%. These differences of results and opinions may be partially explained since the technique is operator-dependant.

With regard to N staging, we demonstrated that the higher the number of metastasized nodes, the higher the probability to identify them by EUS miniprobe. We think that this correlation partially results from the fact that we have looked for nodes in the peritumoral region and also in 10 cm upstream and downstream of the malignancy, which may have

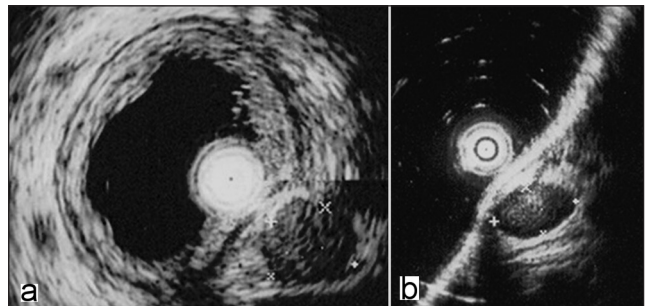


Figure 5. Examples of lymph nodes in the periintestinal fat identified by EUS miniprobe (a and b)

decisively contributed to having achieved a good result in N stage assessment.

We neither observed any relation between T and N staging accuracies and the tumor location in the different segments of the colon and nor with its longitudinal or circumferential extension.

CONCLUSIONS

It is possible to stage colon carcinoma with a 12-MHz EUS miniprobe, obtaining significant concordance with T and N anatomopathological staging. Staging accuracy is not influenced by the tumor location or its longitudinal and circumferential extensions.

Although we know that more studies and more patients are necessary to reinforce our conclusions, we think that EUS miniprobes may play an important role in the assessment of T and N staging in colon carcinoma and therefore, constitute a strong incentive in the research of new therapeutic areas that are being developed for this disease.

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Conflicts of interest

There are no conflicts of interest

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