Rectal cancer staging with endoscopic ultrasonography: correlation with pathological staging

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RESUMEN

Objetivo: nuestro objetivo fue evaluar la precisión diagnóstica (PD) en nuestro medio de la ecotomografía (USE) para la estadificación del cáncer de recto (CR).

Material y métodos: incluimos de manera prospectiva a todos los pacientes con CR estadificados en nuestra unidad entre septiembre de 2002 y febrero de 2006 en una base de datos. Seleccionamos aquellos pacientes en los que se había realizado una ecotomografía completa con USE (uTN) y fueron intervenidos quirúrgicamente sin tratamiento neoadyuvante. Consideramos la estadificación histológica (pTN) como patrón oro, y comparamos los resultados de la uTN previa con los de la pTN. Calculamos la sensibilidad (S), especificidad (E), valores predictivos positivo (VPP) y negativo (VPN) y PD para cada estadio T, y estadio N considerado como positivo o negativo. Calculamos la concordancia entre la uTN y la pTN utilizando el índice de kappa para el estadio N, y el mismo índice con ponderación cuadrática para el estadio T.

Resultados: ciento veinte pacientes con CR fueron estadificados en nuestra unidad, cumpliendo 36 criterios de inclusión y fueron analizados en este estudio (21 hombres, 15 mujeres). La edad media fue de 68,53 ± 10,15 años (rango = 48-90). La PD de la uT global y uN fueron del 83 y 72% respectivamente. Obtuvimos una S, E, VPP, VPN y PD para el T1; 82, 88, 75, 91 y 86% para el T2; 86, 91, 86, 91 y 89% para el T3; y 14, 86, 20, 80 y 72% para el estadio N respectivamente. El índice de kappa para la estadificación T fue de 0,87 (concordancia “muy buena” entre uT y pT); y de 0,005 para la estadificación N (concordancia “pobre”).

Conclusiones: en nuestra experiencia, la PD de la uTN del cáncer de recto alcanza el 83 y el 72% respectivamente, resultados acordes con lo disponible en la literatura. La uT del cáncer de recto muestra una concordancia “muy buena” con la pT.


ABSTRACT

Objectives: our aim was to evaluate the accuracy of endosonography (EUS) in our experience, to stage rectal cancer.

Material and methods: we prospectively included all patients with rectal cancer staged in our unit from September 2002 until February 2006 in a database. We selected those patients who had a complete EUS examination and were surgically treated without neoadjuvant therapy. Once we had the results of the histopathological staging (pTN), which was considered the gold standard, we compared the results of the previous EUS staging (uTN) with those of the pTN. We calculated the sensitivity, specificity, positive predictive value, negative predictive value and accuracy for each T stage, and for N staging considered as N positive or negative. We also calculated the global accuracy for T stage. We also calculated the agreement of uTN with pTN staging using the kappa index for N stage, and quadratic weighted kappa index for T stage.

Results: we staged 120 patients with rectal cancer during the mentioned period. Of these, 36 patients met inclusion criteria and were evaluated, 21 women and 15 men. Mean age was 68,53 ± 10,15 yo (range: 48-90). Global T stage accuracy was 83%. N stage accuracy was 72%. We obtained a S, E, PPV, NPV and A of 91, 100, 100, 96 and 97% for T1; 82, 88, 75, 91 and 86% for T2; 86, 91, 86, 91 and 89% for T3; and 14, 86, 20, 80 and 72% for N stage respectively. Kappa value for T stage was 0.87 indicating a “very good” agreement between uT and pT according to the kappa index criteria. Kappa value for N stage agreement was 0.005; “poor” according to the same criteria.

Conclusions: in our experience, the diagnostic accuracy of EUS for T and N staging of rectal cancer is 83% and 72% respectively, similar results as previously published. uT staging for rectal cancer shows a “very good” agreement with pT staging.

Key words: Endosonography. Rectal neoplasms. Neoplasm staging. Neoadjuvant therapy.
INTRODUCTION

Colorectal cancer represents an important health problem in western countries, with an increasing incidence over the last few years. In Navarre colorectal cancer is the third most frequent tumor in men and the second in women. Between 1998 and 2000, 398 new cases of rectal cancer were diagnosed in our region, with a yearly rate –adjusted to world population– of 17 cases/100,000 inhabitants for men, and 8.3 cases/100,000 inhabitants for women (1).

Moreover, rectal cancer has a high recurrence rate after surgery, which varies between 30 and 65% (2). It has been proven that preoperative neoadjuvant oncological treatment improves survival and diminishes recurrence rates in patients with locally advanced cancer (T3-4Nx or TxN1-2 stage) (3-5).

Therefore, it is of utmost importance that an accurate preoperative staging of rectal cancer be performed. Endoscopic ultrasonography (EUS) is one of the most accurate techniques available nowadays. Reported EUS accuracy in rectal cancer varies between 69 and 97% for T staging (6), and is 70-75% for N staging (7).

Usually, the initially reported results of a new technique are extremely good (8,9). Generalization of the technique plus a moderation in initial enthusiasm lead to more variable results, usually less impressive than first published data (10). In this sense, and concerning EUS accuracy for rectal cancer staging, an inverse relationship between the accuracy obtained in different studies and number of patients included may be seen. Moreover, higher accuracies are found in older studies, possibly related to the previously described effect. A possible explanation for these two phenomena may be that a publication bias exists, with a tendency to publish only those studies with the best results, even those including a small number of patients (7). Taking these facts into account we might think that the actual accuracy of EUS for rectal cancer staging is lower than that described in the literature.

Because of this, we planned to analyze the accuracy of EUS for rectal cancer staging in our setting, taking histological staging as the gold standard.

MATERIAL AND METHODS

To achieve our aim of analyzing EUS accuracy in rectal cancer staging we prospectively included all patients with rectal cancer staged in our unit from September 2002 until February 2006. We defined the following as inclusion criteria: tumors affecting the last 15 cm of the colon (11); patients in whom we could perform a complete EUS staging examination and who were surgically treated without neoadjuvant therapy, which might alter histological staging. We took histological staging as gold-standard for the analysis of EUS staging results.

In order to perform an evaluation of EUS accuracy by taking tumor site into account, we divided the rectum into three parts: upper third from 12 to 15 cm, middle third from 8 to 12 cm, and lower third from 7 cm to the anus.

We considered that an EUS examination was complete when the area located between the iliac bifurcation and the anus was completely assessed. Patients were prepared only with two 250-cc enemas before the procedure, administered with an interval of 12 hours. No sedation was required in any patient, and all the explorations were performed by the same endoscopist with a mechanical radial echoendoscope (Olympus, GF UMQ130) (Olympus Europe, Hamburg). We used the TNM classification to stage patients (AJCC Cancer Staging Manual, Sixth edition (2002), Springer Verlag, New York Inc.).

In our hospital there is a Digestive Oncological Committee to evaluate patients with any digestive cancer. Specifically for rectal cancer we follow a protocol accepted by the departments of Oncology, Radiology, Gastroenterology, and Surgery. Following this protocol those patients with a preoperative stage of T3 or greater, and/or a positive N are treated with neoadjuvant radiotherapy –45 Gy– and concomitant 5-FU-based chemotherapy.

In the statistical analysis we used descriptive data, and to perform the comparative study we used the quadratic weighted Kappa index for T stage, and Kappa index for N stage. With this index we obtained a value within a scale where 1 means maximum concordance and 0 means concordance by chance (Table I). Besides the Kappa index we report p values (differences were considered to be statistically significant when p values lower than 0.05) and 95% confidence intervals (CIs). We also calculated EUS sensitivity, specificity, positive and negative predictive values, and accuracy for global T and N staging, for each T stage, and also for staging results adjusted according to tumor site. Statistical analyses were conducted using the SPSS (Version 12.0) statistical software program (SPSS, Chicago, IL, USA).

<table>
<thead>
<tr>
<th>Table I. Kappa index scale</th>
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<tbody>
<tr>
<td><strong>Kappa value</strong></td>
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<tr>
<td>&lt; 0.20</td>
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<tr>
<td>0.21-0.40</td>
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<tr>
<td>0.41-0.60</td>
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<tr>
<td>0.61-0.80</td>
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<tr>
<td>0.81-1</td>
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</table>

RESULTS

During the aforementioned period 120 patients with rectal cancer were staged in our unit. Thirty six of them met inclusion criteria and were analyzed. Sex distribution for these 36 patients was: 21 men (58.3%) and 15 women (41.7%). Mean age was 68.53 ± 10.15 years with a range of 48-90 years. With regard to tumor location, in 14 pa-
tients the tumor was located in the lower third; in 7 patients in the middle third, and in 15 patients in the upper third. With EUS we staged 10 patients as T1 (27.8%), 12 patients as T2 (33.3%), and 14 patients as T3 (38.9%). Furthermore, we identified lymph nodes suspect for malignancy in 5 patients (13.9%). Finally, in the histological study 11 patients (30.6%) were staged as T1; another 11 patients (30.6%) were staged as T2, and 14 patients (38.9%) were staged as T3. This pathological study also proved the presence of metastatic lymph nodes in 7 patients (19.4%). Data regarding the comparison between EUS and histological staging are shown in tables II and III. According to these data 3 patients (8.3%) were overstaged with EUS regarding T stage: 2 patients who actually were T2 were classified as T3 with EUS, and 1 patient who was T1 was misdiagnosed as T2. Besides, another 3 patients (8.3%) were downstaged with EUS, all of them T3 in the pathological staging that were misinterpreted as T2 with EUS.

Sensitivity, specificity, negative predictive value, positive predictive value, and accuracy results are shown in table IV. Our accuracy for global T stage was 83%. When taking tumor location into account, accuracy results for T stage were 73.3% in the upper third, 100% in the middle third, and 85.7% in the lower third.

We used the quadratic weighted Kappa index for T stage, and the Kappa index for N stage in order to perform the comparative study between pathology and EUS staging. Kappa index for T staging was 0.87 (CI = 0.56-0.93; p < 0.05), corresponding to a very good correlation. Kappa value for N staging was 0.005 (CI = -0.34-0.35; p = 0.24), corresponding to a poor correlation.

**DISCUSSION**

EUS is one of the most accurate techniques for rectal cancer staging, and this is a main indication for EUS (12). Some reports have been published comparing the accuracy of EUS and radiological explorations for rectal cancer staging, and proved the superiority of EUS over CT (2), and similar or better results of EUS when compared to MRI. Nevertheless, MRI has developed some important technological advances that have improved its results, thus becoming a good alternative to EUS for rectal cancer staging (13). In this sense, high resolution MRI has shown better results versus MRI using a rectal or body coil (6). Major MRI drawbacks include high cost, limited availability, and moderate results when staging early rectal cancer as compared to EUS (13,14). However, MRI allows performing a complete examination of the mesorectum, is less operator-dependant than EUS, and can identify the mesorectal fascia, hence determining the circumferential resection margin (15). This can be determinant, as we will discuss later.

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**Table II. Comparison of histological and EUS T staging**

<table>
<thead>
<tr>
<th>Histological staging</th>
<th>T1 (%)</th>
<th>T2 (%)</th>
<th>T3 (%)</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EUS staging</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>10 (27.8)</td>
<td>0</td>
<td>0</td>
<td>10 (27.8)</td>
</tr>
<tr>
<td>T2</td>
<td>1 (2.7)</td>
<td>8 (22.2)</td>
<td>3 (8.3)</td>
<td>12 (33.3)</td>
</tr>
<tr>
<td>T3</td>
<td>0</td>
<td>2 (5.5)</td>
<td>12 (33.3)</td>
<td>14 (38.8)</td>
</tr>
<tr>
<td>Total</td>
<td>11 (30.5)</td>
<td>10 (27.8)</td>
<td>15 (41.7)</td>
<td>36 (100)</td>
</tr>
</tbody>
</table>

**Table III. Comparison of histological and EUS N staging**

<table>
<thead>
<tr>
<th>Histological staging</th>
<th>N positive (%)</th>
<th>N negative (%)</th>
<th>Total (%)</th>
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</thead>
<tbody>
<tr>
<td>EUS staging</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N positive</td>
<td>1 (2.7)</td>
<td>4 (11.1)</td>
<td>5 (13.8)</td>
</tr>
<tr>
<td>N negative</td>
<td>6 (16.6)</td>
<td>25 (69.4)</td>
<td>31 (86.1)</td>
</tr>
<tr>
<td>Total</td>
<td>7 (19.4)</td>
<td>29 (80.5)</td>
<td>36 (100)</td>
</tr>
</tbody>
</table>

**Table IV. Results for sensitivity (S), specificity (SP), positive predictive value (PPV), negative predictive value (NPV) and accuracy (A) of EUS staging for each T stage and or N stage**

<table>
<thead>
<tr>
<th>n</th>
<th>T1</th>
<th>T2</th>
<th>T3</th>
<th>N</th>
<th>S</th>
<th>SP</th>
<th>PPV</th>
<th>NPV</th>
<th>PD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>36</td>
<td>14%</td>
<td>86%</td>
<td>20%</td>
<td>80%</td>
<td>72%</td>
</tr>
</tbody>
</table>

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Rev Esp Enferm Dig 2007; 99 (3): 132-137
EUS has also drawbacks. Results can be influenced by some factors, including inadequate contact between the tumor and the probe because of air, stools, or an irregular tumor surface; interpretative errors with a tendency towards overstaging; anatomical defects from previous biopsies or polypectomy; peritumoral inflammation, which can favor misinterpretation and overstaging; and incomplete exploration (16). When any of these situations occurs, EUS results may be inaccurate, and we should perform an alternative exploration such as an MRI scan, or repeat the endosonographic exploration once the confounding factor has disappeared (15).

Besides radial echoendoscopes, it is possible to perform an endosonographic staging of rectal cancer using other devices such as a rigid probe, a linear echoendoscope, or ultrasonographic miniprob. With the first one, slightly better results have been published when compared to radial echoendoscopes in staging rectal cancer, but its utility is limited to non stenosing tumors located in the lower two thirds of the rectum (17,18). Furthermore, it does not allow evaluating the presence of lymph nodes in the iliac bifurcation, and that is the reason why we prefer to stage rectal cancer with a radial echoendoscope. Ultrasound miniprobes have also been used to stage rectal cancer, and showed very good results to distinguish between tumors limited to the mucosa and those invading the submucosa, which might be very useful in patients who are candidates to undergo an endoscopic or transanal tumor resection (19). Finally, linear array echoendoscopes have the advantage of supporting fine-needle aspiration for perirectal or iliac lymph nodes, thus improving N staging (20).

EUS utility to stage rectal cancer has been recently debated because of some reports quoting worse results than those previously published (21,22). Some of these studies included a high number of patients, but did not include locally advanced tumors, where EUS shows better accuracy (23,24). This could be a selection bias worsening results. Besides, the authors of some of these reports assume that results are operator-dependant.

Taking these new data into account a very interesting report that was recently published—and which analyzes all available reports evaluating the accuracy of EUS for rectal cancer staging, has shown an inverse relationship between accuracy and number of patients. Additionally, older reports show a better accuracy versus recent ones. Authors conclude that there is a publication bias with a tendency towards publishing only those works with the best results. This may create unrealistic expectations about EUS in this setting (7). In our case, we obtained results similar to those of other previously published papers with the same number of patients included (25,26). Actually, the number of patients included is not high, and our report could really become one of those that increase the publication bias. We must argue, in self-defence, that our aim was to know the utility and reliability of EUS for rectal cancer staging under usual daily conditions, and these results reflect the current situation in our hospital during two and a half years.

Noticeably, some patients in our series, staged as T3 or N-positive with EUS, were surgically treated without neoadjuvant therapy. As we said before, in our hospital we treat rectal cancer patients according to an established protocol, by which T3 and N-positive patients receive neoadjuvant therapy before surgery (3-5). However, therapeutic decisions are individualized and some patients with locally advanced disease are surgically treated without neoadjuvant therapy because of advanced patient age, because tumor location facilitates surgery, or also because a patient refuses oncological treatment. This situation has been also described in previous works (2,27). These individualized decisions may constitute a selection bias, with only some specific type of patients with locally advanced disease in our analysis. However, we must also emphasize that the accuracy obtained in T3 tumors is similar to that obtained for lower stages, and so we consider this accuracy close to reality. Furthermore, this potential bias may have influenced the poor correlation obtained for N stages, by not including most tumors staged as N-positive. This influence would not be that strong on the T staging correlation, for in this analysis three categories exist, and two of them (T1 and T2) include all patients; for this reason, the influence of the selection bias present in the third category would be lower. T staging correlation between EUS and histology was very good.

Our results are similar to those reported by other Spanish groups, although our study design differs with respect to those of previous works. We analyzed only the results obtained for early-stage tumors (T1/2-N0 and some T3s with special characteristics as already commented on), while in a report from Novell et al. (28) all tumors are included, since it was published before the usefulness of neoadjuvant therapy had been proved. In another, more recent report from García Sánchez et al. (17), the authors classified patients in a first group of 17 patients with characteristics similar to ours, but they also analyzed the response after neoadjuvant therapy in a second group including those patients with more advanced cancers. The latter analysis is criticizable because it is assumed that every patient with advanced disease is correctly staged with EUS, since that is the reference used to evaluate response to therapy. This is not the case, and may lead to errors when evaluating the response to neoadjuvant therapy. However, the TNM staging system is being criticized mainly because no distinction is made between a limited T3 tumor with a wide circumferential resection margin, and an advanced T3 tumor with a smaller resection margin (6,29). It has been proved that distance from the tumor to the circumferential resection margin is the most powerful predictor of local recurrence, and not T stage (6,27,30-32). Therefore it is important that imaging explorations performed to stage rectal cancer identify the mesorectal fascia and measure the distance between the
tumor and the fascia (29). When this distance is lower than 5 mm it is considered inadequate to perform a good surgical resection (33). The main problem of EUS is that it is not always possible to correctly identify the mesorectal fascia. In this respect MRI has proven its utility, and can predict a circumferential resection margin with a confidence of 97% when that distance is longer than 6 mm, and with a good interobserver correlation (33).

In conclusion, we can affirm that, according to our data, EUS offers high accuracy for rectal cancer staging, with a good correlation with histological staging regarding T stage. However, and looking forward to what new technological advances such as contrast-aided endosonography and 3D endosonography may offer, it is possible that this high accuracy for TN staging in rectal cancer will be less relevant in the future, considering the importance that the distance from the tumor to the mesorectal fascia has been gaining in the last few years as a predictor of good circumferential resection margins. This distance can be reliably measured with MRI, but is difficult to identify with EUS. According to this, it is possible that the role of EUS for rectal cancer staging will be restricted in the future to initial staging, and that tumors staged with EUS as T3 will require further evaluation with MRI to determine their circumferential resection margin.

REFERENCES