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Performance of Endoscopic Ultrasound in Staging Rectal Adenocarcinoma Appropriate for Primary Surgical Resection

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BACKGROUND & AIMS: **Endoscopic ultrasound (EUS) often is used to stage rectal cancer and thereby guide treatment. Prior assessments of its accuracy have been limited by small sets of data collected from tumors of varying stages. We aimed to characterize the diagnostic performance of EUS analysis of rectal cancer, paying particular attention to determining whether patients should undergo primary surgical resection.**

METHODS: **We performed a retrospective observational study using procedural databases and electronic medical records from 4 academic tertiary-care hospitals, collecting data on EUS analyses from 2000 through 2012. Data were analyzed from 86 patients with rectal cancer initially staged as T2N0 by EUS. The negative predictive value (NPV) was calculated by comparing initial stages determined by EUS with those determined by pathology analysis of surgical samples. Logistic regression models were used to assess variation in diagnostic performance with case attributes.**

RESULTS: **EUS excluded advanced tumor depth with an NPV of 0.837 (95% confidence interval [CI], 0.742–0.908), nodal metastasis with an NPV of 0.872 (95% CI, 0.783–0.934), and both together with an NPV of 0.767 (95% CI, 0.664–0.852) compared with pathology analysis. Incorrect staging by EUS affected treatment decision making for 20 of 86 patients (23.3%). Patient age at time of the procedure correlated with the NPV for metastasis to lymph node, but no other patient features were associated significantly with diagnostic performance.**

CONCLUSIONS: **Based on a multicenter retrospective study, EUS staging of rectal cancer as T2N0 excludes advanced tumor depth and nodal metastasis, respectively, with an approximate NPV of 85%, similar to that of other modalities. EUS has an error rate of approximately 23% in identifying disease appropriate for surgical resection, which is lower than previously reported.**

Keywords: Colorectal Cancer; Locoregional Invasion; Neoadjuvant Therapy; Diagnosis.

Rectal cancer comprises a significant burden of disease in the United States, with a projected incidence of 40,340 cases in 2013.[1] The centrality of disease stage in establishing a patient's primary treatment plan has led to sustained interest in the relative accuracy of available imaging modalities. Per the National Comprehensive Cancer Network guidelines, standard management involves the administration of neoadjuvant chemoradiotherapy for any locally advanced disease (T3, T4, or node-positive).[2] Therefore, the ability to distinguish between T2 and T3 levels of local invasion and to detect the presence of nodal metastasis remains particularly salient in evaluating the performance of various imaging techniques.

Over the past several years, endoscopic ultrasound (EUS) and magnetic resonance imaging (MRI) have emerged as the preferred options for the staging of rectal adenocarcinoma. Investigations performed early in the past decade have favored EUS, particularly for the assessment of locoregional invasion. Meta-analyses of EUS staging data have yielded pooled sensitivity estimates ranging from 80.5% to 96.4%, and pooled specificity

Abbreviations used in this paper: **EUS, endoscopic ultrasound; MRI, magnetic resonance imaging; NPV, negative predictive value.**

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estimates ranging from 90.6% to 98.3% for various T stages,[3] superior to those of MRI when an explicit comparison was made.[4] Similar estimates for the detection of nodal disease by EUS were lower (pooled sensitivity, 73.2%; pooled specificity, 75.8%), but still were deemed moderately accurate.[5]

Recent data, however, have suggested that MRI might prove superior for staging.[6,7] Outside the academic setting, large multicenter EUS data have yielded a lower-than-expected correlation between tumor depth estimation and surgical pathology.[8] For the detection of nodal disease, developments in MRI technique such as the use of novel contrast agents have resulted in sensitivity and specificity estimates as high as 80% and 96%, respectively.[9] Most research has focused on phased-array MRI, although endoluminal coil systems represent technical adjuncts with the potential for improved accuracy.[10] High-resolution MRI also has been favored in the exclusion of tumor involvement of the circumferential resection margin, with a measured specificity of 92%.[11] On this basis, some investigators have begun to explore the possibility of low-risk T3 cancers amenable to primary resection, often with an emphasis on MRI over EUS.[12–15]

Given the continued evolution of these 2 modalities, this multicenter retrospective study evaluated the diagnostic performance of EUS in rectal cancer staging. It focuses particularly on the standard threshold for primary surgical resection, comparing cases staged by EUS as uT2N0 lesions to the criterion standard of surgical pathology. Regarding conventional staging abbreviations, the prefix "u" refers to staging results by endoscopic ultrasound, and the prefix "p" refers to staging results by surgical pathology. A staging result of "NX" refers to cases in which insufficient information was available for the description of nodal metastasis.

Materials and Methods

A retrospective review was performed of all rectal cancer cases undergoing staging by EUS at each of 4 participating tertiary care centers. Procedures were performed from August 2000 through October 2012. All performing endosonographers completed a fellowship in advanced endoscopy. Tumor visualization was performed with a radial echoendoscope and sometimes were supplemented by a linear echoendoscope. Tumor stage was evaluated by the endosonographer according to the American Joint Commission on Cancer TNM staging system.[16] When primary surgical resection was pursued, the typical time interval elapsed between EUS and surgery was less than 4 weeks.

Inclusion criteria consisted of a pathologic diagnosis of rectal adenocarcinoma and staging by EUS as uT2N0. Exclusion criteria consisted of election against primary resection for reasons extrinsic to the typical therapeutic algorithm (eg, patient preference) and lack of available surgical pathology data (eg, when surgeries were performed by unaffiliated community providers).

Cases staged as uT2N0 by EUS were isolated for comparison with surgical pathology to calculate diagnostic performance. Cases were reviewed consecutively at each institution over specified timelines of recorded data (Table 1).

Statistical Analysis

SAS software (version 9.3; Cary, NC) was used for all statistical analyses. Exact binomial tests were performed to calculate the negative predictive value (NPV) of EUS for T2 staging, N0 staging, and combined T2N0 staging relative to the criterion standard. NPV was defined in the context of this study as the ability of EUS to exclude nonsurgical disease correctly, that is, to distinguish T2 tumors from more locoregionally advanced disease and to distinguish node-negative from node-positive disease. As such, tumors staged as uT2 by EUS that eventually were found to be pT1 on surgical pathology (ie, overstaged by EUS) were regarded as correctly diagnosed.

Kruskal–Wallis analyses of variance were conducted to evaluate the possible influence of technical variation among endosonographers' diagnostic performance. Univariate logistic regression models were generated to assess potential associations between specific case attributes and diagnostic performance and to evaluate the possibility of variation in diagnostic performance of EUS over time. Case attributes of interest included patient age, patient sex, visualized tumor size, and distance of the tumor from the anal verge. Among cases in which tumor location was reported exclusively as the distance from the dentate line, this value was increased by 2.1 cm (an average difference reported in the literature) to extrapolate the distance from the anal verge.[17] Tumor location also was transformed into a binary categoric variable (with a threshold corresponding to the median

Table 1. Breakdown of Cases Reviewed and Analyzed at Each of Four Participating Centers

Center	Cases reviewed	Cases included	Years surveyed	Estimated volume, cases/y	Timeline surveyed
A	337	24	9	37.4	October 2003 to September 2012
B	284	48	12	23.7	August 2000 to September 2012
C	428	9	7	61.1	August 2005 to October 2012
D	29	5	2	14.5	June 2010 to July 2012
Overall	1078	86	12	-	August 2000 to October 2012