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Clinical Correlation of Endoscopic Ultrasonography with Pathologic Stage and Outcome in Patients Undergoing Curative Resection for Gastric Cancer

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Background: Endoscopic ultrasonography (EUS) is considered valuable for preoperative staging of gastric cancer and defining patient eligibility for enrollment in neoadjuvant protocols. The aim of this study was to correlate EUS staging with pathologic evaluation and outcome in patients undergoing curative R0 resection for gastric cancer.

Methods: All patients who underwent preoperative clinical assessment of T/N stage with EUS and subsequent R0 resection for gastric adenocarcinoma between 1993 and 2003 were identified from a prospective database. Patients who received neoadjuvant chemotherapy were excluded. Clinical staging results from preoperative EUS were compared with postoperative pathologic staging results and correlated with clinical outcome.

Results: Two hundred twenty-five patients with gastric cancer underwent EUS followed by R0 resection, without preoperative chemotherapy. The accuracy of the individual EUS T stage was 57% (127 of 223) and was 50% for N stage (110 of 218). Although EUS was less able to predict outcome according to individual T stage, patients with lesions ≤T2 on EUS had a significantly better outcome than patients with lesions ≥T3. Preoperative assessment of risk was not predicted by EUS N stage alone. Patients identified as high risk on EUS and those with a combination of serosal invasion and nodal disease had both the highest concordance with pathology and a significantly worse outcome ($P = .02$).

Conclusions: The concordance between EUS and pathologic results was lower than expected for individual T and N stages. Patients with lesions ≤T2 had a significantly better prognosis than patients with more advanced lesions. Individual EUS N stage has limited value in preoperative risk assessment. Combined assessment of serosal invasion and nodal positivity on EUS identifies 77% of patients at risk for death from gastric cancer after curative resection.

Key Words: EUS—Stomach neoplasm—Staging—Preoperative.

Approximately 22,280 new cases of gastric cancer will be diagnosed in the United States in 2006, with >11,400 deaths.[1] In the absence of metastatic disease, complete resection of all gross disease with negative microscopic margins offers the only chance for long-term survival.[2,3] Unfortunately, recurrence is common[4] even after a curative resection. Postoperative multimodality therapy has been shown to improve overall survival for high-risk patients.[5] However, even with complete resection and adjuvant chemoradiation therapy, the risk of recurrence remains significant. Furthermore, many patients are

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unfit after surgery to receive additional therapy. Risk stratification before definitive therapy without the aid of pathologic staging is an important challenge in the management of patients with gastric cancer, with the goal of selecting high-risk patients for whom preoperative therapy might be appropriate.[6]

Endoscopic ultrasonography (EUS) is considered to be a valuable staging tool for preoperative assessment of locoregional disease for patients with gastric cancer. It is often used to define high-risk patients who are eligible for enrollment into neoadjuvant protocols. Precise preoperative staging is mandatory in neoadjuvant trials to compare treatments, identify subgroups that will benefit most, and prevent overtreatment in patients who will not benefit.

Early series demonstrated accurate EUS evaluation of depth of wall penetration for T staging in gastric adenocarcinoma.[7,8] The correlation between preresection clinical variables and postresection variables has been examined[9,10] and demonstrated high accuracy, ranging from 70% to 90% for both T and N stage. We previously reported on the high concordance of EUS with pathologic assessment and predictive validity in an initial small series.[8] Less is known about the direct relationship between the assessment of preresection variables and survival after curative resection. As new staging technologies become commonplace, it is incumbent on surgeons to monitor them for accuracy and utility in treatment planning.

The first aim of this study was to correlate EUS staging with pathologic evaluation and outcome in a large contemporary series of patients undergoing curative R0 resection for gastric cancer. The second aim was to assess the prognostic value of EUS assessment—information available before surgery, when pretreatment risk assessment and treatment planning take place.

METHODS

All patients who underwent a preoperative clinical assessment of T/N stage with EUS and subsequent R0 resection for gastric adenocarcinoma between 1993 and 2003 were identified from a prospective database. Review of clinicopathologic features and follow-up of all patients for this study were approved by the institutional review board. To eliminate the possibility of treatment-related downstaging, patients receiving neoadjuvant chemotherapy were excluded from this analysis. Before EUS, each patient routinely underwent flexible esophagogastroduodenoscopy with biopsy of the lesion. EUS was performed by using the 7.5- to 12-MHz transducer from the Olympus Corp. (Lake Success, NY). By filling the stomach with 300 to 600 mL of water, the normal gastric wall was imaged as a five-layered structure, and cancer was imaged as a hypoechoic disruption of those layers.

The ultrasound images were interpreted by a gastroenterologist at the time of the procedure. T1 cancers invade up to the submucosa, involving the first to third layers on EUS. T2 cancers invading the muscularis propria to the subserosa affect the fourth layer. T3 cancers penetrating the serosa disrupt the fifth layer, and T4 cancers invade adjacent organs or structures. The size and shape of identified lymph nodes led to characterizations of N stage. Hypoechoic, round, and well-demarcated nodes were considered malignant in accordance with published criteria.[7] Stage N2 was diagnosed when lymph node metastases were found >3 cm from the primary lesion.

Results from preoperative EUS were compared with postoperative pathologic staging results. The prognostic value of T stage and N stage and the preoperative risk category (low risk, T1/2N0; high risk, T3/4, any N, or any T, N1/2) as determined by EUS were then compared with the prognostic value of the same variables by pathologic evaluation by using survival curves generated by the Kaplan-Meier method. Survival estimates were compared by nonparametric analyses by using the log-rank test. Differences of $P < .05$ were considered significant. Statistical analysis was performed by using SPSS software (SPSS Inc., Chicago, IL).

RESULTS

One thousand seven hundred seventy-seven patients were admitted with the diagnosis of gastric cancer during the study period. Seven hundred seven patients underwent R0 resection. Two hundred ninety-six patients with gastric cancer underwent EUS followed by R0 resection. There was no intentional selection of patients for EUS; patients reported in this series had a stage distribution very similar to that of contemporary R0 patients who did not have EUS performed. Patients who had received neoadjuvant therapy (n = 71) were excluded. The remaining 225 patients comprise our study group. One hundred twenty-four patients had tumors involving the proximal third/gastroesophageal junction of the stomach, 53 had tumors involving the

TABLE 1. *Correlation between individual T stage by endoscopic ultrasonography (uT) and pathology (pT)*

Variable	pT0	pT1	pT2	pT3	pT4	All cases
uT0	1	5	0	0	0	6
uT1	2	41	8	0	0	51
uT2	2	13	23	8	1	47
uT3	2	8	39	62	4	115
uT4	0	0	1	3	0	4
All cases	7	67	71	73	5	223

TABLE 2. *Accuracy of individual T-stage prediction by EUS*

EUS stage	n	EUS correct	EUS understaged	EUS overstaged
uT0	6	1 (17%)	5 (83%)	–
uT1	51	41 (80%)	8 (16%)	2 (4%)
uT2	47	23 (49%)	9 (19%)	15 (32%)
uT3	115	62 (54%)	4 (3%)	49 (43%)
uT4	4	0	–	4
All cases	223	127 (57%)	26 (12%)	70 (31%)

EUS, endoscopic ultrasonography.

TABLE 3. *Accuracy of determining serosal invasion (T1/2 vs. T3/4) by EUS*

EUS stage	n	EUS correct	EUS understaged	EUS overstaged
UT0–2	104	95 (91%)	9 (9%)	–
UT3/4	119	69 (58%)	–	50 (42%)
All cases	223	164 (74%)	9 (4%) Sensitivity 88%	50 (22%) Specificity 66%

EUS, endoscopic ultrasonography.

body, and 48 had tumors involving the antrum. There was EUS T-stage information available on 223 patients and EUS N stage information available on 218 patients. Most patients were designated on ultrasonography as having either serosal disease (≥uT3; n = 119) or nodal involvement (≥uN1; n = 120).

Concordance with Pathology

We compared the individual EUS T stage with the pathologic T stage in this group (Table 1). The accuracy of the individual EUS T stage was 57% (127 of 223) overall. Seventy patients (31%) were overstaged and 26 (12%) were understaged for T stage by EUS. The accuracy for uT1 lesions was 80%, yet the accuracy for uT2 and uT3 lesions was 49% and 54%, respectively (Table 2). EUS demonstrated improved accuracy for identifying the presence of serosal disease (Table 3), with an improved overall accuracy of 74% (164 of 223; sensitivity, 88%; specificity, 66%; positive predictive value, 58%; negative predictive value, 91%). There was an insignificant trend toward improved accuracy when examining proximal gastric lesions (62%) versus distal lesions (49%; $P = .08$).

TABLE 4. *Correlation between individual N stage by endoscopic ultrasonography (uN) and pathology (pN)*

Variable	pN0	pN1	pN2/3	All cases
uN0	71	22	5	98
uN1	31	36	25	92
uN2	6	17	5	28
All cases	108	75	35	218

TABLE 5. *Accuracy of individual N stage prediction by EUS*

EUS stage	n	EUS correct	EUS understaged	EUS overstaged
uN0	98	71 (72%)	27 (28%)	–
uN1	92	36 (39%)	25 (27%)	31 (34%)
un2	28	3 (11%)	2 (7%)	23 (82%)
All cases	218	110 (50%)	54 (25%)	54 (25%)

EUS, endoscopic ultrasonography.

TABLE 6. *Accuracy of determining nodal positivity (N0 vs. N^+) by EUS*

EUS stage	n	EUS correct	EUS understaged	EUS overstaged
uN0	98	71 (72%)	27 (28%)	–
uN^+	120	83 (69%)	–	37 (31%)
All cases	218	154 (71%)	27 (12%) Sensitivity 75%	37 (17%) Specificity 66%

EUS, endoscopic ultrasonography.

The overall accuracy for individual N stage was 50% when compared with pathologic staging (Table 4). One hundred ten (50%) of 218 patients were staged correctly for N stage by EUS, with 54 patients (25%) being overstaged and 54 patients (25%) being understaged (Table 5). When assessing for the presence or absence of nodal disease, there was improved overall accuracy (71%; sensitivity, 75%; specificity, 66%; positive predictive value, 69%; negative predictive value, 72%; Table 6).

When evidence of serosal invasion was grouped with assessment of nodal positivity to assign a preoperative risk category, the overall concordance between EUS and pathology was 77% (sensitivity, 88%; specificity, 61%; positive predictive value, 76%; negative predictive value, 79%). On preoperative EUS assessment, 150 patients were deemed at high risk (≥uT_3, any N or any T, ≥uN_1). Of these, 36 patients (24%) were overstaged as high risk with low-risk

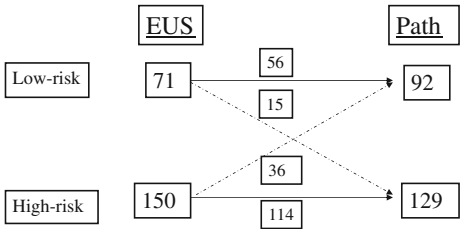

FIG. 1. Comparison of preoperative risk assessment on endoscopic ultrasonography (EUS) with postoperative pathologic results. Of 71 patients identified as low risk (T1/2N0) on EUS, 56 were correctly staged and 15 were understaged. Of 150 patients identified as high risk (T3/4, any N, or any T, N^+) on EUS, 114 were correctly staged and 36 were overstaged. Of 92 patients identified as low risk on pathology, 56 were correctly identified by EUS and 36 were previously overstaged. Of 129 patients identified as high risk on pathology, 114 were correctly identified by EUS and 15 were previously understaged.

pathology (Fig. 5). One hundred fourteen patients (76%) identified as high risk before surgery had high-risk pathologic results. Of 71 patients identified as low risk (≤uT2, N0) before surgery, 15 (21%) patients were understaged and had high-risk pathology. Fifty-six patients (79%) identified as low risk before surgery had low-risk pathology.

EUS Risk Assessment

When predicting outcome, EUS staging was less able to risk-stratify patients than traditional pathology based on individual T stage (Fig. 2). Notably, the outcome for EUS T2 was not significantly different from that for EUS T3. EUS staging did identify patients with serosal disease as higher risk compared with patients with nonserosal disease on preoperative EUS ($P = .01$; Fig. 3). The median survival for patients without serosal invasion on EUS was 104 months, compared with only 38 months for patients with preoperative evidence of serosal invasion ($P = .02$).

Similarly, EUS staging was less able than traditional pathology to risk-stratify patients on the basis of N stage (Fig. 4). The median survival for patients without nodal metastases on EUS was 57 months, compared with 44 months for those in whom nodal disease was detected on preoperative staging ($P = .2$).

The outcome was significantly different for patients identified as low risk (T0–2N0) on EUS compared with patients identified as high risk (T3/4 or N^+) on preoperative EUS (Fig. 5). The median survival for patients without serosal invasion or nodal involvement on ultrasonography was not reached, compared with a median survival of 41 months for patients with evidence of either serosal disease or nodal involvement ($P = .02$).

DISCUSSION

Patients with locoregionally advanced gastric cancer are at significant risk for recurrence and death after complete resection. Although postoperative chemoradiation therapy can reduce this risk, it does not eliminate it. Furthermore, postoperative adjuvant chemoradiation therapy is quite difficult for even the best postgastrectomy patients to tolerate. Because of this, other treatment schemes, especially preoperative (neoadjuvant) systemic chemotherapy with or without radiotherapy, are being investigated.[11–13] However, these regimens have associated toxicity and measurable morbidity. It would therefore be desirable to select patients at high risk for recurrence while minimizing unnecessary treatment for patients at low risk.

Over the last 10 years, EUS has been used as a standard to preoperatively stage patients with gastric carcinoma and to identify patients at high risk of recurrence for enrollment in neoadjuvant protocols. In a previous report from our institution, Smith et al.[8] examined the first 50 patients who underwent preoperative EUS for staging of gastric carcinoma. The concordance of EUS T stage with pathologic T stage in these patients was 86%. The authors observed that patients with uT3 or T4 primary tumors were at high risk for early postoperative recurrence after curative resection. Among contemporary series, however, the optimal criteria for determining high risk by EUS remain to be defined.

In this study, EUS had lower than expected concordance with individual pathologic T and N stages. We did not find the high overall accuracy for preoperative staging that has been described by other authors.[14] Some of these differences are methodological. Prior reports have used pathologic staging as the gold standard and looked back to assess the accuracy of EUS. Our methodology focused on the predictive accuracy of information available before surgery. For example, in this study, among 73 pathologic T3 tumors, 62 (85%) were correctly identified by EUS. However, among 115 EUS T3 tumors, only 62 (54%) were pathologic T3 tumors. Similarly, using the methodology of prior studies, among 129 patients with high-risk pathology (serosal or nodal invasion), EUS identified 114 (88%). By using our method of calculation of predictive accuracy of EUS, among the 150 patients deemed at high risk by EUS, 114 (76%) had high-risk pathology.

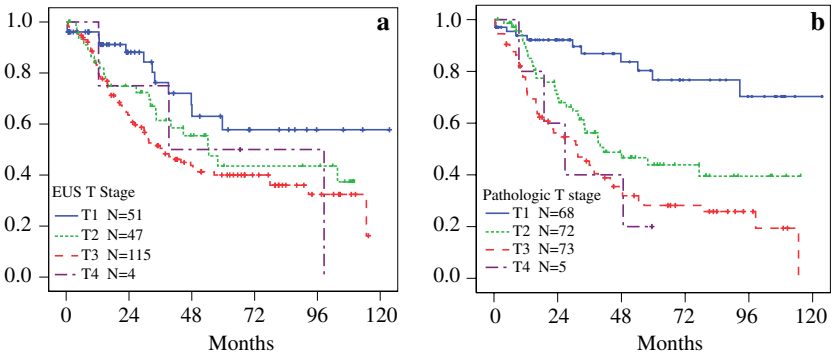

FIG. 2. Outcome by individual endoscopic ultrasound (EUS) T stage (**A**) compared with pathologic T stage (**B**).

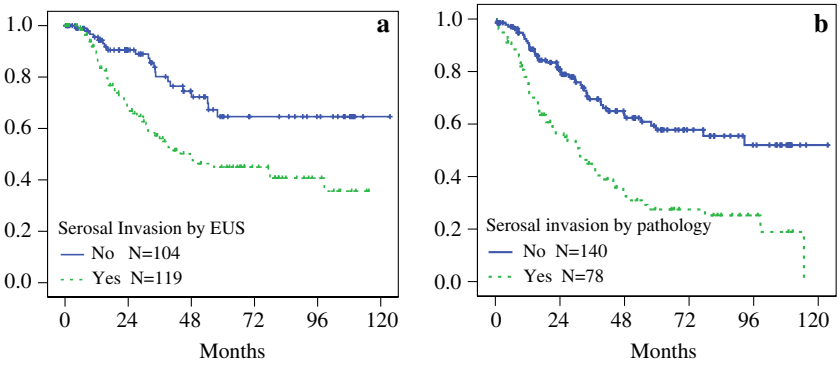

FIG. 3. Outcome by endoscopic ultrasonography (EUS): serosal invasion (**A**) compared with pathologic serosal invasion (**B**).

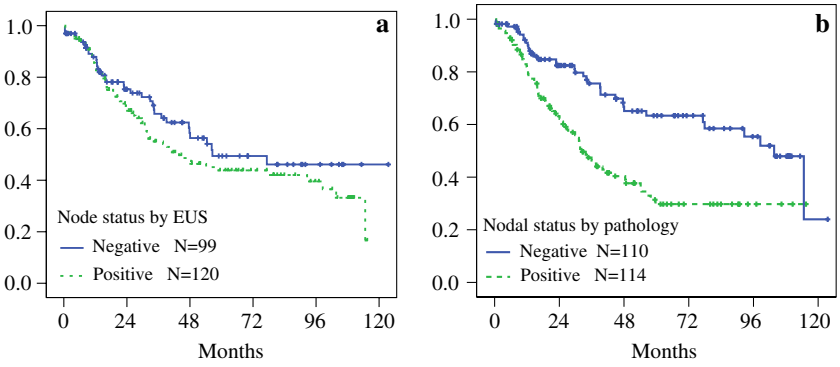

FIG. 4. Outcome by endoscopic ultrasonography (EUS): nodal status (**A**) compared with pathologic nodal status (**B**).

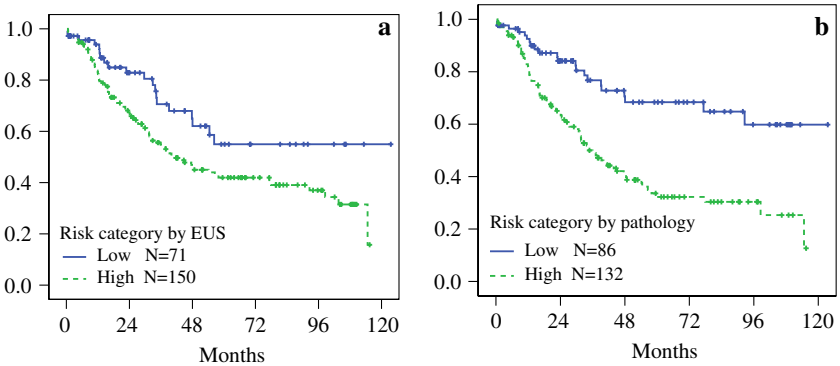

FIG. 5. Outcome by endoscopic ultrasound (EUS) risk category (**A**) compared with pathologic risk category (**B**). Low risk, T1/2N0; high risk, T3/4, any N, or any T, N1/2.

This study highlights the difficulty in distinguishing between T2 and T3 gastric cancers by using EUS. The serosa of the stomach is very thin in some areas, and even the pathologist handling a resected specimen may have difficulty distinguishing isolated sites of a cancer that extends through the muscularis propria into the subserosa (T2) from one that penetrates the serosa (T3). A tumor that penetrates fully into the perigastric fat along the lesser curvature without breaching the peritoneum is technically called T2. The inflammation and fibrosis associated with ulcerated lesions can be difficult to distinguish from tumor, thus leading to EUS overstaging. Furthermore, all serosal lesions will not have the same influence on outcome.[15] Minor degrees of invasion are less likely to be associated with poor outcome than the type of extensive serosal invasion seen with extensively and deeply infiltrating linitis-type cancers. Other potential sources of error in EUS assessment, including the primary tumor site, are currently under investigation.

Ultimately, the correlation of EUS T and N stage with pathology is less important that the ability of this pretreatment diagnostic tool to identify patients at high risk of recurrence after curative resection—patients who would be candidates for neoadjuvant chemotherapy. Patients with serosal invasion had a significantly worse prognosis than patients with less advanced lesions. However, when looking at prognosis by individual EUS T stage, there was a remarkable similarity between EUS T2 and EUS T3 tumors. This suggests that, although serosal penetration is a very important pathologic predictor of outcome, this may not be the optimal threshold for EUS risk assessment. We are currently investigating whether distinguishing the more superficial EUS muscularis propria T2 tumors from deeper EUS T2 tumors invading to the subserosa will lead to better preoperative prognostic discrimination into low- versus high-risk groups. Similarly, although individual EUS N stage is of very limited value in preoperative risk assessment, combined assessment of depth of tumor penetration and nodal positivity on EUS not only had the highest concordance with pathology, but also identified patients at the highest risk for death from gastric cancer.

This is the largest of the contemporary series considering the relationship of EUS staging to survival for patients with gastric cancer. This study is relevant for evaluating ongoing neoadjuvant chemotherapy trials at our institution and others. This not only gives the clinician information necessary for consenting patients for enrollment into neoadjuvant trials, but also enhances the value of the discussion of prognosis before surgery, before pathologic results are obtained. EUS is more sensitive than specific for serosal invasion or nodal disease. This allows for the tendency to overstage and overestimate risk with EUS. In this study, with our current thresholds, one third of patients (36 of 92) with low-risk pathology (no serosal or nodal disease) would have been eligible for neoadjuvant chemotherapy. This must be taken into account when the treatment effects of ongoing neoadjuvant protocols are interpreted.

In conclusion, by using EUS and its ability to characterize disease, most high-risk patients are identified. EUS risk assessment thresholds may be refined to increase the predictive value of this preoperative investigation even further.

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