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DOES ENDOSCOPIC ULTRASOUND IMPROVE DETECTION OF LOCALLY RECURRENT ANAL SQUAMOUS CELL CANCER?

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Abstract

Background—Evaluating patients for recurrent anal cancer after primary treatment can be difficult due to distorted anatomy and scarring. Many institutions incorporate endoscopic ultrasound to improve detection, but the effectiveness is unknown.

Objective—To compare the effectiveness of digital rectal exam and endoscopic ultrasound during routine follow-up of anal cancer patients in detecting locally recurrent disease.

Design—Retrospective, single-institution review

Settings—Oncologic tertiary referral center

Patients—175 patients with nonmetastatic anal squamous cell cancer without persistent disease after primary chemoradiotherapy who had at least one post-treatment ultrasound and examination by a colorectal surgeon.

Main Outcome Measures—First modality to detect local recurrence, concordance, crude cancer detection rate, sensitivity, specificity, and predictive value.

Results—855 endoscopic ultrasounds and 873 digital rectal exams were performed during 35 months median follow-up. Overall, ultrasound detected 7 (0.8%) mesorectal and 32 (3.7%) anal canal abnormalities; digital exam detected 69 (7.9%) anal canal abnormalities. Locally recurrent disease was found on biopsy in 8 patients, all detected first or only with digital exam. Four patients did not have an ultrasound at the time of diagnosis of recurrence. The concordance of

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ultrasound and digital exam in detecting recurrent disease was fair at 0.37 (SE 0.08, 95% CI 0.21-0.54) and there was no difference in crude cancer detection rate, sensitivity, specificity, and negative or positive predictive values.

Limitations—The heterogeneity of follow-up timing and exams is not standardized in this study but is reflective of general practice.

Conclusions—Endoscopic ultrasound did not provide any advantage over digital rectal examination in identifying locally recurrent anal cancer, and should not be recommended for routine surveillance.

Keywords

Anal squamous cell carcinoma; Local recurrence; Endoscopic ultrasound; Digital rectal exam; Surveillance; Chemotherapy

Introduction

Anal cancer is a rare malignancy, with approximately 7,000 new cases diagnosed in 2013.¹ Treatment of anal squamous cell carcinoma (SCC) with modern combined chemoradiation therapy (CRT) results in a 5-year overall survival in excess of 70%, with locoregional recurrence rates of 20%.^{2,3} In our own series, the most common site of locoregional recurrence was within the anal canal and, while 5-year survival rates were reported to be 33%, surgery remains the only curative option after recurrence.⁴ Therefore, aggressive evaluation of the anal canal has been adopted as part of standard surveillance.

One of the primary goals of follow-up after treatment is the identification of disease within the anal canal; however, the anatomy may be distorted, and distinguishing residual fibrotic scar from invasive recurrent disease can be challenging. Endoscopic ultrasound can demonstrate a decrease in tumor volume during and immediately after CRT.⁵ Therefore, transanal endoscopic ultrasound (EUS) during routine follow-up after primary treatment has been proposed as a strategy to improve the detection of recurrent anal SCC, and potentially improve survival with early salvage surgery.

The clinical practice at our institution has encouraged routine evaluation with EUS for patients before and following primary combined modality treatment for anal carcinoma for some time. However, we observed within the practice that most recurrences may have been detected on digital exam prior to performing the EUS, making the EUS unnecessary. We sought to evaluate the effectiveness of digital rectal examination (DRE) and EUS in determining the presence of recurrent anal SCC following primary treatment. We hypothesized that EUS does not improve the identification of patients with recurrent disease compared to physical examination and DRE alone.

Materials and Methods

An informed consent waiver approval from the Institutional Review Board was obtained for a retrospective chart review of patients followed at Memorial Sloan Kettering Cancer Center after treatment of primary anal SCC. Patients were identified from a prospectively

maintained database of all patients undergoing EUS in the outpatient setting between January 1, 1998 and October 31, 2012. Patients were included if they met the following criteria: a pathologic diagnosis of primary invasive anal canal or anal margin squamous cell carcinoma, a minimum of one EUS performed at our institution, a minimum of one follow-up visit at our institution after completion of multi-modality treatment for primary anal SCC. Patients with persistent disease, defined as recurrence or incomplete response within six months of completing CRT, were excluded, as they had a persistent mass that was being followed by DRE.

While there is some variation, the colorectal surgeons follow patients beginning at 2-3 months post-treatment, every 3-4 months for the next 2 years, and every 6-12 months thereafter. At 5 years post-treatment without evidence of disease recurrence, patients are eligible for annual follow-up. At each visit a DRE is routinely performed. The use of EUS and/or anoscopy at each follow-up visit has varied between practitioners and ranges from infrequent use for specific indications to routine use at each visit. Random surveillance biopsies are not performed by any of the colorectal surgeons. Interval imaging studies are performed post-treatment and at 6-month intervals. Abnormal symptoms or exam findings prompt earlier imaging and biopsy.

Our practice is to perform DRE immediately prior to proctoscopy and EUS, with findings recorded in real-time by an assistant. Endoscopic ultrasounds are performed using BK Medical Profocus (Peabody, MA, USA) 2Dimension 10 MHz endoanal probes. Patients are placed in the left lateral decubitus position, and 40cc sterile water is instilled into the balloon in order to image the mesorectum for adenopathy. This is followed by removal of the water and a hard plastic cap is then used on the probe for examination of the anal canal.

Data was extracted from chart review regarding demographic information, pathologic results, treatment administered, and outcomes. Follow-up visits with the colorectal surgeon were reviewed for physical exam, DRE, and EUS results. Follow-up was defined as the time from completion of primary treatment to last clinic visit with the colorectal surgeon. Abnormal DRE was defined as any documented discrete abnormality or perceived change from previous exam findings, excluding those clearly documented as “post-treatment scar.” An abnormal EUS was defined as any documented abnormal lesion, increase in thickness, size or depth of abnormality compared to previous findings, or lymph nodes greater than 5mm in size, excluding those clearly documented as “post-treatment scar or fibrosis” or unchanged from previous exam. Independent blinded review of a subset of DRE and EUS reports was performed to assess bias and internal validity, and was acceptable with <10% discrepancy.

Recurrence was defined by pathologic biopsy, excluding anal PAP, except where biopsy results were unavailable or clinical treatment for recurrent disease was instituted without pathologic confirmation. After chart review, patients were classified into one of two categories: No Recurrence, which included patients with no evidence of disease after primary treatment; or Recurrence, which included patients who developed evidence of recurrent disease—either local, nodal, or distant—more than 6 months after completion of

primary treatment. Only first recurrences were evaluated; subsequent recurrences were not measured in this study.

Statistical analysis for comparison of demographic data between the No Recurrence and Recurrence groups was conducted with Students' *t*-test. To determine the degree of agreement between DRE and EUS, an unweighted Cohen's *kappa* statistic, a conservative estimate of the concordance, was calculated. All statistical analysis was performed on SPSS v.22 (Armonk, NY, USA). The crude cancer detection rate was calculated as the number of true positive tests divided by the number of tests performed per person-year of follow-up. When evaluating the sensitivity, specificity, negative and positive predictive values, patients with short follow-up (i.e. 18 months, n=42) and/or no post-treatment EUS (n=17) were excluded to control for false negative examinations. Comparison of the >18 month follow-up group to the original sample did not demonstrate any demographic differences on Student's *t*-test (data not reported).

Results

A total of 368 patients were seen at our institution during the allotted time period and underwent at least one EUS; 80 patients were followed outside our institution and were therefore excluded, and 94 patients were excluded for a diagnosis other than nonmetastatic invasive anal squamous cell cancer. 194 patients met our inclusion criteria; of these patients, 19 patients were excluded from further analysis for persistent disease. Thus, 175 patients in the Recurrence and No Recurrence groups were included for analysis. Table 1 shows the patient demographics. Seventeen (10%) patients developed recurrent disease. There was no statistical difference in the average age, gender, or the proportion of patients with HIV between the groups, though there is a trend for more men among those with recurrent disease. The groups all had similar rates of primary treatment modality with CRT. The Recurrence group was more likely to have advanced disease, as measured by the AJCC Stage at diagnosis ($p < 0.01$).

873 DREs were performed during the 35-month median follow-up period; 69 (7.9%) were recorded as abnormal. A total of 855 EUS exams were performed, including 32 (3.7%) abnormal exams; 25 of these showed abnormal anal canal findings and 7 demonstrated abnormal mesorectal lymph node findings. Patients without recurrence underwent an average of 4.9 EUS studies during the follow-up time period, while patients with recurrence underwent 2.9 EUS. There were 17 patients who had no EUS performed following primary treatment, most often because of intolerance to the exam.

The location and patterns of recurrent disease in our cohort can be seen in Table 2. Eight patients developed an anal canal recurrence, one patient developed a regional iliac nodal recurrence, and seven patients developed distant recurrence. One additional patient had synchronous inguinal lymph node and distant recurrence. No patient with nodal or distant recurrence had synchronous local recurrence.

The first modality for detection of anal canal recurrence in all cases was DRE (Figure 1A), while all nodal and distant recurrences were first detected with CT or PET imaging (Figure

1B). No local or nodal recurrences were detected first by EUS. Approximately 75% of the anal canal recurrences arose within 21 months after completion of treatment. A total of 40 anal canal biopsies were performed in 33 patients, of which 32 were negative and eight positive for malignant disease. Of the eight patients with local recurrence, four did not undergo an EUS at the time of local recurrence; however, all had abnormal DRE, which prompted the biopsy. Three patients had their first post-treatment visit with a colorectal surgeon more than six months after completing CRT, and were found to have local recurrence (Table 3). Two patients with local recurrence had previous negative DRE and EUS exams, and three patients had previous positive DRE and EUS exams with negative biopsies.

The concordance of DRE and EUS in detecting abnormal results in patients, when performed at the same visit, was fair ($\kappa = 0.37$ (95% CI 0.21-0.54, Table 4). To estimate the ability of each test to detect recurrent disease, we calculated the crude cancer detection rate per person-year of follow-up. There were a total of 6370 months of follow-up in our cohort, resulting in 530.8 person-years. For DRE, there were eight true positive tests and 1.64 DRE per person-years; for EUS, there were four true positives and 1.61 per person-years. The crude cancer detection rate was 4.9% for DRE and 2.5% for EUS. We sought to evaluate the sensitivity and specificity of DRE and EUS in detecting recurrences by performing two separate analyses. First, we evaluated all test performed in all patients, demonstrating poor sensitivity and positive predictive value but excellent specificity and negative predictive value (see Table 5). We recognize that including all tests on any given patient biases our interpretation of the data as it assumes all earlier tests done in patients who eventually had local recurrence were falsely negative. Thus, we performed a second analysis including only those tests done at the time of biopsy, with positive biopsy results being the standard (see Tables 6 and 7). The results for this analysis are reported in Table 8. The results reflect that both tests are equally good at detecting the presence of an abnormality within the anal canal, but are less accurate at differentiating benign from recurrent disease. Even the gold standard test, local biopsy, may have a false negative rate as two patients who had local recurrence had previous negative biopsies (see Table 3).

Table 8 shows the long-term outcomes for the patients included. The results for all patients treated at our institution after primary treatment and salvage surgery have been reported previously.^{4,6,7} In patients who developed recurrence, 9 (53%) are currently alive without evidence of disease after salvage treatment, 2 (12%) are currently alive with disease, undergoing active treatment, and 6 (35%) have succumbed to their disease.

Discussion

In this retrospective study of our institution's experience following 175 nonmetastatic anal squamous cell carcinoma patients, we evaluated 855 synchronously performed DRE and EUS over a median of 35 months, and found no recurrences identified by EUS that were not evident on DRE. Not a single case of locally recurrent disease that had been missed on DRE was subsequently detected by EUS. Furthermore, DRE and EUS were found to have similar crude cancer detection rates, sensitivities, specificities and predictive values, along with fair concordance between exams. Our results also suggest that both DRE and EUS are poor at

differentiating tumor from residual scar tissue, but have excellent negative predictive values. Given the increased cost of EUS, potential exposure to latex, and the discomfort experienced by patients during the exam, there was no evidence in our cohort to support the routine use of EUS for surveillance in all patients after primary treatment of anal squamous cell cancer.

Our study is the largest single institution cohort of patients followed for recurrence of anal squamous cell cancer to date, and as such we were able to closely analyze and compare the impact of different surveillance strategies. EUS is a technically challenging study to perform and the results can vary significantly, depending on operator and interpreter experience; at our institution, EUS is frequently used for both anal and rectal cancers, and a dedicated full-time support technician with years of experience performing and interpreting EUS is present for assistance. The sequence of performing DRE and EUS is standardized at our institution and results are recorded in real-time, reducing recall and reporting bias in our cohort. Therefore, our results represent the best case in ascertaining the ability of EUS to detect recurrence; these results may not be generalizable to most clinical practices.

Due to the nature of our institution as an oncologic referral center, patients may have been lost to follow-up, and some recurrences may not be included in our analysis, thereby biasing our results. In addition, because of the variability in the use of EUS for surveillance within our group, 50% of patients did not undergo an ultrasound at the time of diagnosis of their recurrence, and 17 patients had no EUS post-treatment. While these factors may have contributed to discrepancies in outcomes, they do accurately reflect general clinical practice outside of the rigorous structure seen in many clinical trials, and could be considered more generalizable. Moreover, the majority of local recurrences were identified within 21 months and, as such, at least 70% of the cohort was adequately followed for this endpoint. We were not able to discern a role for EUS in detecting malignant mesorectal lymph nodes, a feature which would seem perfectly suited to this modality. In our series, mesorectal lymphadenopathy on EUS was an infrequent finding (seven patients), and did not predict clinical or pathological recurrence in the mesorectal lymph nodes during follow-up or at resection. The use of EUS in the presence of persistent disease and partial response to primary treatment was not assessed in this study; thus, we cannot exclude the possibility that EUS may be helpful for this purpose.

There are limited data on EUS in the follow-up of anal SCC. EUS was first proposed as a follow-up strategy in 1994, after a case series reported increasing tumor volume observed on EUS in a patient with recurrent anal SCC.⁵ This was followed by a larger series of 25 patients where complete tumor resolution was seen in only two patients; the remaining 23 patients had hyperechoic, indeterminate wall thickening that was confirmed as recurrence in two patients, suggesting that EUS had poor specificity.⁸ Conversely, other studies have shown that EUS is able to successfully differentiate fibrotic post-treatment changes from recurrent disease, with specificities ranging from 57% to 100%; however, the authors included only patients with suspicious exam findings, thus introducing bias.^{9,10} The addition of color Doppler or 3-D ultrasound technologies has also been shown to increase the sensitivity and specificity of EUS for detecting recurrent disease in a fibrotic scar; however, these procedures require a high-level of training and skill to interpret, and would not be appropriate for widespread use.^{11,12} Lund *et al.*,¹³ who examined their experience with 82

patients who were followed after primary treatment, had findings similar to ours. In their series spanning 16 years, 14 patients developed local recurrence, none of which were detected solely on EUS, and all had recurrence detected on digital and/or visual examination.¹⁴

In a previous report from our institution, a failure-free survival at 5 years of 65% for patients after primary treatment for anal SCC was identified. Patients with higher T-stage tumors, and those who failed to complete their course of radiation therapy, were at increased risk of recurrence.⁷ The current study also found an association with advanced tumors and recurrent disease, though we did not evaluate the rate of completion of CRT. Our finding that recurrence in the anal canal was the most common location of locoregional recurrence is consistent with our previously reported series, as well as the findings of larger randomized trials.^{2,6} Therefore, a strategy to identify these patients early to facilitate optimal treatment intervention may have a meaningful impact on long-term outcomes.

Current practice parameters and guidelines do not endorse routine use of any imaging strategy for local surveillance in the post-treatment surveillance period, but suggest consideration in select cases such as advanced tumors or nodal disease pretreatment.¹⁵⁻¹⁷ We did not specifically evaluate the efficacy of anoscopy, an examination that is advocated by both the ASCRS and NCCN guidelines, as it is performed simultaneously with EUS in our practice; therefore, separating the reporting of results to reduce bias is not possible.^{15,17} In our opinion there is little evidence that anoscopy detects additional recurrent disease in our cohort that would not otherwise be palpable on DRE. This examination may be a useful adjunct for practitioners with less experience performing DRE, and should be evaluated in future studies. PET/CT is increasingly used for radiation oncology follow-up in this setting and warrants further investigation, though small lesions and recurrences may still be below the threshold of detection. Furthermore, pelvic MRI can provide detailed anatomic information but fails to differentiate recurrence from benign scarring. Our practice has reserved the use of MRI for evaluating the extent of invasion and resectability in patients in whom recurrence is already documented.

These results have already led to a change in our approach to patients, with fewer EUS exams performed. In general, we reserve its use for patients with suspected mesorectal nodes, who may have the most to gain. As new technology continues to be developed to improve patient care in a variety of ways, these types of studies evaluating the effectiveness of different modalities, strategies, and treatments will become increasingly important. Identifying the situations and settings in which a particular test or treatment will have the most impact is a critically important element in maintaining a vibrant health care economy. Fortunately, recurrence of anal squamous cell cancer is infrequent; however, it can have a devastating impact on quality of life and survival. Future studies aiming to improve the detection of recurrent disease via functional analyses or targeted microscopic imaging may have a significant impact on our treatment of these patients.

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Figure 1.

A representation of the first modality on chart review to document recurrent disease. A. The first modality to detect local recurrences. B. The first modality to detect nodal and distant recurrences.

Demographic information for patients included who had undergone primary treatment for anal squamous cell cancer and were followed at our institution with at least one endoscopic ultrasound.

Table 1

	Total	No Recurrence	Recurrence	p-value
Number	175	158 (90%)	17 (10%)	
Ave. Age	60	57	62	0.10
Women	135 (77%)	123 (78%)	12 (71%)	0.06
HIV+	14 (8%)	12 (8%)	2 (12%)	0.13
CRT	159 (91%)	144 (91%)	15 (88%)	0.91
Initial AJCC Stage				<0.01
Stage I	33 (19%)	33 (100%)	0	
Stage II	55 (32%)	51 (95%)	4 (5%)	
Stage III	85 (49%)	72 (85%)	13 (15%)	

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Table 2

Frequency of location of recurrent anal squamous cell cancers.

	Number
Anal canal	8
Mesorectal Lymph Nodes	0
Iliac Lymph Node	1
Inguinal Lymph Node	1
Distal	8
Total	18

Table 3

Biopsy results for patients during follow-up.

Exam Performed at Detection of Recurrence	Positive At First Post-CRT Exam (>6mo)	Previous Negative DRE & Negative EUS	Previous Positive DRE & Positive EUS with Negative Biopsy
DRE alone	2	1	1
EUS alone	0	0	0
DRE + EUS	1	1	2

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Table 4

Characteristics of patients with local recurrence.

	Negative EUS	Positive EUS	Total
Negative DRE	784	14	798
Positive DRE	39	18	57
Total	823	32	855

Table 5

Frequency of abnormal digital rectal exams and endoscopic ultrasounds in paired tests performed during the same follow-up visit.

	Crude Cancer Detection Rate	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
DRE (95% CI)	4.9%	0.35 (0.15-0.61)	0.94 (0.93-0.96)	0.13 (0.05-0.27)	0.98 (0.97-0.99)
EUS (95% CI)	2.5%	0.29 (0.11-0.56)	0.98 (0.96-0.99)	0.22 (0.08-0.44)	0.98 (0.97-0.99)

Table 6

Comparison of digital rectal exam and endoscopic ultrasound effectiveness at diagnosing recurrent anal squamous cell cancer (negative vs. positive biopsy) (95% confidence interval in parentheses).

	Negative Biopsy	Positive Biopsy
Negative DRE	7	0
Positive DRE	19	11
Negative EUS	14	0
Positive EUS	6	6

Table 7

Comparison of digital rectal exam and endoscopic ultrasound effectiveness at diagnosing recurrent anal squamous cell cancer (sensitivity, specificity, PPV, NPV) (95% confidence interval in parentheses).

	Sensitivity	Specificity	PPV	NPV
DRE (95% CI)	1.0 (0.6-1.0)	0.35 (0.16-0.6)	0.38 (0.19-0.61)	1.0 (0.56-1.0)
EUS (95% CI)	1.0 (0.52-1.0)	0.7 (0.46-0.87)	0.5 (0.22-0.78)	1.0 (0.73-1.0)

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Table 8

Long-term outcomes of patients in our cohort.

	No Recurrence	Recurrence	Total
Total Patients	158	17	175
No Evidence of Disease	147 (93%)	9 (53%)	156 (89%)
Alive With Disease		2 (12%)	2 (1%)
Deceased of Other Causes	11 (7%)	0	11 (6%)
Deceased Of Disease		6 (35%)	6 (3%)