

ORIGINAL ARTICLE

Use of a new jumbo forceps improves tissue acquisition of Barrett's esophagus surveillance biopsies

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Background: The major risk factors for the development of esophageal adenocarcinoma remain long-standing GERD and resultant Barrett's esophagus (BE). Finding the exact method of adequate tissue sampling for surveillance of dysplasia in BE remains a dilemma.

Objective: We prospectively compared standard large-capacity biopsy forceps with a new jumbo biopsy forceps for dysplasia detection in BE.

Setting/Design: Prospective, single-center investigation.

Patients/Interventions: We prospectively enrolled 32 patients undergoing surveillance endoscopy for BE. Biopsy samples were obtained in paired fashion alternating between the experimental (jumbo) and control (large-capacity) forceps.

Main Outcome Measurements: Each sample was assessed for histopathology, specimen size, and adequacy.

Results: A total of 712 specimens were available for analysis for this investigation. Six patients were found to have dysplasia, and in 5 of those patients, the dysplasia was only detected with the jumbo forceps. The mean width was significantly greater in the Radial Jaw 4 jumbo group (3.3 mm vs 1.9 mm [$P < .005$]) as was the mean depth (2.0 mm vs 1.1 mm [$P < .005$]). Sixteen percent of samples obtained with the standard forceps provided an adequate sample, whereas the jumbo forceps provided an adequate sample 79% of the time ($P < .05$).

Limitations: A lack of a validated index for assessment of tissue adequacy in BE.

Conclusion: The Radial Jaw 4 jumbo biopsy forceps significantly improves dysplasia detection and adequate tissue sampling in patients undergoing endoscopy for BE. (Gastrointest Endosc 2009; ■:■-■.)

The increase in the incidence of esophageal adenocarcinoma since 1970 is remarkable and surpasses that of both breast and prostate cancers.¹ The major risk factors for the development of esophageal adenocarcinoma remain long-standing GERD and resultant Barrett's esophagus (BE).^{2,3} Prolonged acid reflux results in transformation in the squamous epithelium of the esophagus to the special-

Abbreviations: BE, Barrett's esophagus; DGS, depth grade scale; HGD, high-grade dysplasia; IBD, inflammatory bowel disease; LGD, low-grade dysplasia; RJ3, Radial Jaw 3; RJ4, Radial Jaw 4.

DISCLOSURE: The forceps for this investigation were provided by the Boston Scientific Corporation. The following author disclosed financial relationships relevant to this publication: S. Komanduri: Speaker for Boston Scientific; consultant for Tap Pharmaceuticals. All other authors disclosed no financial relationships relevant to this publication.

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0016-5107/\$36.00
doi:10.1016/j.gie.2009.04.009

ized intestinal metaplasia, which is the hallmark of BE. Patients with BE are at risk of the development of dysplasia and the genetic alterations necessary for the development of adenocarcinoma.^{4,5} The annual progression of BE to adenocarcinoma is estimated at 0.5% per year.^{6,7} Despite advances in surgical techniques, the 5-year survival rate for esophageal adenocarcinoma remains near 20%.^{8,9}

Because of the alarming increase in the incidence and poor outcomes of esophageal adenocarcinoma, there has been a shift in focus toward improving preventive strategies. Patients with a diagnosis of BE are placed in a long-term endoscopic surveillance program. Current surveillance guidelines recommend a 3-year interval for non-dysplastic BE, a 6-month to 1-year interval for low-grade dysplasia (LGD), and therapeutic intervention or a 3-month interval for high-grade dysplasia (HGD).^{7,10} One of the main challenges for monitoring patients with BE is in the technique of endoscopic surveillance used to detect dysplasia. Dysplasia may develop in any area of

BE and may endoscopically appear flat and inconspicuous. Typical endoscopic biopsies therefore rely on random tissue samples to detect dysplasia and have been associated with a high sampling error rate.¹¹ It seems that the major reason for this deficiency is inadequate tissue acquisition.¹¹⁻¹³ For example, in patients with HGD who underwent esophagectomy, 30% to 40% were found to have invasive adenocarcinoma on resected esophageal specimens.¹⁴ Recent data also confirm that systematic 4-quadrant sampling improves detection of BE and early cancers.¹¹ Peters et al⁷ retrospectively assessed patients with early esophageal adenocarcinoma, all of whom were part of a long-standing surveillance program. They found that 21% had never had a previous biopsy that demonstrated dysplasia. This group of patients was found to have a median biopsy percentage of 23% of the Seattle Protocol.⁷ Therefore, systematic biopsy protocols appear to detect more dysplastic areas likely secondary to an increased number of samples or greater surface area sampled.

The exact method of adequate tissue sampling in surveillance of BE remains a dilemma. There has been a limited amount of data on the efficacy of larger or jumbo biopsy forceps in obtaining adequate tissue specimens and dysplasia detection rates.¹⁵ We hypothesize that obtaining larger samples per biopsy will result in increased dysplasia detection. To this end, we prospectively compared the standard Radial Jaw 3 (RJ3) (large-capacity biopsy forceps Boston Scientific Corp, Natick, Mass) with the new Radial Jaw 4 (RJ4) (Boston Scientific Corp) jumbo biopsy forceps for dysplasia detection, specimen adequacy, and safety.

PATIENTS AND METHODS

Study population

This prospective, single-center investigation was performed over 6 months in 2007. During this period, the principal investigator (S.K.) saw 54 patients with BE. Of these patients, 34 met inclusion criteria. Two patients, who originally consented, ultimately declined participation at the time of endoscopy. Subsequently, we prospectively enrolled 32 patients undergoing surveillance endoscopy for BE in this study. All patients had been in an active surveillance program that used a 4-quadrant 2-cm protocol. All patients had nondysplastic BE on their last surveillance endoscopy, performed approximately 3 years earlier. Patients were seen and recruited by the principal investigator during their routine clinic visit. Subjects were included in the study if they met the following criteria: (1) a history of BE without dysplasia in our surveillance program, (2) older than the age of 18, and (3) provision of informed consent. Subjects were excluded from study eligibility if they met the following criteria: (1) unable or unwilling to provide informed consent and

Capsule Summary

What is already known on this topic

- Following a systematic 4-quadrant biopsy protocol improves tissue sampling in Barrett's esophagus (BE), likely through a greater number of specimens and surface area sampled. However, the optimal technique for tissue acquisition in BE is still unclear.

What this study adds to our knowledge

- In this prospective study, a new jumbo forceps (Radial Jaw 4) improves dysplasia detection in surveillance of BE.
- Use of the Radial Jaw 4 jumbo biopsy forceps provides a significantly larger number of adequate specimens than standard forceps with no change in safety profile.

(2) endoscopy revealed any nodularity, ulceration, or mass lesions. All patients were contacted 1 week after endoscopy to discuss biopsy results and assess for complications. This study was approved by the human subjects review board at our institution.

Endoscopy biopsy protocol

After informed consent was obtained, all patients, under conscious sedation, underwent endoscopy per routine at our institution. All endoscopies were performed by a single endoscopist (S.K.) with expertise in BE. A standard upper endoscope (Olympus America, Center Valley, Pa) was used for all endoscopies. Biopsy samples were obtained in paired fashion alternating between the experimental (RJ4 jumbo) and control (RJ3 large capacity) forceps in 4-quadrant fashion at 2-cm intervals (Fig. 1). Two specimens, 1 with each type of forceps, were obtained at every site sampled. One specimen was obtained per pass of the forceps. Because of a differential in size of each forceps catheter, blinding of the endoscopist was not possible. The order of forceps was alternated for each site sampled. Each sample was placed in a separate bottle and labeled for interval (in centimeters) and forceps used (8 bottles per interval sampled). The bottles were labeled by our research coordinator, who used a coding system corresponding to our control and experimental forceps. The bottles were otherwise labeled per routine with interval (in centimeters) and location (esophagus). On completion of the study, patients continued in their surveillance program per routine. If dysplasia was detected during this study, the appropriate change in surveillance intervals or management was made.

Biopsy forceps

Our control for this investigation was the RJ3 large-capacity forceps (Boston Scientific Corp) (one of the most commonly used forceps for surveillance biopsies), and the experimental forceps was the RJ4 jumbo biopsy

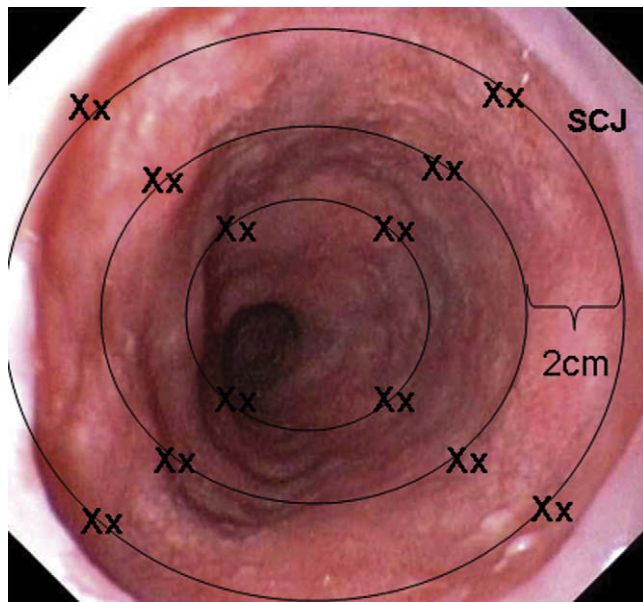


Figure 1. Endoscopic biopsy protocol. X, RJ4 jumbo forceps biopsy; x, RJ3 large-capacity forceps biopsy; SCJ, squamocolumnar junction.

forceps (Boston Scientific Corp). **Figure 2** provides an image of both forceps and their corresponding open-mouth diameter and jaw width. Although both forceps have nearly the same open-mouth diameter (jumbo 8.8 mm vs control 8.6 mm), the jaw width is significantly larger for the jumbo forceps (jumbo 2.84 mm vs control 2.14 mm). Both forceps have U.S. Food and Drug Administration classification as a class I device and are exempt from the premarket notification and/or good manufacturing practices regulation. To overcome the potential for dysplasia to be removed by 1 set of forceps and therefore not by the other set, we excluded all patients with mucosal abnormality, alternated the order of forceps, and adhered to a strict 4-quadrant protocol.

Clinical data

A chart review was performed for all enrolled subjects. Demographic characteristics including age, race, and sex were recorded. Other parameters recorded included presence or absence of GERD symptoms, use of a proton pump inhibitor, duration of disease, Prague classification of intestinal metaplasia, presence of hiatal hernia, body mass index, and tobacco use. The number of previous endoscopies and findings from these examinations were also recorded. All data were collected and maintained in our password-protected database.

Outcome measures

Our primary outcome measure was dysplasia detection. Our secondary outcome measures included specimen size, specimen adequacy, and safety.

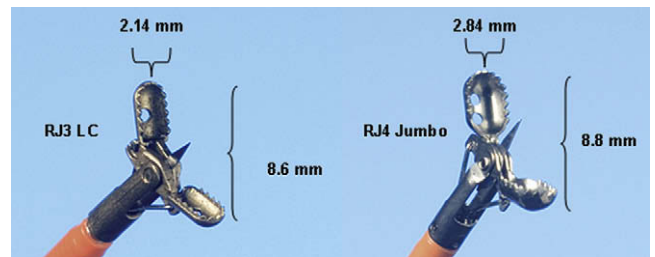


Figure 2. RJ3 large-capacity and RJ4 jumbo forceps. Illustration depicts open-mouth diameter (8.6 mm vs 8.8 mm) and jaw width (2.14 mm vs 2.84 mm).

Pathological assessment

One GI pathologist (S.J.) evaluated each sample for our primary and secondary outcomes. Evaluation for dysplasia was performed on specimens per our institution's routine, and for this investigation, 1 of 2 other GI pathologists at our institution reviewed all specimens. In the evaluation for dysplasia, orientation of each specimen was also assessed. In tissue preparation, the presence of muscularis mucosae causes the specimen to contract. This creates a pyramidal gross specimen, which allows improved tissue sectioning in which all glands are arranged in columns from the luminal side outward. Such orientation is crucial in differentiating dysplasia, which lacks surface maturation, from regenerative changes in which maturation occurs toward the surface. The ultimate result is a representative specimen with proper orientation, allowing a more accurate assessment of dysplasia. Both pathologists were blinded to the forceps used and to each other's reading to allow assessment of intraobserver variation.

Our secondary histological outcomes were specimen size and specimen adequacy. All specimens were processed with the same steps of fixation, dehydration and paraffin embedding, microtome sectioning at 5 μ m, and staining with hematoxylin and eosin. Proper fixation was defined by our pathologist as the ability to process, cut, stain, and evaluate tissue histologically. Crush artifact was defined as "smearing of cells and tissue with artificial elongation and distortion." The pathologist performed detailed measurements on every specimen for width and depth. These measurements were performed with a standard pathology software program (Spot 4.7; Diagnostic Instruments, Inc, Sterling Heights, Mich). A depth grade scale (DGS) ([Appendix A](#)) was used to further stratify depth of sampling based on the presence or absence of muscularis mucosae. Our final assessment of adequacy of a sample was made based on the following criteria: (1) the presence of muscularis mucosae (DGS ≥ 3), (2) the presence of crush artifact, and (3) fixation.¹⁶

Safety and complications

We assessed the control and experimental forceps for immediate and delayed complications. Specifically, we recorded any perforation, bleeding requiring hemostasis,

and unusual postprocedural pain. To account for patient-related differences, we also recorded emergency department visits and postprocedure patient phone calls. Finally, all patients were questioned regarding side effects during a follow-up phone call 7 days after endoscopy.

Statistical analysis

Sample size for our primary outcome measure was calculated a priori to detect a difference between forceps groups on dysplasia detection, first as a function of size and adequacy of tissue. Accounting for individual variability in segment length of BE and within-subjects comparisons, we estimated a 25% difference between the size of tissue collected from the same patient with each forceps with the premise that the size and adequacy of tissues would represent the sensitivity of dysplasia detection. We based this expectation of difference on a previous study that looked at tissue acquisition in inflammatory bowel disease (IBD).¹⁷ We conservatively applied an α of .01 and 100% power and determined that a total of 50 specimens per group would be needed to detect a difference between groups.

We performed a post hoc power analysis to determine the number of unique patients that would be required to identify a difference in proportion between groups in the presence of dysplasia. We had sufficient power ($N > 27$, $\alpha = .01$, $B = 100\%$, critical $t = 2.1$) to detect differences, within subjects, between the 2 forceps.

Data were stored and analyzed in SPSS statistical software (version 17.0; SPSS, Chicago, Ill). Data are presented as means for descriptive statistics with a normal distribution. Independent-sample t tests were used to assess our primary outcome measure, and a Pearson χ^2 test was used to assess our secondary outcome.

RESULTS

Baseline characteristics

Thirty-two patients undergoing surveillance of known nondysplastic BE were enrolled. Two patients were excluded after endoscopy, the first for a nodular mass and the second for an ulcerated lesion within the BE. Thirty patients ultimately completed this study. A total of 712 specimens were available for analysis for this investigation. Patient demographics and significant clinical characteristics are shown in Table 1.

Dysplasia detection

A total of 6 patients (20%) of our cohort had progression of disease. All of these patients had long-segment BE and a hiatal hernia. A total of 12 of the 712 samples demonstrated dysplasia. A second GI pathologist from our institution confirmed all samples with 100% agreement. Three samples were found by the standard forceps and 9 by the jumbo forceps. The dysplasia found by the

TABLE 1. Patient demographics (N = 30)

Mean (range) age (y)	68 (42-94)
Male	24
Female	6
White	27/30 (90%)
Hiatal hernia	21/30 (70%)
Daily proton pump inhibitor	30/30 (100%)
Long-segment BE	10/30 (33%)
Short-segment BE	20/30 (67%)
Mean duration (range) of disease (y)	6.7 (3-10)
Mean time (range) since last endoscopy (y)	3.3 (2.8-3.5)
Mean no. (range) previous EGD for BE	3.1 (1-5)

BE, Barrett's esophagus.

standard forceps was in 1 patient, which was also detected by the jumbo forceps. Dysplasia in the remaining 5 patients was not detected by the standard forceps but was detected by the jumbo forceps ($P < .005$) (Table 2, Fig. 3). Dysplasia found in more than 1 sample per patient was considered multifocal, whereas patients with a single dysplastic specimen were considered to have unifocal dysplasia. Multifocal dysplasia was detected in 5 of 6 patients who progressed in our study. Four of 5 of the patients with dysplasia that was detected only by the RJ4 jumbo forceps had multifocal dysplasia (2 HGD, 2 LGD), whereas the fifth patient had HGD on a single specimen. The patient with LGD detected by both forceps was considered multifocal.

Specimen size assessment

All specimens were measured for width and depth in micrometers and expressed in millimeters. The mean (standard deviation) width was significantly greater in the RJ4 jumbo forceps group at 3.3 (0.6) mm versus 1.9 (0.7) mm ($P < .005$), as was the mean (standard deviation) depth at 2.0 (0.3) mm versus 1.1 (0.3) mm ($P < .005$) (Table 3, Fig. 4).

Specimen adequacy

All specimens were then graded by using a DGS (Appendix A). For our study, a specimen was deemed adequate if (1) it reached a value of 3 on the DGS (inclusion of muscularis mucosae), (2) no significant crush artifact was noted, and (3) it had proper fixation. These criteria have been internally validated at our institution. In our investigation, there were no fixation errors with any of the samples. We demonstrated that the mean (standard deviation) depth achieved with the standard forceps was 2.0 (0.4) mm (mucosa without muscularis mucosae), whereas the RJ4 jumbo forceps reached a mean (standard deviation) DGS

TABLE 2. Dysplasia detection by forceps

	Control forceps	Jumbo forceps	P value
Any dysplasia (multifocal)	1 (1)	6 (5)	.014
Low-grade dysplasia (multifocal)	1 (1)	4 (3)	N/A
High-grade dysplasia (multifocal)	0	2 (2)	N/A

N/A, Not available. Values expressed as number of patients.

value of 3.1 (0.4) (including muscularis mucosae, $P < .176$) (Table 3). Although the mean DGS value did not achieve statistical significance, the overall difference in forceps for specimen adequacy was significant. To this end, 16% of samples obtained with the standard forceps were adequate, whereas the jumbo forceps provided an adequate sample 79% of the time ($P < .05$) (Fig. 5).

Safety and complications

There were no complications in our cohort. Anecdotally, there seemed to be a significant increase in visualized bleeding after using the RJ4 jumbo forceps in comparison with the standard forceps. There were no clinically evident episodes of perforation or bleeding after biopsy, as documented by no hospital emergency department visits, admissions, or patient calls. Furthermore, all patients denied any evidence of bleeding or increased pain after the procedure compared with previous endoscopies at the time of the 7-day follow-up phone call.

DISCUSSION

Optimal tissue sampling remains a significant diagnostic dilemma for gastroenterologists in the surveillance of patients with BE. Our investigation demonstrated that the RJ4 jumbo forceps are superior to standard forceps for tissue acquisition in this setting. In our study, we showed a significant increase in dysplasia detection with the RJ4 jumbo forceps.

As the incidence of esophageal adenocarcinoma continues to increase, there is increased interest in improving our diagnostic capabilities for dysplasia detection in BE. Improved imaging modalities such as narrow-band imaging, confocal endomicroscopy, and optical coherence tomography have had limitations in widespread applicability. With the advent of promising therapeutic modalities such as radiofrequency ablation, the ability to improve our detection of early dysplasia may ultimately have an impact on the incidence of esophageal cancer.

From our investigation, it seems that the width of each sample taken with the RJ4 jumbo forceps is approximately

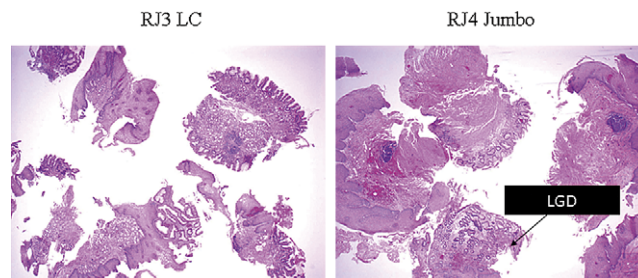


Figure 3. Dysplasia detection between forceps.

1.7 times greater than that with standard forceps. This would translate to nearly double the surface area sampled per endoscopy session for surveillance. The RJ4 jumbo forceps identified dysplasia (3 LGD, and 2 HGD) in 5 of 6 patients that was not identified by the standard forceps. In the other patient with LGD, both forceps identified the dysplastic change. All our patients with progression to dysplasia had long-segment BE and a hiatal hernia. The remainder of the baseline demographics was not different among patients with and without dysplasia. Although this study is not powered for segment length or presence of hernia, this agrees with previous data that there is an increased risk of progression with long-segment BE.^{18,19} Furthermore, all but one of the patients with dysplasia detected by the RJ4 jumbo forceps had multifocal dysplasia. This further strengthens our conclusion that the increased dysplasia detection is a direct result of the forceps used and not simply previous sampling error. Our cohort was very compliant with surveillance recommendations. The mean interval since their last endoscopy was 3.3 years. Therefore, our results cannot be attributed to poor patient follow-up. The mean duration of disease was 6.7 years and the mean number of previous endoscopies was 3.1. This also decreases the likelihood that our increased dysplasia detection was owing to sampling error alone.

Elmunzer et al¹⁷ observed a similar improvement in tissue acquisition in patients with IBD undergoing surveillance. They demonstrated that the RJ4 jumbo forceps obtained 25% larger specimens than did standard forceps. Although their study did not assess dysplasia, they also believed that this improvement in surface area sampled will ultimately improve dysplasia detection in IBD. From our current investigation, it also appears that a greater surface area sampled has resulted in improved dysplasia detection.

It is evident that dysplasia detection relies on sample orientation, which is dependent on tissue size. An adequate specimen should be representative of the area sampled. This is manifest by improved surface characterization of the specimen. Such orientation is crucial in differentiating dysplasia, which lacks surface maturation, from regenerative changes in which maturation occurs toward the surface. The importance of obtaining the muscularis

TABLE 3. Specimen size and adequacy by forceps

	Control forceps	Jumbo forceps	P value
Width, mm (range)	1.9 (0.78-3.4)	3.3 (1.5-4.9)	.008 (95% CI, 1.4-1.2)
Depth, mm (range)	1.1 (0.57-2.2)	2.0 (1.2-2.9)	.018 (95% CI, 0.98-0.88)
Depth grade scale (range)	2.0 (1.0-3.0)	3.1 (2.0-4.0)	.176 (95% CI, 1.19-1.05)
Crush artifact	None	None	N/A
Fixation	Normal	Normal	N/A

CI, Confidence interval, N/A, not available.

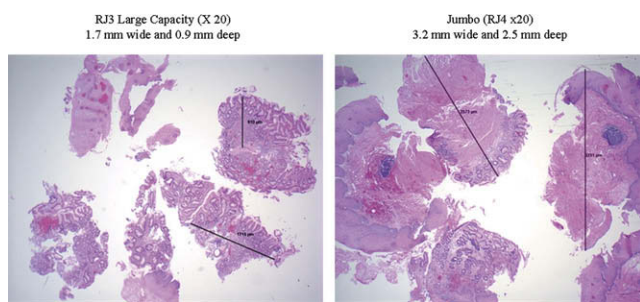


Figure 4. Histological size comparison between forceps (μm).

mucosae in each sample needs to be emphasized. Specimens not achieving this depth may ultimately be missing dysplastic areas and thus account for sampling error. The ultimate result is a representative specimen, which provides better overall orientation for pathological interpretation. In this investigation, we found a 79% specimen adequacy with the jumbo forceps and only 16% with the control forceps. Although the amount of previous data is limited, this finding is lower than expected. Elmunzer et al¹⁷ did find a higher rate of adequacy at 48% with the standard large-capacity forceps. They defined adequacy as “penetration of muscularis mucosae,” whereas we defined this as the “presence of muscularis mucosae.” This discrepancy may be the result of the definition of adequacy, the variability of the interpretation of pathological findings, or endoscopic technique.

There were no complications in our investigation with either forceps used. Specifically, no perforations or clinically significant bleeding was observed. However, this investigation was not powered to assess for perforation risk. There was no significant increase in postprocedural discomfort or patient phone calls after these procedures. It is important to note that endoscopically, there is a moderate increase in the visualized bleeding after each sample obtained with the RJ4 jumbo forceps. This is likely secondary to the deeper sampling of the vascular-rich superficial submucosa.

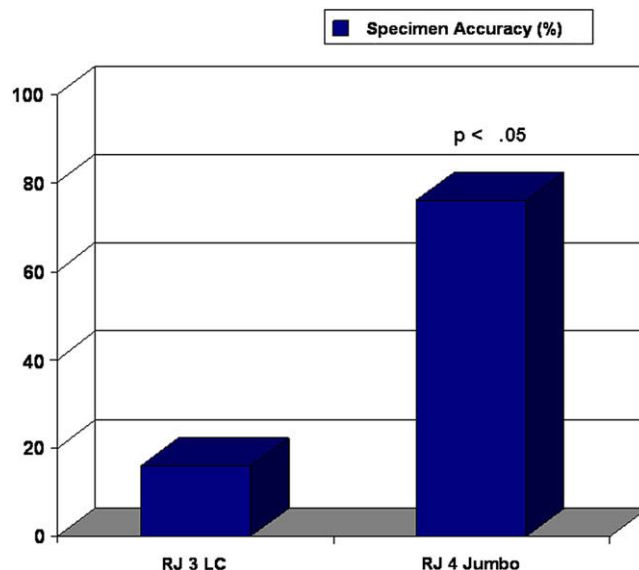


Figure 5. Specimen accuracy between forceps (%).

The largest limitation for any study of this nature is the lack of a validated index for assessment of tissue adequacy in BE. We used criteria that we have internally validated in our institution and that has been previously published.¹⁶ Our technique of side-by-side paired biopsies may not allow an exact comparison of biopsy forceps. In theory, the dysplasia may be removed by one set of forceps and may be unable to be sampled by the next. To overcome this, we excluded all patients with mucosal abnormality, alternated the order of forceps, and maintained a strict 4-quadrant protocol. We also acknowledge the possibility that the grossly larger specimens obtained by the jumbo biopsies may inadvertently bias the pathologist to read more dysplasia. However, the fact that nearly all of our patients had multifocal dysplasia should ideally decrease the impact of such a bias. Our current investigation did not have intraobserver variation in histological assessment, but we acknowledge that this would likely change with a larger sample size.

It is also important to note that all our endoscopies were performed with a standard Olympus upper endoscope (180 series). The specifications for the RJ4 jumbo forceps state that it requires a 3.2-mm working channel. The actual mean outer diameter of the jaw is 2.8 mm. We have not encountered any difficulties obtaining specimens with a standard endoscope with a 2.8-mm channel. We have performed more than 1000 endoscopies using this forceps and have not had any direct endoscope damage.

Our current investigation was not powered for a cost-effectiveness analysis. The price differential is a modest one, and if we are able to improve our dysplasia detection rate, as we have shown, this would clearly be cost-effective. In the recent study, Elmunzer et al¹⁷ demonstrated a very small increase in incremental costs for each adequate biopsy sample obtained. We also have not compared the

RJ4 large-capacity forceps with the RJ3 large-capacity and the RJ4 jumbo forceps. Ultimately, we may find that the RJ4 large-capacity forceps provides similar improved tissue acquisition compatible with that of the RJ4 jumbo forceps.

It is our belief that it is both the larger size and improved orientation of the specimen that accounts for this increased rate of dysplasia detection. Although we believe that this study is adequately powered, a larger sample size would be optimal to confirm this finding and account for intraobserver variation.

In conclusion, the RJ4 jumbo biopsy forceps significantly improves dysplasia detection in patients undergoing BE surveillance. Inherent in the success of any sampling technique in BE is the diligence of the endoscopist and adherence to a strict 4-quadrant biopsy protocol. Further study is ongoing at our institution to assess the cost-effectiveness of using the RJ4 jumbo and the RJ4 large-capacity forceps in the long-term surveillance of BE.

REFERENCES

- Pohl H, Welch HG. The role of overdiagnosis and reclassification in the marked increase of esophageal adenocarcinoma incidence. *J Natl Cancer Inst* 2005;97:142-6.
- Johansson J, Hakansson HO, Mellblom L, et al. Risk factors for Barrett's esophagus: a population-based approach. *Scand J Gastroenterol* 2007;42:148-56.
- Campos GM, DeMeester SR, Peters JH, et al. Predictive factors of Barrett esophagus: multivariate analysis of 502 patients with gastroesophageal reflux disease. *Arch Surg* 2001;136:1267-73.
- Rastogi A, Puli S, El-Serag HB, et al. Incidence of esophageal adenocarcinoma in patients with Barrett's esophagus and high-grade dysplasia: a meta-analysis. *Gastrointest Endosc* 2008;67:394-8.
- Souza RF, Krishnan K, Spechler SJ. Acid, bile, and CDX: the ABCs of making Barrett's metaplasia. *Am J Physiol Gastrointest Liver Physiol* 2008;295:G211-8.
- Shaheen NJ, Crosby MA, Bozyski EM, Sandler RS. Is there publication bias in the reporting of cancer risk in Barrett's esophagus? *Gastroenterology* 2000;119:333-8.
- Peters FP, Curvers WL, Rosmolen WD, et al. Surveillance history of endoscopically treated patients with early Barrett's neoplasia: nonadherence to the Seattle biopsy protocol leads to sampling error. *Dis Esophagus* 2008;21:475-9.
- Zhang HY, Spechler SJ, Souza RF. Esophageal adenocarcinoma arising in Barrett esophagus. *Cancer Lett* 2009;275:170-7.
- Swisher SG, Deford L, Merriman KW, et al. Effect of operative volume on morbidity, mortality, and hospital use after esophagectomy for cancer. *J Thorac Cardiovasc Surg* 2000;119:1126-32.
- Wang KK, Sampliner RE. Updated guidelines 2008 for the diagnosis, surveillance and therapy of Barrett's esophagus. *Am J Gastroenterol* 2008;103:788-97.
- Abela JE, Going JJ, Mackenzie JF, et al. Systematic four-quadrant biopsy detects Barrett's dysplasia in more patients than nonsystematic biopsy. *Am J Gastroenterol* 2008;103:850-5.
- Corley DA, Kubo A, DeBoer J, et al. Diagnosing Barrett's esophagus: reliability of clinical and pathologic diagnoses. *Gastrointest Endosc* 2009;69:1004-10.
- Harrison R, Perry I, Haddadin W, et al. Detection of intestinal metaplasia in Barrett's esophagus: an observational comparator study suggests the need for a minimum of eight biopsies. *Am J Gastroenterol* 2007;102:1154-61.
- Heitmiller RF, Redmond M, Hamilton SR. Barrett's esophagus with high-grade dysplasia. An indication for prophylactic esophagectomy. *Ann Surg* 1996;224:66-71.
- Falk GW, Rice TW, Goldblum JR, et al. Jumbo biopsy forceps protocol still misses unsuspected cancer in Barrett's esophagus with high-grade dysplasia. *Gastrointest Endosc* 1999;49:170-6.
- Woods KL, Anand BS, Cole RA, et al. Influence of endoscopic biopsy forceps characteristics on tissue specimens: results of a prospective randomized study. *Gastrointest Endosc* 1999;49:177-83.
- Elmunzer BJ, Higgins PD, Kwon YM, et al. Jumbo forceps are superior to standard large-capacity forceps in obtaining diagnostically adequate inflammatory bowel disease surveillance biopsy specimens. *Gastrointest Endosc* 2008;68:273-8, quiz 334, 336.
- Gopal DV, Lieberman DA, Magaret N, et al. Risk factors for dysplasia in patients with Barrett's esophagus (BE): results from a multicenter consortium. *Dig Dis Sci* 2003;48:1537-41.
- Musana AK, Resnick JM, Torbey CF, et al. Barrett's esophagus: incidence and prevalence estimates in a rural Mid-Western population. *Am J Gastroenterol* 2008;103:516-24.

Received January 4, 2009. Accepted April 10, 2009.

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APPENDIX A

1. Depth grade scale
 - 1: Superficial mucosa only
 - 2: Including mucosa and base of glands or crypts without muscularis mucosae
 - 3: Including muscularis mucosae without submucosal connective tissue
 - 4: Including submucosal connective tissue
 - Comment on lateral extension
2. Crush artifacts
 - 1 = 75% to 100% of biopsy sample without artifact
 - 2 = 50% of biopsy sample without artifact
 - 3 = 25% of biopsy sample without artifact
 - 4 = Entire biopsy sample involved, cannot be used for diagnosis
3. Fixation
 - Yes: well fixed
 - No: poor fixation