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Quantitative endoscopy in the chemoprevention of Barrett's Esophagus Trial

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SUMMARY

The Chemoprevention for Barrett's Esophagus Trial (CBET) was a phase IIb, multicenter, randomized, placebo-controlled trial of celecoxib in patients with Barrett's esophagus. The overall outcome of the study was that there were no significant differences in primary, secondary, or tertiary outcomes. The purpose of the current study is to focus on results related to the method of measuring lesion size called quantitative endoscopy (QE). The design includes a review of a total number of studies and then restricts analyses to the four clinics that enrolled more than four patients each for whom a baseline and 1-year QE study was performed, comparing intra- and inter-patient and clinic differences in Barrett's esophagus. Measurements include the number of total QEs and adverse events, changes in areas from baseline to 1 year and other intervals, classification of Barrett's lesion type with respect to patients, clinics, and treatment. A total of 309 QE studies were completed with no adverse events. Differences in surface area measurements over time for a particular patient are smaller than the differences for randomly selected patients. The complexity mix (as defined by the mix of circumferential, tongues, and islands) of the Barrett's lesions varied with different clinics. In conclusion, QE is an efficient, safe, and accurate way to measure the area of Barrett's lesions variation between different clinical sites may be attributable to a subtle type of selection bias at the individual clinics rather than to regional differences.

Keywords

Barrett's esophagus; chemoprevention; quantitative endoscopy; selection bias

BACKGROUND

Barrett's esophagus is a premalignant condition in which normal squamous epithelium of the esophagus is replaced by specialized columnar mucosa. It occurs as a result of chronic gastroesophageal reflux and is associated with an increased risk of developing esophageal adenocarcinoma. Esophageal adenocarcinoma is a disease rapidly rising in incidence.^{1–4} The 5-year survival rate achieved from surgical resection of esophageal cancer is approximately

24%. The Chemoprevention for Barrett's Esophagus Trial (CBET) was a phase IIb, multicenter, randomized, placebo-controlled trial of celecoxib in patients with Barrett's esophagus and low- or high-grade dysplasia. Descriptions of the trial and its outcomes have been documented,^{5,6} and the purpose of this paper is to further investigate some statistically significant outcomes of quantitative endoscopy (QE).

QUANTITATIVE ENDOSCOPY

QE: general results

In CBET, the surface area of Barrett's esophagus was measured with QE utilizing an enhancement of the computer image analysis system, described elsewhere.⁷⁻¹⁰ The system (US Patent #7,011,625) transformed photographs of Barrett's esophagus into 2-D maps, and quantitative measurement of the surface area of Barrett's esophagus was calculated from the reconstructed images.

The formal procedures for endoscopists are relatively simple: (i) begin recording at the gastroesophageal junction; (ii) capture images at the end of expiration with the lumen maximally distended; (iii) capture images with the center of the lumen as the focus; (iv) image every 2 cm starting at the gastroesophageal junction and continue to 2 cm past the proximal border of the metaplastic epithelium.

Digitized images taken during the upper endoscopy procedure in selected clinics were sent to one expert study investigator for evaluation. The investigator was masked to the patient's treatment assignment. Standard procedure guidelines for imaging were used by all study gastroenterologists. QE was performed at baseline (BL), 6 months, 1 year, and then yearly, up to 3 years. Figure 1 illustrates the QE process.

Over the course of CBET there were a total of 309 studies carried out on 116 separate patients (not all of whom were enrolled in CBET). There was not a single adverse event associated with the QE procedure. Although Kim *et al.*^{7,8} showed that QE yields accurate measurements and is replicable with different endoscopists, those studies were confined to no more than two patients with two studies. The CBET experience demonstrates that QE can be performed across multiple centers with large numbers of patients safely and with minimal additional effort.

The remainder of this paper is focused on some related measurements associated with CBET and QE. Measurements of total surface area affected by Barrett's esophagus were obtained using QE at BL and 1 year (48 weeks of treatment). The original analysis showed no statistically significant differences in the median change of total surface area affected by Barrett's esophagus as measured by QE after 1 year (48 weeks of treatment) with respect to treatment assignment and grade of dysplasia ($P=0.12$). This current work is focused on other, more targeted statistical analyses.

Quantitative endoscopy: statistical analyses

In CBET, as opposed to Kim *et al.*,⁸ there is only one area measurement for each patient so that it is not possible to compare two measurements for a single visit. However, if QE is accurately measuring area, then one would expect the change in area from one visit to the next to be more stable than random. In order to conduct valid statistical analyses, it was necessary to restrict the data set to clinics where there were sufficient numbers of patients and comparable data collection. For this reason, attention was restricted to the clinics coded as CPMC (Columbia Presbyterian Medical Center), HVA (Hines VA Medical Center), JHH (Johns Hopkins Hospital), and UCLA (UCLA Medical Center). For these patients, 72 had QE measurements at BL, and 52 of these also had QE measurements at 48 weeks (F04).

A method called variance components analysis is used to estimate the standard deviation of measurements within and between patients.¹¹ The estimated standard deviations for QE measurements for visits between patients (Patient ID) and for visits within patients (Visit) are given in Table 1. Note that interpatient variability accounts for 92.16% of the total variation in QE measurements, while the inpatient variation, estimated from the BL and F04 visits, only accounts for 0.82% of the total variation. The estimated inter-patient standard deviation is 25.48, while the estimated intra-patient standard deviation is 2.40. The row entitled Residual represents variation that remains once Patient and Visit are accounted for. Note that this residual variation is small, compared with what is explained by Patient.

This analysis is reinforced by Figure 2, which shows area measurements by patient. Note that the variability within patients appears much smaller than the patient-to-patient variability. This is true for both celecoxib- and placebo-treated patients.

Inter-clinic differences

Although not part of the QE protocol, it appeared on casual inspection that there were differences in patents at different clinics. In order to study these potential inter-clinic differences, patients were distributed into three complexity classes, defined as follows.

- C – If the Barrett's was classified as circumferential
- CTI – If there was circumferential plus at least one tongue and/or island
- TI – If there was no circumferential and at least one tongue and/or island.

It is important to note that this classification of Barrett's esophagus is new. To test the hypothesis that there is no difference between the clinics, a standard contingency table was constructed (Fig. 3). The statistical tests shown in the 'Tests' box (likelihood ratio and Pearson) indicate that there are statistically significant differences ($P < 0.01$) in the proportions of C, CTI, and TI patients included in the study at the four clinics.

Graphically, these differences are reinforced in Figure 4.

CONCLUSIONS

The major conclusion of QE in CBET is that QE is an efficient, safe, and accurate way to measure the area of Barrett's lesions.

The inter-clinic differences in Complexity Class are more surprising. It is possible to argue that there are differences in the patient populations at the various sites, but there does not appear to be any evidence to lead one to expect different manifestations of the same disease. However, even though clinics enroll patients in clinical trials subject to a set of inclusion/exclusion criteria, there likely are other factors that could lead to different decisions, especially in a chemo-preventive trial. The availability of other treatments, concern for the treatment of certain disease states (e.g. short segment, multiple tongues or islands), and the existence of other trials can all affect enrollment. This may be a manifestation of a subtle type of selection bias that should be investigated.

References

1. Devesa SS, Blot WJ, Fraumeni JF Jr. Changing patterns in the incidence of esophageal and gastric carcinoma in the United States. *Cancer*. 1998; 83(10):2049–2053. [PubMed: 9827707]
2. Brown LM, Silverman DT, Pottern LM, Schoenberg JB, Greenberg RS, Swanson GM, et al. Adenocarcinoma of the esophagus and esophagogastric junction in white men in the United States:

- alcohol, tobacco, and socioeconomic factors. *Cancer Causes Control*. 1994; 5(4):333–340. [PubMed: 8080945]
3. Drewitz DJ, Sampliner RE, Garewal HS. The incidence of adenocarcinoma in Barrett's esophagus: a prospective study of 170 patients followed 4.8 years. *Am J Gastroenterol*. 1997; 92(2):212–215. [PubMed: 9040193]
 4. 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(2):333–338. [PubMed: 10930368]
 5. Heath EI, Canto MI, Wu TT, Piantadosi S, Hawk E, Unalp A, et al. Chemoprevention for Barrett's esophagus trial. Design and outcome measures. *Dis Esophagus*. 2003; 16(3):177–186. [PubMed: 14641306]
 6. Heath EI, Canto MI, Piantadosi S, Hawk E, Montgomery E, et al. Secondary chemoprevention of Barrett's esophagus with celecoxib. *J Natl Cancer Inst*. 2007; 99(7):545–557. [PubMed: 17405999]
 7. Kim R, Baggott BB, Rose S, Shar AO, Mallory DL, Lasky SS, et al. Quantitative endoscopy: precise computerized measurement of metaplastic epithelial surface area in Barrett's esophagus. *Gastroenterology*. 1995; 108(2):360–366. [PubMed: 7835577]
 8. Kim R, Rose S, Shar AO, Weiner M, Reynolds JC. Extent of Barrett's metaplasia: a prospective study of the serial change in area of Barrett's measured by quantitative endoscopic imaging. *Gastrointest Endosc*. 1997; 45(6):456–462. [PubMed: 9199900]
 9. Shar AO, Baggott BB, Reynolds JC. Computer enhanced endoscopic visualization. *Proc Annu Symp Comput Appl Med Care*. 1995:544–546.
 10. Shar AO, Weiner M, Kim R, Reynolds JC. Automated reconstruction of endoscopic images of the esophagus. *Proc Annu Symp Comput Appl Med Care*. 1995:547–550. [PubMed: 8563344]
 11. Montgomery, DC. *Design and Analysis of Experiments*. 6th edn.. Hoboken, NJ: Wiley; 2004.

Fig. 1.
QE process flow: raw image, outlined image, transformed image.

Variability Gage Treatment=Celocoxib

Variability Gage Treatment=Placebo

Fig. 2.
QE charts illustrating intra and inter-patient variability.

	Complexity Class			
	Count	C	CTI	TI
Row %				
CPMC	10	6	3	19
	52.63	31.58	15.79	
HVA	4	5	8	17
	23.53	29.41	47.06	
JHH	7	19	4	30
	23.33	63.33	13.33	
UCLA	3	8	10	21
	14.29	38.10	47.62	
	24	38	25	87

Tests

Source	DF	-LogLike	RSquare (U)
Model	6	8.848938	0.0946
Error	79	84.711607	
C. Total	85	93.560545	
N	87		

Test	ChiSquare	Prob>ChiSq
Likelihood Ratio	17.698	0.0070*
Pearson	18.374	0.0054*

Fig. 3.
Complexity class contingency table.

Fig. 4.
Complexity class mosaic.

Table 1

Intra- and inter-patient variance analysis

Source	Variance component	Total (%)	SD
Patient ID	649.01	92.13	25.48
Visit	5.77	0.82	2.40
Residual	49.43	7.02	7.03
Total	704.21	100.00	

SD, standard deviation.