Accuracy of histologic inflammation scores in active ulcerative colitis: Dependence on biopsy sampling density

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INTRODUCTION

• Histological evaluation of colonic mucosal biopsies in patients with ulcerative colitis (UC) is a potentially informative adjunct to endoscopic evaluation in assessing disease activity in the clinical trial setting.
• Validated indices to grade inflammation, such as the Geboes, Nancy and Roberts indices, are based on pathological grading of individual inflammatory changes such as mononuclear and granulocytic infiltration and ulceration.
• Although mucosal inflammation in UC is characteristically uniform on the endoscopic scale, the histological changes are distributed non-uniformly on the microscopic scale of individual biopsies, imposing biopsy sampling error of uncertain magnitude.

AIM

The aim of the present study was to utilize statistical modeling to calculate the accuracy of histological inflammation scores in localized regions of mucosa as a function of sampling density and to determine the densities needed to achieve a specified accuracy for biopsy-based histological grading.

METHODS

Colecctiony specimens of 11 consecutive patients with severe pan-UC were selected for histology. A randomly selected side from the left and right side of each specimen was digitally scanned at 40X and the mucosal image was segmented into consecutive 1 mm-diameter fields to simulate biopsies. The patients comprised 7 males and 4 females, median age 29 y. Ten to 67 fields were scored per slide (median 44, IQR= [33,61]) for a total 995 fields.

For each slide (mean 45 mm) (A)

• 1. Consecutive 1 mm fields (virtual biopsies) are scored by two pathologists
• 2. Select 1 field at random and a window of 10 fields on either side
• 3. Reference score (Sr) = mean histologic score of 21 fields
• 4. Generate agreement statistics (Sr vs. Sk)
• 5. Repeat steps 4 and 5 2500 times
• 6. Generate agreement statistics (Sr vs. Sk)
• 7. Repeat steps 4 and 5 2500 times
• 8. Use bootstrap to obtain mean, 95% CI
• 9. Repeat steps 2 through 8 for k=1,2,…,10

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CONCLUSIONS

• Using statistical modeling we show that the accuracy of histological grading improves across all indices as the biopsy density increases, the largest proportional gains occurring with the addition of the second and third biopsies but diminishing thereafter.
• One biopsy can achieve moderate to good accuracy (mean interclass correlation coefficients [ICC] of 0.73; 95% CI [0.60-0.86]) with the Nancy histologic index and 0.76 95% CI (0.60-0.86) with the Roberts histologic index), whereas sampling three biopsies results in a large proportional gain in achieving good accuracy (ICC ≥ 0.75) with 95% confidence.
• Our results provide a set of benchmarks and guidance for the design and interpretation of clinical trials using biopsies to assess inflammation in UC.

Table 1. Study population descriptive statistics

Table 2. Intraclass correlation coefficients and error tolerance statistics for NHI and RHI by biopsy density

Table 2a. Intraclass correlation coefficients and error tolerance statistics for NHI and RHI by biopsy density

Table 2b. Intraclass correlation coefficients for Geboes subscores by biopsy density

Table 2c. Intraclass correlation coefficients for Geboes subscores by biopsy density

REFERENCES


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