Diagnosis of Upper Gastro-intestinal Lesions by Endoscopy, Cytology and Biopsy

GLADWYN LEIMAN, L. OU TIM, I. SEGAL

SUMMARY
A prospective consecutive series of 210 upper gastro-intestinal endoscopic procedures, at which material for both cytological and histopathological examination was obtained, was conducted at Baragwanath Hospital. The purpose of the study was to determine the respective and combined diagnostic value of endoscopic visualization, cytological brushings and histological sections in benign and malignant lesions of the oesophagus and stomach; and in particular to assess the contribution, if any, of exfoliative cytology to the diagnostic regimen.

Endoscopic visualization alone was inconclusive or incorrect in 13% of procedures, cytology alone in 9%, and biopsy alone in 12% (the latter 2 figures corrected for adequacy of material submitted). When assessed together, the diagnostic accuracy achieved by all 3 techniques was 99%. The major contribution of cytology was the correct positive diagnosis in 20% of procedures, performed on patients with malignant lesions, whose initial biopsy specimen was inadequate or normal.

It is concluded that for maximal diagnostic accuracy of upper gastro-intestinal lesions, a combined approach, utilizing endoscopic examination, lesion-directed brushings and biopsy specimens, is required.


Before the introduction of the flexible fibre-optic gastro-scope, first described by Hirschowitz et al., diagnosis of upper gastro-intestinal tract lesions was essentially reliant on radiographic examination. The value of direct-vision endoscopy as a superior diagnostic tool has since been established, and its use may be either complementary or alternative to radiology. The major advantage of the endoscopic procedure is the opportunity afforded to obtain confirmatory histological diagnosis by selective, directed tissue sampling.

A new dimension in lesion sampling was introduced by Kameya et al., who reported the use of a brush technique whereby cell samples were obtained for cytological investigation. This communication reports the individual and combined experience gained from endoscopy, cytology and biopsy at Baragwanath Hospital, in benign and malignant lesions of the oesophagus and stomach, in a prospective consecutive series of 210 procedures performed on 188 patients.

PATIENTS AND METHODS
During the 18-month period from January 1977 to June 1978, 210 endoscopies were performed on 188 patients referred to the gastro-enterology service at this hospital with diagnostically difficult clinical or radiological features related to the upper gastro-intestinal tract.

Endoscopic examination was carried out in all instances with the Olympus oblique-viewing fibre-optic endoscope (model GIF-K). The patients were fasted overnight and received diazepam 10 mg and atropine 60 mg intramuscularly 1 hour before the examination. For apprehensive or anxious patients, 5-10 mg diazepam was administered intravenously. The pharynx was anaesthetized with 2% xylocaine spray, and the endoscope was introduced orally with the patient in the left lateral position. As part of a prospective study, complete visualization of the oesophagus, stomach and upper duodenum was obtained, and an endoscopic diagnosis, based on direct visualization of the lesion, was noted. At least 4 biopsy specimens from each quadrant of a malignant, suspicious or abnormal area were obtained. In addition the lesions were brushed with a standard cytological brush (type BC-2J), introduced through the biopsy channel of the endoscope. The brush was withdrawn and the material was smeared on 2 clear glass slides, immediately sprayed with an alcohol-based fixative and stained by the Papanicolaou method. Patient tolerance was excellent and no complications attributable to the procedures occurred.

The cytological and histological specimens were assessed and reported on independently, neither the cytologist nor the pathologist being aware of each other's diagnosis. Thus for each procedure, 3 independent reports were issued, namely endoscopic, cytological and histological.

Correlation of these 3 findings formed the basis of the final diagnosis for each patient. When discrepancies occurred, additional information was sought by referral to results of radiographic studies, and by repeated endoscopic examination with cell and tissue sampling, until concurrent diagnoses were obtained and all discrepant findings were fully explained. The histological examination of specimens from lesions in those patients subjected to subsequent surgery, or those cases which reached autopsy, provided additional means of confirmation and quality control.

Particular attention was paid to the follow-up of patients with lesions assessed as benign at the initial diagnostic
workup. These patients were seen at 1-2-monthly intervals after discharge from hospital at the gastro-enterology out-patient clinic, until complete healing, as assessed by endoscopic examination and radiographic studies, was achieved; thereafter they were seen at 3-6-monthly intervals. Cytological brushings and biopsies were repeated during this time if endoscopic visualization caused concern.

The possibility of an in situ or early carcinoma having been missed is valid, particularly in patients with gastric ulcers. By the end of the study period, with 6-24 months' follow-up as outlined above, no patient initially diagnosed by all 3 techniques as having a benign lesion had developed a malignant lesion.

RESULTS

A total of 210 endoscopic procedures was carried out on 188 patients, whose final diagnoses are listed in Table I. Analysis of these patients and the achievements of the 3 study techniques under investigation was performed according to the site and nature of the lesion.

**TABLE I. FINAL DIAGNOSIS IN STUDY GROUP**

<table>
<thead>
<tr>
<th>Site</th>
<th>Benign</th>
<th>Malignant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oesophagus</td>
<td>9 strictures</td>
<td>56 squamous</td>
</tr>
<tr>
<td>(88 patients)</td>
<td>7 normal</td>
<td>carcinomas</td>
</tr>
<tr>
<td></td>
<td>5 reflux</td>
<td>3 adenocarcinomas</td>
</tr>
<tr>
<td>Stomach</td>
<td>46 benign ulcers</td>
<td>32 adenocarcinomas</td>
</tr>
<tr>
<td>(100 patients)</td>
<td>10 gastritis</td>
<td>1 leiomyosarcoma</td>
</tr>
<tr>
<td></td>
<td>7 normal</td>
<td>3 leiomyomas</td>
</tr>
<tr>
<td></td>
<td>1 polyp</td>
<td></td>
</tr>
</tbody>
</table>

**Oesophagus**

Table II shows a composite analysis of the performance of endoscopy, brushings and biopsy in all patients with benign and malignant oesophageal lesions. It can be seen that the diagnostic accuracy of endoscopic visualization as a single procedure was high (88.9%), but when figures for brushings and biopsy were corrected for adequacy of material, brushings achieved a slightly higher rating (89.9%). This difference was not statistically significant.

The accuracy of biopsy was, however, significantly lower than for the other 2 techniques (77.8%).

All 3 methods were initially inconclusive in only 1 patient, a 75-year-old woman with a midoesophageal polyloid carcinoma. The endoscopist reported the presence of the tumour but thought it was benign. The brushings revealed atypical degenerate squames, and the biopsy specimen contained normal squamous epithelium with groups of atypical lymphoid cells in the underlying stroma. Subsequent endoscopically directed biopsy conclusively proved the presence of a keratinizing squamous carcinoma.

Separate analysis of the benign and malignant lesions of the oesophagus revealed notable differences in the value of the 3 techniques for diagnostic purposes.

**Benign Lesions**

This group of 29 patients underwent 32 endoscopic procedures. There were 17 males and 12 females (M : F ratio 1.4 : 1) whose average age was 50 years (range 29-76 years). A benign lesion was correctly diagnosed by endoscopic evaluation in 23 instances (71.9% accuracy), but on 8 occasions the possibility of malignancy was queried. In 1 patient who had undergone postoesophagectomy assessment for dysphagia, a false-positive diagnosis of recurrent carcinoma was made.

Inadequate brushings were submitted from 3 procedures, and 27 of the remaining 29 specimens were reported as negative (93.7% accuracy). One specimen from a benign ulcer contained atypical basal squames and was labelled inconclusive, while the remaining report was a false-positive one, squamous carcinoma being incorrectly diagnosed from a specimen which, on subsequent review, should have been considered too poorly preserved for cytodiagnosis. This was the only cytological false-positive diagnosis in the entire series.

Two biopsy specimens were considered unsuitable for comment, while 1, from a patient with a hiatus hernia, whose subsequent course was entirely benign, was reported as being dysplastic. No false-positive diagnoses were made on the remaining 29 biopsy specimens (96.9% accuracy).

**Malignant Lesions**

Oesophagoscopy was performed on 67 occasions on 59 patients with oesophageal carcinoma (3 recurrent post-oesophagectomy). There were 40 males and 19 females.
(M: F ratio 2.1:1) with this lesion, their average age being 51 years (range 25 - 77 years). Histological examination of 56 of these specimens revealed a squamous carcinoma, 2 lesions were cephalad extensions of adenocarcinomas primary at the cardio-oesophageal junction, and the remaining specimen was of an autopsy-proven adenocarcinoma, arising in a columnar-lined Barrett’s oesophagus in a 25-year-old woman, the youngest patient in this group.

Malignancy was correctly identified endoscopically in 65 procedures (97% accuracy), but was missed in 1 instance and in another the lesion was thought to be a benign polyp.

Inadequate biopsy material (due to poor epithelial representation) prevented cytological diagnosis in 7 specimens, while malignancy was suspected but not conclusively diagnosed in 5 specimens. Three negative reports were issued and the remaining 52 brushings, including those from patients with adenocarcinoma, were correctly diagnosed as malignant. Corrected for adequacy, the accuracy was 88.1% (77.6% uncorrected).

The biopsy was diagnostic in only 42 instances, 4 specimens being inadequate. Fourteen specimens contained no malignant tissue, while a further 7 specimens were abnormal, atypical or suspicious, but not conclusively malignant on histological examination. Thus the accuracy was 68.7% when corrected for adequacy (62.7% uncorrected).

The positive contribution of cytology in this site was the correct identification of malignancy in 17 (25%) procedures in which the diagnosis was not made histologically.

Stomach

The findings of 111 gastroscopic investigations performed on 100 patients with benign and malignant lesions of the stomach are summarized in Table III. In this area, biopsy proved to be the procedure which contributed the highest accuracy of diagnosis (94.6%, increasing to 96.4% with correction for adequacy of specimens provided). Inconclusive assessment of gross appearances was the major failing of endoscopic visualization (84.7% accuracy), while inadequate cell samples and false-negative reports contributed equally to the cytological rating (85.6% uncorrected; 91% corrected for adequacy).

A final diagnosis was not reached in 1 patient, a 50-year-old man, on the basis of the findings of the 3 techniques. Gastroscopy revealed a polyoid tumour, the brushings contained spindle-shaped smooth-muscle cells, and the biopsy specimen showed the presence of a smooth-muscle tumour. However, in no instance was a definitive diagnosis of the benign or malignant nature of this tumour made. Histological examination of the subsequent antrectomy specimen conclusively proved the presence of a benign leiomyoma.

Separation of benign and malignant gastric lesions again provided noteworthy differences in diagnostic achievement.

Benign Lesions

A total of 76 procedures was performed on the 67 patients with benign lesions of the stomach. The group consisted of 36 males and 31 females (M: F ratio 1.2:1) whose average age was 48 years (range 20 - 74 years).

Gastric biopsy was the single technique of choice (97.4% accuracy) and no inadequate specimens were submitted. Two reports were inconclusive, one with regard to the case quoted above, and the other in a patient with stomatitis and stomal narrowing 8 months after gastrectomy, and whose biopsy specimen showed atypical epithelium. Subsequent observation of this patient over a period of 1 year showed no recurrent malignancy.

A slightly lower accuracy obtained by brushings (93.4%) was due to inadequate samples which contained no gastric epithelial cells in 3 cases. Correction for adequacy equated the cytological figure with that for biopsy (97.4%). Gross visualization of the lesion led to suspicion of malignancy in 9 instances and a false-positive diagnosis of malignancy in a further 5, all these patients having gastric ulcers which proved to be benign. Endoscopy thus achieved the lowest diagnostic rating (81.6%).

Malignant Lesions

Malignancy was found in 33 patients who underwent 35 endoscopic procedures. The group consisted of 23 males and 10 females (M: F ratio 2.3:1) whose average age was 58 years (range 21 - 85 years). The definite superiority of biopsy was noted. Only 2 specimens were negative while a further 2 were inadequate for assessment, giving an 88.6% accuracy (94.3% when corrected for adequacy). Gastric carcinoma was misdiagnosed endoscopically as a benign ulcer in 1 instance, while a further 2 malignancies in this situation were suspected, but not definitively diagnosed at endoscopy (91.4% accuracy).

Cytological brushings gave poor results in this category. In addition to 3 specimens being inadequate, 2 were inconclusive, and in a further 6 instances, no diagnosis of

<table>
<thead>
<tr>
<th>TABLE III. DIAGNOSTIC ACCURACY OF ENDOSCOPY, CYTOLOGY AND BIOPSY IN BENIGN AND MALIGNANT LESIONS OF THE STOMACH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endoscopy</td>
</tr>
<tr>
<td>Inadequate specimen</td>
</tr>
<tr>
<td>Inconclusive findings</td>
</tr>
<tr>
<td>False-negative report</td>
</tr>
<tr>
<td>False-positive report</td>
</tr>
<tr>
<td>Accuracy (%)</td>
</tr>
<tr>
<td>Corrected for adequacy</td>
</tr>
<tr>
<td>Overall accuracy</td>
</tr>
</tbody>
</table>

14 April 1979 SA MEDIESE TYDSKrif 621
malignancy was made. The accuracy was therefore 68.6\% (77.1\% corrected for adequacy). However, there were 3 procedures (8.6\%) performed in which the brushings gave a correct diagnosis of gastric carcinoma; the biopsies taken simultaneously showed no abnormality. These lesions were all subsequently confirmed on histological examination, 2 on repeated biopsy and 1 at autopsy.

**Total Study**

The results of the combined total of 210 procedures performed for evaluation of benign and malignant oesophageal and gastric lesions in 188 patients are noted in Table IV. Without making allowance for inadequate cell and tissue samples, endoscopy as a single technique gave the best results (87\%). However, when specimen inadequacy was accounted for in computations, cytological brushings achieved the highest rating (91\%), biopsy accuracy being 88\%. The differences between these scores were not statistically significant.

**DISCUSSION**

Many authors have attested to the usefulness of one or other of the procedures investigated in this study, but have often not incorporated the achievements of direct visual assessment in their publications, or have confined their studies to one particular organ, for example the oesophagus, or stomach, and in many instances to the diagnosis of malignant lesions only at these sites. Few workers have correlated and compared all 3 techniques in benign and malignant conditions at both sites. The prevalence of these diagnoses at Baragwanath Hospital enabled the present study to be undertaken which yielded sufficient numbers for conclusions to be drawn with regard to the 3 techniques in the entire spectrum of upper gastrointestinal disease.

Benign conditions of the oesophagus proved diagnostically difficult to assess at endoscopy only, features of oesophagitis, lower oesophageal ulceration, stenosis and polyp formation leading to inconclusive reporting. Most of these reports erred on the side of malignancy or suspicion of malignancy because of the high incidence of oesophageal carcinoma in patients seen at this hospital. This experience was paralleled by endoscopic visual diagnosis of benign lesions of the stomach where 14 cases of benign gastric ulcer were incorrectly interpreted as malignant or were regarded as strongly suspect. Cytological and histological methods in these two categories proved almost equally valuable. Biopsy of the oesophagus has previously been noted to be difficult and inferior to brushings because the technique of attempting an en face biopsy in an essentially linear organ through an end-viewing endoscope is awkward. Stenotic or anatomically distorted segments may preclude access to the biopsy target area completely, or force tangential sampling. This difficulty was readily reflected in the present study in malignant lesions of the oesophagus, where biopsy rated poorly in comparison with brushings and endoscopy, and failed to identify malignancy positively on 14 out of 67 occasions. The brush used had the advantages of being readily passed through structures too small for directed biopsy, and of sampling much larger areas of diseased tissue than was possible even with multiple-punch biopsy specimens. A complete reversal of this situation occurred in malignant lesions of the stomach, where biopsy proved highly accurate. Brushings from these lesions were inadequate, inconclusive or negative in 11 out of 35 instances, whereas biopsy and endoscopy were of almost identical value.

The poor performance of brushings at this site prompted a retrospective re-assessment of all cytological failures in the series, in an attempt to assess the causes of failure and areas of possible improvement in cytological diagnosis. All specimens from patients with proven malignancies not definitely diagnosed on brushings were reviewed (15/67 oesophagoscopies, 11/35 gastroscopies).

The 10 preparations (7 oesophageal and 3 gastric) originally reported as inadequate, were again assessed as unrepresentative and unsuitable for cytodiagnosis. Seven specimens were inconclusive (5 oesophageal and 2 gastric), all originally showed the presence of atypical or suspicious cells without sufficient criteria for a definite diagnosis of malignancy. On review, it was felt that in 1 of these cases, malignancy should have been conclusively reported. Completely negative reports were originally issued in 9 instances (3 oesophageal and 6 gastric). Review of these slides confirmed the absence of malignant cells in 3 cases. However, in 5 specimens atypical cells were observed on rescreening. If these had been noted at the initial examination, ‘suspicous’ but not definitively positive reports would have resulted. In the remaining case in this category, a profuse exfoliation of malignant cells was present in the smears of a patient with a signet-cell carcinoma of the stomach. These cells were small, pale, and admixed with inflammatory cells, and were erroneously regarded as histiocytes at the original screening.

Table V presents an analysis of these missed malignancies, categorized according to the review diagnosis. It can be seen that better sampling of lesions would have improved the diagnosis by 10\%, and more alert screening by 7\%. However, inevitable failures were evident in 9\% of procedures, due either to insufficient malignant criteria, or to the absence of malignant cells in otherwise adequate cellular samples. From these observations it is concluded.

**TABLE IV. DIAGNOSTIC ACCURACY IN ENTIRE STUDY GROUP**

<table>
<thead>
<tr>
<th></th>
<th>Endoscopy</th>
<th>Brushings</th>
<th>Biopsy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Accuracy (%)</strong></td>
<td>87</td>
<td>83</td>
<td>84</td>
</tr>
<tr>
<td>Corrected for adequacy (%)</td>
<td>—</td>
<td>91</td>
<td>88</td>
</tr>
<tr>
<td><strong>Overall accuracy</strong></td>
<td>208/210 = 99%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

210 procedures in 188 patients.
that brushing techniques can never replace biopsy as a diagnostic tool, but may augment microscopical confirmation of endoscopically visualized lesions.

One of the aims of the study was to determine whether cytological brushings would provide any practical or meaningful contribution to the diagnostic workup of patients under investigation. An affirmative conclusion was reached, based primarily on the detection of malignancy in 17 patients with oesophageal and 3 with gastric cancer which were missed on initial biopsy specimens. These cases comprised 19.6% of the procedures performed on patients with malignancies, and were felt to represent an important contribution. In addition, the low false-positive rate for cytology (less than 1%) was not thought to be a deterrent to the further use of this technique. The collection of specimens for cytological examination did not noticeably increase operating time, and the specimens themselves were readily incorporated into the routine screening programme of the cytology laboratory.

Although endoscopy, cytology and biopsy have been considered and analysed separately, and the major areas of success and failure of each outlined individually, the combined diagnostic success rate of 99% leads readily to the final conclusion, namely that the techniques are not mutually exclusive, but, in fact, highly complementary, and should be used in close conjunction with each other wherever facilities exist. The optimal results obtained by the combined diagnostic programme outlined above would obviate the need for exploratory surgery in all but a few patients.

**CONCLUSION**

Endoscopic visual evaluation of lesions was of great importance, and as a single technique had the highest diagnostic accuracy rate (87%). However, when corrected for adequacy of specimens provided, cytological brushings achieved a slightly higher score (91%). Brushings were significantly superior to biopsy in detecting malignant lesions of the oesophagus (88% v. 69%). Biopsy was significantly superior to cytology in detecting malignant lesions of the stomach (94% v. 77%).

The major contribution of brushings was the correct identification of malignancy in 20 (19.6%) instances where biopsy was inadequate or inconclusive. This was especially apparent in the oesophagus. Assessed together, endoscopic visualization, brushings and biopsy achieved a 99% diagnostic accuracy. The 3 techniques are complementary and should all be used for maximal assessment of upper gastrointestinal lesions.

**REFERENCES**

4. Prolla, J. C., Reilly, R. W., Kirchner, J. B. et al. (1977): Ibid., 21, 399.