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Comparative Evaluation of Endoscopic Brush Cytology and Biopsy in the Diagnosis of Upper Gastrointestinal Neoplasm

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Abstract
A prospective study was carried out on 120 patients undergoing endoscopic evaluation to assess the diagnostic utility of endoscopic biopsy and brush cytology in the diagnosis of upper gastrointestinal neoplasm. The findings of brush cytology were compared with that of endoscopic biopsy and/or excision biopsy. The sensitivity, specificity, positive predictive value, negative predictive value and accuracy of brush cytology in diagnosing upper gastrointestinal malignancies are 85.7%, 98.4%, 98%, 88.7% & 92.5% respectively and for endoscopic biopsy the values are 89.3%, 98.4%, 98%, 91.3% & 94.2% respectively. Whereas when the brush cytology and biopsy findings were taken together the diagnostic value was significantly improved with 98%, 96.8%, 96.5%, 98.4% & 97.5% respectively. Hence brush cytology is a useful adjunct in the diagnosis of upper gastrointestinal neoplasm and should be considered as a routine method in combination with endoscopic biopsy. Combined use of endoscopic biopsy and brush cytology together increases the sensitivity, negative predictive value and accuracy of diagnosis of malignancy.
Keywords: *Brush cytology, endoscopic biopsy, upper gastrointestinal neoplasm.*

Introduction

Gastrointestinal lesions represent a heavy burden on health care system with malignancies constituting a major cause of morbidity and mortality. In 2012, worldwide an estimated 951,600 stomach cancer cases with 723,100 deaths and 455,800 oesophageal cancer cases with 400,200 deaths have occurred.(1) In India, according to National Cancer Registry (2012-2014), oesophageal and gastric cancers are among

the most common cancers found in men and women.[2] The stomach and oesophageal cancer are often reported late in advanced stage of the disease with a 5-year survival around 20-30% for gastric carcinoma and 5% for oesophageal carcinoma whereas an early detection of malignancy greatly improves the survival rate to more than 90%. [3] [4] [5] Within this fifty years endoscopy proved to be a major breakthrough in the diagnosis of oesophago-gastro-doudenal lesions which permits a thorough inspection and provides the information on the nature , extent, and location of the lesion with a directed biopsy for a tissue diagnosis of surface lesions from the upper part of the esophagus to the second portion of the duodenum. Cytologic techniques like brush cytology can be adopted for diagnosing the upper gastrointestinal conditions, including benign and malignant lesions. Literature shows that brush cytology increased the diagnostic accuracy in conjunction with endoscopic biopsy with conflicting reports regarding the superiority of screening madality.[6] [7] However, on the basis of the available data there is no general consensus as to whether cytology should be done regularly.

In the light of the difficulties in deciding whether an endoscopically visualized lesion is benign or malignant and the high value of a correct preoperative diagnosis, it is considered to be important to assess the reliability of both procedure, i.e., endoscopic biopsy and brush cytology in a prospective study. Hence the present study is carried out to evaluate the utility of brush cytology and combined use of brush cytology and biopsy in diagnosing upper gastrointestinal neoplasm.

Materials and methods

The present prospective study is undertaken for a period of 1 year from January 2011 to December 2011. Patients having upper gastrointestinal symptoms such as dysphagia, vomiting, retrosternal pain, anorexia, loss of weight and mass abdomen etc. are subjected to upper gastrointestinal endoscopy. On endoscopy patients with visible mucosal lesions such as ulcer, polypoid or ulcerative growth are included in the study with formal informed consent of the patient.

A cytology brush, which is made up of small nylon bristles at the tip with an outer protective sheath with an outer diameter of the brush 3 mm, outer diameter of the sheath 7.0 Fr and the total length of the brush 160 cm with brush present at the distal 3 cm, is introduced through a separate channel in the endoscope. The brush is advanced up to the lesion and the exfoliated cells are obtained by leading the brush several times across the lesion until mucosal bleeding is observed. The brush is withdrawn into its sheath and removed. Four smears are made directly smearing the brush onto the glass slides. Two slides are air-dried and stained with Diff-Quik and May-GrunWald-Giemsa stain. Two slides are fixed with 95% ethyl alcohol and stained with H&E and Papanicolaou stain. After brushing, multiple punch biopsies are taken from all the quadrants, surface and margins of suspicious lesions by using double pronged 2.8 mm or 3.6 mm channel biopsy forceps. The tissue fragments are fixed in 10% buffered formalin and processed routinely. Histological sections were stained by H&E method. Special stains for demonstration of mucin are done with Periodic Acid-Schiff wherever required.

The cytological interpretations are made as per the criteria proposed by Malhotra et al.[8] The smears are categorized as follows. Positive cytology when there is presence of frankly or unequivocally malignant cells. These smears are further categorised into squamous cell carcinoma and adenocarcinoma, depending upon the cytologic features whenever possible. Suspicious cytology when atypical cells suspicious for, but not confirmatory of malignancy are present. Negative cytology for those cases having unequivocally negative or atypical cells consistent with an inflammatory or reparative process or those cases in which a diagnosis cannot be made because of inadequacy of the material.

The histopathological interpretations are derived according to WHO classification[9] and the criteria

proposed by Vienna Classification of Gastrointestinal Epithelial neoplasia as: (1) Negative for neoplasia/ dysplasia, (2) Indefinite for neoplasia/ dysplasia, (3) Non-invasive low-grade neoplasia (low grade adenoma / dysplasia), (4) Non-invasive high-grade neoplasia- 4.1 High grade adenoma/ dysplasia, 4.2 Non-invasive carcinoma (carcinoma in situ), 4.3 Suspicion of invasive carcinoma, (5) Invasive neoplasia, 5.1 Intramucosal carcinoma, 5.2 Submucosal carcinoma or beyond. [10]

Statistical analysis: categorical variables are presented as frequency or percentage. Continuous variables with normal Gaussian distribution are presented as mean and standard deviation and with non-Gaussian distribution are analysed as median and inter quartile range. The diagnostic utility of brush cytology, endoscopic biopsy and brush cytology and endoscopic biopsy together is evaluated by calculating sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy. For analysis purpose all the cytological findings and endoscopic biopsy findings are compared with either the excision biopsy findings or multiple repeated punch biopsy findings in highly suspicious lesions, taken as the gold standard. For the purpose of statistical analysis, those smears reported as suspicious for malignancy with endoscopy showing frank growth were included in the positive group.

Results

During 1 year period, both brush cytology and endoscopic biopsy could be obtained from in 120 suspicious malignant cases on upper gastrointestinal endoscopy which formed the study population.

A wide range of age was covered while evaluating for upper GI endoscopy from 5 years (a female child) to 85 years (a male) with mean age of 52 years. Out of 120 cases 79 cases (66%) were males whereas 41 (34%) cases were females. Maximum number of cases was from stomach 97 (80.84%) cases, 19 (15.83%) cases were from oesophagus and only 4 (3.33%) cases from duodenum have been observed. Out of 120 cases 64 (53.3%) cases were diagnosed to be benign and 56 (46.7%) cases as malignant. Oesophagus and stomach showed 12 (21%) cases and 44 (79%) cases to be malignant lesions. All the 4 (3.3%) cases of duodenal lesions were benign in nature.

Out of 12 cases of oesophageal malignancies, middle third of oesophagus was involved in 6 (50.0%) cases followed by upper third 4 (33.3%) cases. 2 (16.7%) cases of oesophageal carcinoma were present in the lower oesophagus which on histo-section proved to be adenocarcinoma. All malignancies distributed in the upper and middle third were squamous cell carcinoma 10 (83.3%) cases.

Out of 44 cases of gastric malignancies, antrum was the most common site of involvement with 32 (73%) cases followed by body 6 (14%) cases and fundus 4 (9%) cases respectively. Only 2 (4%) cases were found to be diffuse carcinoma. All cases were proved to be adenocarcinoma of stomach, 43 (97.7%) cases on histo-section except 1 case of squamous cell carcinoma involving the cardia and fundus.

Brush cytology was negative for malignancy in 68 (57%) cases, suspicious of malignancy in 20 (17%), and positive for malignancy in 29 (24%) cases respectively. In 3 (2%) cases the yield was inadequate or unsatisfactory because of bloody background, mucus, dirty materials with scanty cellular yield.

Out of 29 (24.2%) cases presenting with positive cytologic features of malignancy, 28 (23.3%) cases were true malignant lesions while 1 (0.9%) case was falsely diagnosed to be malignant, which was benign in nature. All cases of suspicious of malignancy on cytology were confirmed to be malignant on final histopathological evaluation. Out of 68 (56.6%) cases of negative for malignancy, 60 (50%) cases were benign lesions but brush cytology failed to diagnose 8 (6.6%) malignant cases.

When 29 (24.2%) cases yielding a positive malignant cytology compared with endoscopic

biopsy, it was seen that 27 (22.5%) cases were positive in endoscopic biopsy with 1 (0.83%) case showing features of dysplasia and 1 case showing inflammatory lesion without any malignancy. Similarly, out of 20 (16.7%) cases of suspicious on cytology, 15 (12.5%) cases came positive in endoscopic biopsy with 1 (0.83%) case showing features of dysplasia but remaining 4 cases were negative for malignancy in endoscopic biopsy. Out of 68 (56.6%) cases found to be negative in cytology 17 (14.1%) cases yielded negative endoscopic biopsy findings, 44 (36.7%) were inflammatory lesions but 7 (5.8%) cases found to be malignant in endoscopic biopsy. 3 (2.5%) cases of inadequate smears were benign in nature on histopathological evaluation.

For comparison purpose we have taken suspicious for malignancy as positive cytology and inadequate specimens as negative cytology. The table shows 48 (40%) cases true positive (T.P.), 01 (0.8%) case false positive (F.P.), 63 (52.5%) cases true negative (T.N.) and 08 (6.7%) cases false negative (F.N.) in cytologic evaluation.

Of all the endoscopic biopsies, 50 (41.7%) cases true positive (T.P.), 01 (0.8%) case false positive (F.P.), 63 (52.5%) cases true negative (T.N.) and 06 (5%) cases false negative (F.N.) in endoscopic biopsy evaluation.

By combining both brush cytology and endoscopic biopsy finding, a positive diagnosis was considered when either of the two is positive and a negative diagnosis was done when both biopsy and cytology were negative. It was found that 55 (45.9%) cases true positive (T.P.), 02 (1.6%) case false positive (F.P.), 62 (51.7 %) cases true negative (T.N.) and 01 (0.8%) cases false negative (F.N.) in combined evaluation.

It is observed that sensitivity of cytology is 85.7% and biopsy 89.3% respectively. But the sensitivity increased to 98% when both are combined together. Similarly the diagnostic accuracy of combined biopsy and cytology is 97.5% in comparison to 92.5% of cytology and 94.5% of biopsy. Other statistical values were comparable in three series as depicted in table no.1.

Table 1: Comparative evaluation of brush cytology, endoscopic biopsy and combined use of brush cytology and endoscopic biopsy in the diagnosis upper gastrointestinal malignancies (n=120).

Methods	Brush cytology	Endoscopic biopsy	Brush cytology & endoscopic biopsy
Sensitivity	85.7%	89.3%	98%
Specificity	98.4%	98.4%	96.8%
Positive predictive value	98%	98%	96.5%
Negative predictive value	88.73%	91.3%	98.4%
Diagnostic accuracy	92.5%	94.4%	97.5%

Discussion

The primary role of gastrointestinal tract cytology is cancer detection. Development of fully flexible endoscopes by Basil Hieschowitz (1957) and use of brush cytology under direct endoscopic vision by D. G. Williams renewed the interest in exfoliative cytology for detection of upper gastrointestinal malignancies.[11] Endoscopy allows the visualization of mucosal lesions, and at the same time, it permits the sampling of cytology and biopsy for a definitive diagnosis.

In the present study, total 120 cases were evaluated by brush cytology, and endoscopic biopsy. The results of this study underline that a reliable classification of endoscopically visualized findings is not possible on the macroscopic aspect in a considerable proportion of oesophago-gastric lesions. 120 cases were suspected to be malignant under endoscopic visualization in our series. But after all evaluation 56 cases (46.7%) were established to be malignant which indicates that basing on endoscopic findings the malignancies were over diagnosed being 53.3% cases were false positive. Ricardo Moreno-Otero et al, Bita Geramizadeh et al also found 65% (out of 20 cases) and 42.4% cases (out of 229 cases of patients with suspicious endoscopic findings) proven to be malignant.[12][13] So each suspected cases should be confirmed by adjunctive

diagnostic modalities like exfoliative cytology and endoscopic biopsy.

Brush cytology was performed in 120 cases of endoscopically suspected malignancy showed negative for malignancy in 57% of cases with suspicious of malignancy, positive for malignancy in 17% and 24% respectively. In 2% of cases the yield was inadequate or unsatisfactory because of bloody background, mucus, dirty materials with scanty cellular yield. For statistical calculation we considered positive for malignancy and suspicious of malignancy under positive diagnosis and negative for malignancy and inadequate or unsatisfactory smears under negative diagnosis.

On evaluation of brush cytology from 120 lesions 24% (29 cases) showed positive cytologic findings of malignancy. Out of which 28 cases were proved to be malignant on final diagnosis and 1 case diagnosed as false positive malignant which came out to be inflammatory lesion with mucosal ulceration, epithelial inflammatory atypia, and inflammatory cell infiltration without any features of invasion of atypical cells into the lamina propria. All 20 cases (17%) found to be suspicious for malignancy proved to be malignant on final diagnoses. Thus the inclusion of the 'suspicious' category alerts the clinician about the possibility of malignancy. Out of 68 cases diagnosed as negative for malignancy on brush cytology, 8 cases were proved to be malignant on histology. Patient management is altered in these situations so that a repeat endoscopy biopsy becomes mandatory. Similar results were obtained by Vidyavathi et al (2008), J M O' Donoghue et al (1995) who advocated for inclusion of suspicious category in the reporting of brush cytology which could alert the physician of possible malignancy. (14) (15)

While comparing endoscopic brush cytology findings and endoscopic biopsy finding we found that 80% (16 cases) of suspicious cases on brush cytology came positive in endoscopic biopsy. While 4 cases the endoscopic biopsy yielded a negative results. When these 4 cases were subjected to repeat endoscopic biopsy 3 became positive but 1 case was negative.

The single case which was negative on repeat endoscopy was actually a case of post-operative partial gastrectomy case for adenocarcinoma of stomach presenting after 1 year with upper GI symptoms. The case was for the third time evaluated with multiple biopsies and this time it came positive. This indicates that as brush cytology covers a greater surface area the diagnostic yield of brush is better than biopsy which covers patchy areas by which residual malignancy could be missed. Similar opinion was suggested by Hong-Qi Peng *et al (*2008).(16)

All those 3 suspicious cases came positive only on repeat biopsy were having severe gastric outlet obstruction in one case and 2 cases with gastric carcinoma in the region of cardia and fundus where the biopsy forceps could not be introduced through it but brush easily got access to some extent. Thus it is evident in our study that brush has advantage over biopsy in sampling stenotic lesions and lesions of cardia and fundus of stomach.

The diagnostic utility of brush cytology in our study is compared with other studies which show very similar findings. The endoscopic biopsy has established its role as an important diagnostic modality for detecting malignancy in upper GIT. The diagnostic sensitivity of multiple endoscopic biopsies matches well with that of other series which varies from 70% to 96%. The combined diagnostic accuracy of endoscopic biopsy and brush cytology was 97.5% with the sensitivity, specificity, positive predictive value and negative predictive value are 98%, 96.8%, 96.5% and 98.4% respectively. It is evident that by combining both cytology and biopsy the sensitivity increased to 98% from 85.7% of brush cytology and 89.3% biopsy alone. Previous reports have also shown an increase in accuracy rate using combination of two methods. (Table-2)

Table -2: Diagnostic accuracy of different tests by different authors

Authors	Cytology alone	Biopsy alone	Combined Cytology & biopsy
Giovani et al (1975)(17)	85%	73%	93%
Qizilbash et al (1980)(18)	88.6%	93.2%	95.4%
Gupta et al (1983)(19)	81%	72%	91%
Meebakshi et al (2008)(20)	89.71%	88.24%	100%
Present study (2011)	92.5%	94.2%	97.5%

The limitation of cytology is its inability to distinguish between dysplastic / carcinoma in situ and invasive carcinoma. A tumor diathesis and a high cellularity in a smear may indicate invasion, but not with certainty. Another issue is whether the brushing should be performed before biopsy or after biopsies. Some of the authors prefer to perform the brushing after biopsy believing that it might decrease the yield of biopsy. However, studies have shown that accuracy of brush cytology in patients with carcinoma was significantly higher when brushing was performed before biopsy than after biopsy. In the present study, brushing was performed before biopsy, although 3 smears yielded inadequate or unsatisfactory smears. Those cases on endoscopy found to be benign in nature.

The study is limited by its small sample size and a prospective study with larger sample size is required.

Conclusion

The Brush cytology is simple practical tool possessing the potential for screening of upper GI malignancies as an office procedure with comparable diagnostic sensitivity to that of endoscopic biopsy. It is a useful adjunct in the diagnosis of upper GI malignancies and should be considered as a routine method in combination with biopsy.

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