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Medical and Endoscopic Management of High-grade Dysplasia in Barrett's Esophagus

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Abstract

The management of high-grade dysplasia in Barrett's esophagus has clearly changed over recent years. The risk of cancer development is still substantial with about 1 in three patients developing cancer but a number of patients do not develop cancer. The nature of high-grade dysplasia has also been genetically elucidated with more evidence of chromosomal instability being present at this stage than previously thought. Therapy of the condition has evolved more towards endoscopic therapy given the good results of radiofrequency ablation and photodynamic therapy in eliminating dysplasia and decreasing cancer development in randomized controlled trial. The best candidates for treatment include compliant patients that have relatively short segments of Barrett's esophagus, an anatomically straight segment, lack of nodularity, and an intact p16. However, even with excellent long-term results similar to surgical resection, the risk of recurrence is present in over 14% of patients which indicates that there will be a need to continue surveillance endoscopy in these patients.

Introduction

Barrett's esophagus with high-grade dysplasia has traditionally been viewed as a surgical condition that necessitated esophagectomy. However, recently, it has been established that the risk of cancer progression is not as certain as once assumed and that there are specific patient populations can be identified that are at higher risk. Histologic classification of dysplasia has also been called into question with issues of sampling and interpretation error being identified. At the current time, histology is still used as the "gold standard" for classifying cancer risk in Barrett's esophagus but other biomarkers are appearing on the horizon. In addition, new methods of imaging are being developed that can identify areas of dysplasia. Once the high-risk patients can be identified, the novel therapies currently available have already been demonstrated to be effective in decreasing dysplasia and development of cancer.

What is High-Grade Dysplasia ?

High-grade dysplasia criteria have been defined and primarily derive from observations made in colonic polyps. The histological definition implies evidence of a enlarged nuclei with nucleolar disorganization ¹, stratification of columnar cells that persists to the surface of the glands, disorganization of the glands, and increased nuclear crowding ². The agreement of expert pathologists in distinguishing high-grade dysplasia or cancer from low grade dysplasia is associated with a kappa of 0.65 which is excellent ³. However, it is also clear that the patient tissues used for this study must have been very clearcut high-grade dysplasia cases with over 60% of these patients progressing to cancer which is a higher rate than any other series reported in the literature ⁴. Criteria have emerged recently that suggest high grade dysplasia with features such as more than three dilated glands with intraluminal debris or more than a single foci of single cell infiltration of the lamina propria was associated with concomitant cancer ⁵. These criteria help identify a patient cohort that are likely more neoplastic than typical high grade dysplasia.

Subsets of high-grade dysplasia have been identified at lower risk of cancer as well based upon the amount of high-grade dysplasia appear to have less risk. Focal high-grade dysplasia defined as finding less than 5 glands containing high-grade dysplasia in any of the biopsies taken in a surveillance endoscopy is actually associated with a risk of development of cancer similar to low grade dysplasia ⁶. It is very difficult to find large cohorts of patients with high-grade dysplasia and one of the major weaknesses in the field is the heterogeneity of the reports that was found in a recent meta-analysis on cancer risk ⁷. This meta-analysis found marked differences between studies in the incidence of cancer. This may be due to a mixture of prevalent and incident high-grade dysplasia cases in most reported studies with those studies with prevalent high-grade dysplasia having much higher risks of cancer development. Studies that eliminated prevalent high-grade dysplasia result in much lower cancer incidences ⁸. As studies have found histology to be a poor marker for cancer, alternative biomarkers have been sought.

Where are Potential Biomarkers ?

The difficulties of using high-grade dysplasia as a marker of potential neoplasia was recognized decades ago as well as the ability to define a subgroup of patients with flow cytometric abnormalities as being at higher risk ⁹. However, although these techniques have been described, commercial acceptance of these as potential biomarkers as well as other molecular markers such as p53 loss of heterozygosity have not been used in practice due to the complexity of the procedures needed to obtain the biomarkers ¹⁰. Though carefully investigated as a research tool, translatability into a clinical tool has been limited since the specimens were obtained from flow cytometry sorted nuclei that are identified as being proliferative (Ki-67 positive) which not only purifies the epithelial cell population, it also increases the chance of finding dysplastic cells that generally are dividing more rapidly. The ability to conduct this type of flow sorting is not widely available in the typical clinical setting. Though image cytometry would be simpler to perform and yield similar information, this technology has not been validated in a large prospective trial.

Molecular markers have been investigated with several promising techniques being identified. These markers have to be successful outside of the laboratories of investigators who develop them. These assays need to be translated to clinical laboratories and be made robust enough for everyday usage. This requirement certainly has been developed in areas such as virology where rapid assays for viral subtypes are being utilized routinely. However, in areas such as Barrett's esophagus, these arrays have not been commercialized. Whole genome sequencing or deep sequencing of exons has also reached the point that the technology could become cost effective enough to be applied to clinical use. However, there are complex statistical analysis that must be applied to trillions of bits of sequencing information. One common approach is to investigate specific gene or chromosomal abnormalities that are correlated with progression. These studies have included markers such as gene expression profiles, single nucleotide polymorphisms, gene methylation, microRNA, and protein kinases ¹¹⁻²⁰. It is interesting that despite the work that has been done, there is inconsistency between biomarkers that have been found. An example has been the use of methylation arrays to identify potential biomarkers. In one study, the methylation of RUNX3, p16, and HPP1 were found to be predictive of cancer development in Barrett's esophagus ²¹. In another study, p16 and APC hypermethylation were found to be correlated with progression of disease ²². The identified biomarkers are often inconsistent between studies and have not been validated in long-term study prospective cohorts.

Other studies have been focused more on detection of genetic or epigenetic processes that indicate that neoplastic progression is possible. One promising area is the detection of chromosomal instability. This was also recently found in a study in Barrett's esophagus that examined copy number abnormalities. This study found that when 70 megabases or more were involved with changes, there was a hazard ratio of 4.9 of developing malignancy ¹⁹.

Fluorescence in situ hybridization can also be used to assess gene copy number. Probes can be directed to specific areas that are known to be affected by gene copy alterations. Fluorescent in situ hybridization is a very translatable biomarker since it is already being performed in commercially available labs and abnormalities can be diagnosed based on a single abnormal nuclei. This is an advantage over traditional gene arrays that require that the sample contain at least 10% abnormal tissue to discern a copy number abnormality. Fluorescent in situ can hybridize probes to specific areas of the DNA including genes (locus specific probes) or centrosomal probes to define whole chromosomes. Multiple probes are needed to find evidence of loss of heterozygosity (LOH) ²³. However, the most reliable FISH predictor of cancer development has been found to be polysomy which is associated with multiple gains in two or more loci which generally is found in the setting of chromosomal instability ²⁴. This is consistent with studies that have examined the copy number changes found in dysplasia and clearly show that chromosomal instability is associated with neoplastic progression in Barrett's esophagus ¹⁹. FISH can be applied on cytological specimens that are much easier to apply than biopsy based assays ^{25, 26}. Although cytology has not been traditionally used in Barrett's esophagus, these new technologies have lead to a re-evaluation of this technology that can allow for more rapid clinical assessment of the Barrett's mucosa more rapidly than surveillance biopsies ²⁷.

Imaging Techniques

The use of chromoendoscopy for Barrett's esophagus has been attempted with several different agents used to contrast non-dysplastic mucosa from dysplastic mucosa. These range from indigo carmine that provides surface contrast to methylene blue that is absorbed by the cells. Methylene blue was initially used by pathologists to visualize crypts in the colon but these techniques were also applied to the esophagus. However, studies have found that though methylene blue does aid in identifying areas of intestinalized metaplasia, their ability to detect dysplasia is more limited^{28, 29}. These techniques tend to emphasize the glandular patterns (pit patterns) that are observed in Barrett's esophagus and were more useful when endoscopes were fiberoptic and magnification and resolution were limited³⁰. However, with high magnification endoscopy, the contrast agents were again introduced since cellular appearance is difficult to appreciate without some topical enhancement.

Electronic enhancement with narrow band imaging has increased the ability to detect dysplasia in Barrett's esophagus. This as well as other processing techniques such as I-Scan and FICE from other manufacturers tend to emphasize vascular abnormalities by increasing contrast between the capillaries and mucosal tissues. In addition, these techniques tend to enhance mucosal patterns as well. These two criteria have been used to determine the dysplastic potential of the mucosa in multiple prospective randomized trials comparing narrow band imaging to either high resolution white light imaging or other imaging modalities³¹⁻³⁴. A recent meta-analysis has found that narrow band imaging had a pooled sensitivity of 96%, specificity of 94%, and diagnostic odds ratio of 342 for the detection of high grade dysplasia on a per lesion basis³⁵.

Newer techniques have also evolved that allow endoscopist to visualize the mucosa at even a higher magnification with intravenous fluorescein contrast given to enhance the vasculature. This is primarily laser confocal endomicroscopy that can be performed with either a probe or a modified endoscope³⁶⁻³⁸. The images are usually very limited views of the mucosa at 400 times magnification. Recent studies suggest that laser confocal endomicroscopy can detect more areas of high grade dysplasia than the use of NBI and white light endoscopy³⁹.

Medical Management

Although medical management was once a standard of care, with the development of successful ablation therapies, it is primarily reserved for individuals that have limited life expectancy or are unable to tolerate endoscopic or surgical management. There are no medical therapies that have been proven to decrease evolution to cancer from high-grade dysplasia. Although non-steroidal anti-inflammatory agents appear to be useful from a population standpoint, a randomized controlled trial using celecoxib was not found to be beneficial in reducing pre-determine intermediate endpoints in a prospective multicenter trial^{40, 41}. The use of proton pump inhibitors are also a tempting chemoprevention agent and are known to decrease inflammation as well as inflammatory mediators. However since proton pump inhibitors are ubiquitous in their usage in Barrett's esophagus, it is difficult to find an adequate control group for case control studies. In patients with Barrett's esophagus,

statins are associated with an almost 50% reduced odds ratio of cancer development but the interpretation is limited by likely unidentified confounders.⁴² None of the possible medications available have been demonstrated to have an effect in high-grade dysplasia.

Evolution of Ablation Therapy

Ablation in Barrett's esophagus began in the era of endoscopic cautery devices that were originally developed for the treatment of bleeding lesions or for palliation of cancer. These included thermal lasers, argon plasma coagulation, and bipolar cautery devices. An argon laser was one of the first devices that were reported to be able to ablate Barrett's mucosa⁴³. This study demonstrated the importance of squamous regeneration from adjacent squamous mucosa and forms the foundation of therapies today that ablate columnar mucosa with regeneration from adjacent squamous mucosa proximally.

The evolution of ablation therapy rapidly incorporated multipolar coagulation and argon plasma coagulation. Multipolar coagulation was more difficult to apply as a contact method but in randomized controlled trials performed as well as argon plasma coagulation⁴⁴⁻⁴⁷. These technologies functioned well but soon fell out of favor since ultimately it was a case of treating a widespread mucosal problem with technologies designed to treat point areas. Gaps in treatment occurred and the issue of buried Barrett's mucosa surfaced^{44, 48, 49}. Adenocarcinoma and buried high grade dysplasia were noted. Although there has been recent evidence that burying the mucosa may be protective against further progression, this has not been confirmed⁵⁰.

Photodynamic therapy with a variety of agents was attempted. The first randomized controlled trial using sodium porfimer demonstrated a significant decrease in cancer formation in patients with high grade dysplasia (13% versus 28% in the control population)^{51, 52}. Recent updates have found that these benefits were found on 5 year follow-up. However, this therapy was associated with cutaneous phototoxicity which could persist 30-90 days after receiving the photosensitizer. In addition, since most patients had several courses of photodynamic therapy, there is an esophageal stricture rate of 31%.

Radiofrequency ablation has come to supplant photodynamic therapy for most patients since it is not associated with phototoxicity and it has a much reduced side effect profile.

The treatment is initially delivered using a 3-centimeter long radiofrequency balloon with a coil mounted on the balloon surface (Figure 2). The tissue is treated at a dose of 12 Joules/square centimeter⁵³ after the surface is carefully inspected to ensure good contact between the coil of the device and the esophageal mucosa. The radiofrequency energy is delivered in less than a second and creates very superficial injury to the mucosa. The eschar from the injury is thoroughly removed with a cap fitted endoscope and then the Barrett's segment is again treated with the balloon. This works very well but careful attention must be paid to selecting the correct sizes of the treatment balloon. In addition, the surface should be cleansed of mucus with n-acetyl-cysteine. The problem areas with this treatment is in patients with very tortuous or strictured esophagus which makes obtaining contact between the treatment balloon and the surface difficult. Overall results are excellent with elimination of high-grade dysplasia in 80% of treated patients with only a 6% stricture rate⁵³. More

recent studies have found that the squamous mucosa that reepithelializes the mucosa stays intact for at least three years with an cumulative stricture rate of 8% ⁵⁴..

Prior to the ablative therapy, all nodules should be removed since they interfere with contact of the coil to the mucosa surface and studies have found that cancer can be found in these nodular lesions ⁵⁵. Focal treatment of nodules generally consists of endoscopic mucosal resection which can provide treatment of the dysplasia as well as histological confirmation that the lesion has been eliminated ⁵⁶.

Endoscopic mucosal resection can be performed with either a cap or a band technique. Both techniques yield comparable sized tissue and have similar complication rates (with comparable numbers of mucosal resections) ⁵⁷. Elimination of the area of the known neoplasia is not generally curative with risks of recurrence if there is residual intestinal metaplasia ⁵⁸. Widespread mucosal resection has been used to treat the entire Barrett's segment since it can provide histological information about occult malignancy that may be present. A recent cohort study has found that about 14% of patients have their diagnosis upgraded upon widespread mucosal resection but this occurs at the expense of a 37% esophageal stricture rate ⁵⁹. A recent European cohort study has confirmed the very high stricture rate with this technique that limits its widespread applicability. In addition, despite the aggressive endoscopic treatment, there is still a 20% rate of subsquamous Barrett's mucosa found on follow-up surveillance. Endoscopic mucosal dissection techniques have also been used to treat Barrett's esophagus using circumferential mucosal cutting techniques that have mainly been developed in Asia. Although these potentially can remove large areas of malignancy, it is unclear that in the West early cancers that are removable with these techniques remain superficial beyond 2 centimeters in diameter.

Conclusions Current management of Barrett's esophagus with high-grade dysplasia is deficient in terms of tools for risk stratification. Improved biomarkers that are readily translatable such as image cytometry and fluorescent in situ hybridization are becoming available to aid clinicians. This is a major step forward as these tools are needed to help determine the therapy. Treatments have clearly advanced with radiofrequency ablation becoming the cost effective treatment of choice for high-grade dysplasia. Mucosal resection techniques are now well established for the treatment of early cancers within Barrett's esophagus. Significant advances have been made in the management of Barrett's esophagus and it is anticipated that this will improve further with newer developments in molecular diagnosis.

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Fig. 1. Fluorescence in situ hybridization. On the left is a normal disomic cell with two copies of each of the chromosomal probes utilized (red, gold, blue, and green) that in this case represent 9p21, 5q21, cep 9 (centrosomal), and 5p15. On the right are two cells with multiple copies of these genes representing polysomy. Polysomy is an indicator of chromosomal instability.

Fig. 2. Narrow-band imaging views of a nodule on the left. This shows the dilated vasculature with irregular appearance to the mucosa. On the right is an area of high-grade dysplasia with flat, irregular appearing mucosa along with vascularity that is haphazardly arranged.

Fig. 3. The 360-degree radio-frequency ablation catheter is shown on the left. The post-ablation appearance of the Barrett's segment is shown on the right.