Management of Barretts oesophagus – Are we there yet?

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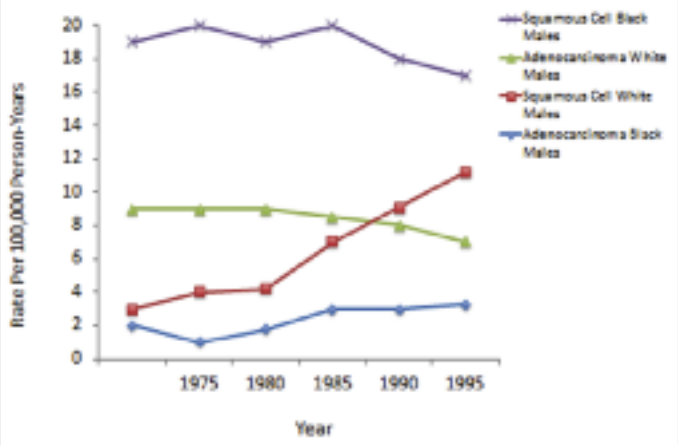
No management strategy for patients with Barrett's oesophagus has been proven to prolong life. To date guidelines have been proposed by a number of medical societies each differing on the optimal management.[1,2,3,4] The most recent, the American Gastroenterology Association (AGA) position paper for Barrett's oesophagus published in 2011 advocates 3 pillars of management: acid suppression; surveillance and treatment of dysplasia. Chemoprevention strategies still threaten on the horizon as a possible 4th.[1]

Globally, South Africa has one of the highest incidences of oesophageal cancer. The vast proportions of these cases are squamous cell carcinoma as opposed to adenocarcinoma. This however is set to change, with epidemiological studies demonstrating a definite reversal in the incidence with adenocarcinoma becoming more prevalent in mature westernized countries. Figure 1.[5] The current situation in South Africa is unknown. Presumably if the current upward trend of obesity, GERD and H.Pylori eradication continues in our ever-westernizing society, an increase incidence of Barrett's oesphagus and primary oesophagus adenocarcinoma should be expected in all population groups.[6,7,8,9,10] This would be in line with the worldwide trend where the incidence of primary oesophagus adenocarcinoma is increasing at rate higher than any other cancer.[11]

The purpose of this review is to highlight to the reader the fundamental issues in the management of Barrett's oesophagus and to appreciate and have insight into the challenges facing the South African Barrett's population.

Figure 1: Incidence of oesophageal carcinoma by cell type and race



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Acid Suppression

The premise of this management strategy is partly based on the strong association of GERD[14] with Barrett's oesophagus and that in clinical in vitro studies metaplastic intestinal epithelium exposure to acid resulted in an over expression of cycloxygenase -2 and increased activation of mitogen activated protein kinase, both driving hyperproliferation and decreased apoptosis in metaplastic cell lines.[15,16,17] It was further demonstrated that with PPI use for symptomatic GERD patients with Barrett's oesophagus there was a decline in proliferating cell nuclear antigen (PCNA, a proliferation marker) and increased expression of villin, a biomarker of differentiation. This however only occurred in a proportion of patients where acid suppression was effective.[18]

The clinical goal of acid suppression is regression of the Barrett's metaplastic epithelium and the reduction of cancer risk. Clinical studies have been mixed in their results with both full and partial regression being reported with aggressive PPI use.[19,20] Of concern to the endoscopist, is the entity of buried intestinal metaplasia in areas of mucosal regression.[21,22] Some observational trials have shown reduced dysplasia and cancer risk with PPI use, however overall the results are heterogonous.[23,24] Possibly due to the differences in accrued genetic mutations along the multi –hit hypothesis of malignant transformation.[24]

Complete acid suppression is pivotal however practically this seems unattainable. Clinical studies have however shown up to 80% of Barretts patients have persistent acid reflux, particularly nocturnal gastric acid breakthrough, and that resolution of GERD symptoms does not correlate with complete acid suppression.[25,26,27] Even with considerable appropriate acid suppression, a profound reflux diathesis exists that exposes the

metaplastic epithelium to a low pH.[28]

Evidence that suggests that surgery can reduce the risk of adenocarcinoma of the oesophagus is based purely on uncontrolled studies and is currently not recommended as a management option.[29]

The current stance adopted by the AGA is that aggressive acid suppression may prevent cancer but the evidence is not conclusive.[1]

Surveillance

The yearly incidence rate of oesophageal adenocarcinoma in the Barretts population ranges between 0.1 and 0.5%.[30-38] Although the relative risk is some 30 x greater than the normal populous, the absolute risk is negligible/low.[39] A metanalysis in 2010 and several studies showed that the cancer incidence rate in a Barretts population was between 4 -5 per 1000 years.[40]

Subsequently controversy surrounds the value of surveillance in Barrett's patients where studies cite the overall mortality incidence due to oesophageal adenocarcinoma as 3 per 1000 patient years or 0.4% per year whilst other causes of mortality accounted for 37 per 1000 years. Furthermore there are no randomized prospective trials that demonstrate a survival benefit of surveillance with only a few flawed observational studies (lead time and healthy volunteer bias) showing benefit.[41-46]

Variable risks have been reported in studies of cancer progression in low and high grade dysplasia. This is found more so in low grade dysplasia studies where the annual incidence rate varies between 0.6% and 13%.[47-52] The histopathological interpretation of low grade dysplasia can perhaps be held accountable for this variability. The recommendation now is that low grade dysplasia must be diagnosed by 2 pathologists with an expertise in oesophageal histopathology.[1] Consensus currently places the cancer incidence in the setting of low grade dysplasia between 0.5% reported in the overall Barretts population and the 5-8% in high grade dysplasia.[48,49,53,54]

Sampling error further reduces the efficacy of surveillance. Several studies have shown the presence of adenocarcinoma both in situ and invasive in 40% of oesophagectomy specimens from patients diagnosed with high grade dysplasia.[55,56,57] To reduce sampling error, multiple biopsies and high resolution white light endoscopy is recommended.[58,59,60,61] High resolution white light has been able to show subtle mucosal changes in dysplastic tissue. Several other endoscopic techniques have been used to reduce sampling error however none has shown superiority over white light endoscopy. These include chromoendoscopy, endosonography, optical coherence tomography, high resolution endoscopy, confocal microendoscopy, absorption, light-scattering, fluorescence, narrow band imaging, and Raman detection methods.[1] This may soon change with molecular imaging progressing with a recent discovery of fluorescent labeled lectin. Wheat agglutinin, as a surrogate to lectin, was shown to have variable binding patterns to cellular glycan whose expression changes with progression from non-dysplasia, dysplasia and adenocarcinoma.[62] Refinement of this modality is expected to strengthen current surveillance methods. As it stands the AGA recommends biopsies every 2 cm from 4 quadrants with this interval decreasing to every 1cm (Seattle biopsy protocol) in patients with known or suspected dysplasia.[1]

There are varying incidences of dysplasia and adenocarcinoma in short and long segment Barrett's oesophagus. It appears that patients with short-segment Barrett's oesophagus have a lower incidence of dysplasia since less mucosa is involved (6 to 8 versus 15 to 24 percent in long-segment.[63,64,65] Retrospective data also suggests that the risk of cancer for patients with short-segment Barrett's oesophagus is less than that for patients with long-segment disease. A prospective study demonstrated this by showing risk of developing high-grade dysplasia or cancer was higher with longer segments of Barrett's esophagus (risk ratio of 1.1 for every centimeter increase in length.[50] Despite this, there is no allowance for this in current surveillance methods, as practice is identical in both grades of dysplasia.

The use of molecular biomarkers as an alternative method to oesophageal biopsy has been studied. Abnormalities in p53 and cyclin D expression were initially promising; however none to date have shown any value in clinical practice.[1]

AGA 2011 position paper recommends the following intervals for surveillance: non dysplastic – 3years; low grade dysplasia – 6 to 12 months and high grade dysplasia - 3months.[1]

Treatment of High Grade Dysplasia

The efficacy of all the following modalities of treatment in reducing cancer deaths is unknown. This is largely due to the fact that the follow up durations in most studies for the treatment of Barretts are considerably less than 5 years.

Oesophagectomy

Although complete dysplastic tissue removal is certain, it has the highest procedure related mortality and long term morbidity. Several studies have shown an inverse relationship between oesophagectomy mortality rates and how often the procedure is done at the institution.[66,67] At centers doing less than 5- 10 procedures a year a mortality rate of 12% is reported and at least 1 serious post-operative complication (pneumonia, arrhythmia, myocardial infarction, heart failure, wound infection, anastomotic leak) occurs.[68,69] High volume centers the average mortality rate is 5 %. This is extrapolated from series where patients had advanced carcinoma of the oesophagus including both squamous and adenocarcinoma sub types and multiple comorbidities. Recent series reveal that mortality rates in oesophagectomy patients with early invasive adenocarcinoma and/or high grade dysplasia is considerably lower than 5 %.[70,71] Minimally invasive techniques report similar post-operative morbidity and mortality rates. The only benefit illustrated is reduced blood loss, postoperative pain, and ICU stay.[72] 2011 AGA guidelines have omitted oesophagectomy as a potential treatment for high grade dysplasia, and recommend only endoscopic ablative therapies or endoscopic mucosal resection.[1]

Endoscopic Ablative Therapies

There are a number of modalities described (argon etc). The 2 most widely investigated is photodynamic and radiofrequency ablation.

Photodynamic therapy is a welcomed innovation in the treatment of high grade Barrett's esophagus. Its ease of use, the need for fewer endoscopic sessions compared with thermal ablative techniques, and reduced morbidity, mortality, cost when compared with surgery make it an attractive alternative therapy modality. Currently 2 photosensitizing agents predominate: porfimer sodium (PHOTOFRIN) and 5-aminolevulinic (5-ALA). Photofrin accumulates in neoplastic tissue at a concentration twice that of normal tissue at 48hrs after IV injection, however it persists in all tissues for up to 30 days. The drawback is photosensitivity to sunlight and artificial light. The newer agent 5-ALA causes an accumulation at the ferrochelase rate limiting step of heme synthesis. The subsequent accumulation of the heme precursor protoporphyrin-IX (PpIX) makes the tissue photosensitive. This preparation can be taken orally and photosensitivity remains for only 48 hours. It only involves the mucosa and therefore potentially reduces complications. This may prove not to be beneficial in Barrett's esophagus where deeper penetration maybe required.[73,74,75]

Concerns regarding this modality of treatment include: stricture formation in about 30 – 40% of patients[76,77]; the adequacy of treatment of invasive foci within the high grade dysplasia and the histopathology of buried metaplasia in the neosquamous epithelium.[78] Post procedural surveillance is yet to be defined.

In summary photodynamic therapy can be considered for patients with high-grade dysplasia who are poor operative candidates after thorough discussion of the risks and alternatives. Notably, photodynamic therapy for high-grade dysplasia reduces, but does not eliminate, the risk of progression to cancer. In the multicenter study with Photofrin® progression was observed in 13 percent of patients despite treatment.[79] Future ambitions are more refined photosensitizers, and general white light use instead of the current laser applicators.

Radiofrequency ablation (RFA) is an option for the treatment of patients with dysplastic Barrett's epithelium (BE) since RFA decreases their risk of malignant progression. Short to intermediate-term follow-up is promising, and five-year follow-up data suggest that the eradication of BE following RFA is maintained in more than 90 percent of patients. RFA is performed with the HALO system, which is comprised of two distinct ablation systems: the HALO360 system for primary circumferential RFA and the HALO90 system for secondary focal RFA of BE.[80-85]

Patient selection is very important. Patients with high grade dysplasia with visible mucosal changes require combined endomucosal resection. The motive is that should such patients have sub mucosal invasion there is a 15 - 30% chance of local lymph node involvement and require surgery.[86,87,88] Apart from staging prior to RFA, EMR provides a flatter surface which improves the RFA efficacy. The value of combined EMR and RFA is that it addresses the possibility of other metachronous lesions of intramucosal carcinoma. The jury is still out on the use of RFA in patients with low grade dysplasia or non-dysplastic Barrett's oesophagus. Complications of RFA are milder in comparison to the other ablative therapies. Stricture rates in studies of radiofrequency ablation (RFA) for Barrett's oesophagus have been shown to be lower at 6%.[89,90]

Acid suppression post RFA is vital to allow adequate squamous regeneration. Esomeprazole 40 mg twice per day supplemented with ranitidine 300 mg at bedtime and sucralfate suspension (200 mg/mL) 5 mL four times a day is recommended for two weeks after each blation session.[91,92] Two to three months after the last treatment, the absence of residual Barrett's epithelium is confirmed by endoscopic inspection. The use of high-resolution endoscopes with Lugol's staining (2 percent) or preferably narrow band imaging is important to detect even small areas of residual intestinal metaplasia. Since no long-term follow-up data after RFA are available, it is recommended to schedule patients for follow-up endoscopy two and six months after the last treatment and then annually.

Endomucosal resection

The advent of endoscopic mucosal resection (EMR) has displaced oesophagectomy for the treatment of high grade dysplasia and intramucosal carcinoma. Several studies have demonstrated its safety and efficacy in high grade dysplasia and early adenocarcinoma with results comparable to surgery with fewer complications.[93-101] There are however a number of issues.

Internationally, EMR with adjunctive ablative therapies is practiced in Japan and Europe while EMR is more consistently combined with ablative therapies in the USA. The reported recurrence rate of 15 -30% of HGD or early carcinoma from metachronous loci has strengthened the proponents of the combined approach. Remission rates are variable ranging between 59 and 99%. This largely has to do with patient selection where best outcomes are from patients where the lesions are macroscopic types I (protruded type), IIa (flat elevated type), IIb (flat type), and IIc (flat depressed type); a diameter less than/equal to 20 mm; limited to the mucosa; and histologically a well to moderately well differentiated tumor.[101-110]

It can thus be appreciated that successful EMR relies on a thorough initial evaluation involving histopathology, endoscopy and staging procedures. In terms of histology, depth of invasion is the greatest predictor for lymph node metastasis justifying surgery.[86,87,88] Once again, 2 expertise oesophageal histopathologists are required to confirm the diagnosis of high grade dysplasia. Endoscopic assessment requires high resolution white light with a systematic approach to mucosal assessment with the Seattle biopsy protocol being advocated.[1] Finally astute endoscopic ultrasound (EUS) skills are required to determine depth of invasion. This can particularly challenging in Barrett's oesophagus where concurrent inflammation causes doubling of the muscularis mucosae (the histological/EUS landmark of invasive carcinoma) and the oesophageal gastric junction is notoriously difficult to assess.[111] EUS does have a high negative predictive value (>95 percent) for the absence of tumor infiltration into the deeper wall layers and local lymph nodes.[112] This however

can be overridden by the histology assessment from the mucosal resection.[113]

Complete mucosal resections show promise in the future; however this requires significant expertise with significant risk of complications. As of today all data series in EMR are from highly specialized centers which raise concern in its practical application in the community setting.

Chemoprevention

Epidemiological studies from 2003 suggested that NSAIDS (Cox -1 and COX -2 inhibitors) might be protective in Barrett's oesophagus. Cyclooxygenase- 2 (COX-2), whose expression is induced by cytokines, grow factors and mitogens, mediates hyperproliferation and inhibits apoptosis in intestinal metaplasia and adenocarcinoma cell lines. Subsequent metanalysis of cohort studies and observational studies have showed a protective effect of both NSAIDS and aspirin.[114-117] A subsequent study investigating the value of celecoxib showed no benefit in altering progression to dysplasia/carcinoma in Barrett's patients.[118]

The results of a large prospective cohort study were published in Gastroenterology (Dec 2011) again proposes evidence that NSAIDs are protective against further progression in Barretts oesophagus. Low dose aspirin was however not shown to be beneficial.[119] The ASPECT trial in the UK, looking at the efficacy and safety of aspirin in cancer prevention in Barrett's patients is awaited with in the future.

The above mentioned study also reported that statins were also protective and moreover that in combination with NSAIDS a greater protective effect was seen.[119] Statins have long since been investigated for their pleitropic effects particularly their anti-cancer potential.[120-124] Statins competitively inhibit 3-hydroxy-3-methylglutaryl coenzyme A reductase thereby inhibiting the biosynthesis of farnesyl and geranylgeranyl. These metabolites are vital in a process called prenylation whereby intracellular proteins (Ras, Rho and Rac) are activated. Consequently a number of mitogenic cellular pathways are inhibited. Despite several large metanalysis in cancer prevention debunking the benefits of statins[125,126], it remains to be seen in whether these protective characteristics are confirmed in randomized controlled studies in the Barrett's population.

Chemoprevention is currently not a recommendation in the AGA guidelines.[1]

Conclusion

Barrett's oesophagus -Where we are at? The answer to this unfortunately is ''Nowhere near the end!'' If the incidence of Barretts oesophagus and oesophageal adenocarcinoma in South Africa follows the trends seen in other mature westernized countries our health service will be woefully unprepared. Not only are there no standardized management guidelines applicable to the South African context, there is also a complete lack of epidemiological data of what the current incidence is of Barrett's oesophagus and oesophageal adenocarcinoma in 2012. These problems are compounded by the fact that global consensus on management remains elusive and current long term follow-up results of the mentioned newer treatment modalities are still awaited. This negates finding definitive guidance from the international arena. Furthermore the current state of our health fiscus in terms of our HIV burden and financial constraints makes access to most of these modalities of treatment very difficult. Perhaps refined efficacious chemoprevention holds the answer to this but first epidemiological studies are needed.

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