UPDATE ON BARRETT'S OESOPHAGUS

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ABSTRACT

Barrett's oesophagus (BO) is a precancerous lesion associated with the development of oesophageal adenocarcinoma (OAC). Although different types of metaplasia have been described in BO, only the presence of intestinal metaplasia with goblet cells seems to be indispensable for an accurate diagnosis. Surveillance in BO is still controversial and, to date, the endoscopic screening is recommended only for patients who have at least one risk factor for OAC in addition to chronic gastroesophageal reflux disease (GERD), including being 50 years of age, male gender, Caucasian ethnicity, hiatal hernia, increased body mass index, intra-abdominal distribution of fat, nocturnal reflux symptoms, and tobacco use. Moreover, genetic factors play an important and critical role in the development of BO. In particular, genes related to inflammation, DNA repair, and xenobiotic metabolism have been investigated. To date, relatively little is known about the mechanisms that confer susceptibility to BO carcinogenesis even though several risk factors, genetic and acquired, have been identified. Since BO is a complex disease we support the use of advanced intelligent systems to integrate all the variables involved in this complex pathology and in its progression to cancer. In this review we summarise some of the most interesting controversial topics about the diagnosis, pathogenesis, management, and treatment of BO.

Keywords: Barrett's oesophagus, pathogenesis, management, clinical features.

BARRETT'S OESOPHAGUS (BO) OVERVIEW

BO is defined as a change in the tissue lining the oesophagus. In this condition the normal squamous epithelium (SE) of the oesophagus is replaced with specialised columnar-lined epithelium, a type of tissue that is very similar to the intestinal lining. This process, called metaplasia, usually depends on the gastroesophageal reflux disease (GERD), and it is thought to be an adaptation to chronic acid exposure from reflux since columnar cells are more resistant to acid than squamous cells. After BO identification, patients should undergo a periodic surveillance endoscopy in order to identify early dysplasia: the best histological markers for cancer risk. Different studies have established an association between the presence of BO and the risk of progression to the oesophageal adenocarcinoma (OAC). Indeed, the medical significance of BO is its strong association (about 0.5% per patient-year) with OAC, very often a deadly cancer.[1,2] The prevalence of the disease varies from 0.45-2.2% in patients who undergo upper endoscopy and is >12% when the indication is for reflux symptoms. The prevalence has progressively increased in recent years, mainly in the Western world, where it is actually higher at 5.5%.[3-5] The male/female ratio for BO patients is about 5:1; the difference in distribution of fat among men (more central) and women (more peripheral) may explain the increased risk observed in males.[6]

Symptoms, Diagnosis, and Definition

BO does not have any specific symptoms, but BO patients may have symptoms related to GERD. Currently, diagnosis is made by an upper oesophagogastroduodenoscopy (OGD) and biopsy. The OGD allows detection of the metaplastic columnar epithelium that is characterised by a

particular salmon-pink colour and a coarse texture in the distal oesophagus extending up from the gastroesophageal junction (GEJ), compared with the pale, glossy features of the normal tissue of an oesophagus (Figure 1).[7] Endoscopy detects most, but not all, cases of BO because of the individual variations in the anatomy of the oesophagus and the differences in the squamocolumnar junction location in patients with BO. During the OGD, a biopsy is performed; guideline recommendations provide four quadrant biopsies every 2 cm for nondysplastic BO, as well as four quadrant biopsies every 1 cm for dysplastic BO.[8] However, this protocol investigated only a small portion of metaplastic epithelium (5%) and skipped areas with ambiguous and unapparent BO.[9]

The histological spectrum of BO includes one or a combination of three types of columnar epithelium: gastric fundic-type, junctional-type, and specialised intestinal metaplasia (SIM).[10] SIM means intestinal metaplasia with goblet cells, this is the oesophageal epithelial type usually associated with OAC, and has been considered the precondition for BO diagnosis in past years.[8] In the USA, the presence of intestinal goblet cells is widely accepted as a BO diagnostic criterion, even if this definition could recently include the presence of columnar-lined oesophagus without goblet cells. Once the diagnosis is confirmed, it is the difficult task of the pathologist to distinguish whether or not dysplasia is present and even the different grade of dysplasia.[11] The American Gastroenterological Association[8] has defined BO as: "The condition in which any extent of metaplastic columnar epithelium that predisposes to cancer development replaces the stratified SE that normally lines the distal oesophagus."[12]

Screening Strategies

Screening modalities to detect epithelial changes could be divided into endoscopic and non-endoscopic. Specifically, BO can be diagnosed by endoscopic biopsy, endoscopic white-light visual inspection, or high-definition endoscopy (chromoendoscopy) - a newer endoscope with trimodal imaging capacity. However, white-light endoscopy, as well as chromoendoscopy, is expensive and unsuitable for a population-based screening. Therefore, transnasal endoscopy is a cheaper alternative strategy that is well tolerated and specific in BO detection.[9] Recently, new molecular imaging technologies have been developed. Sturm et al.[13] have produced a peptide that binds specifically to BO presenting with high-grade dysplasia (HGD) and BO associated OAC. This peptide proved to be quite safe and useful for addressing both tissue biopsies and the early detection of BO.[13] New advances have been studied in order to detect precancerous lesions, reducing invasive diagnostic examinations such as targeted imaging with novel fluorescent dye, next generation molecular imaging with proteomics, and novel biomarkers.[14-16]

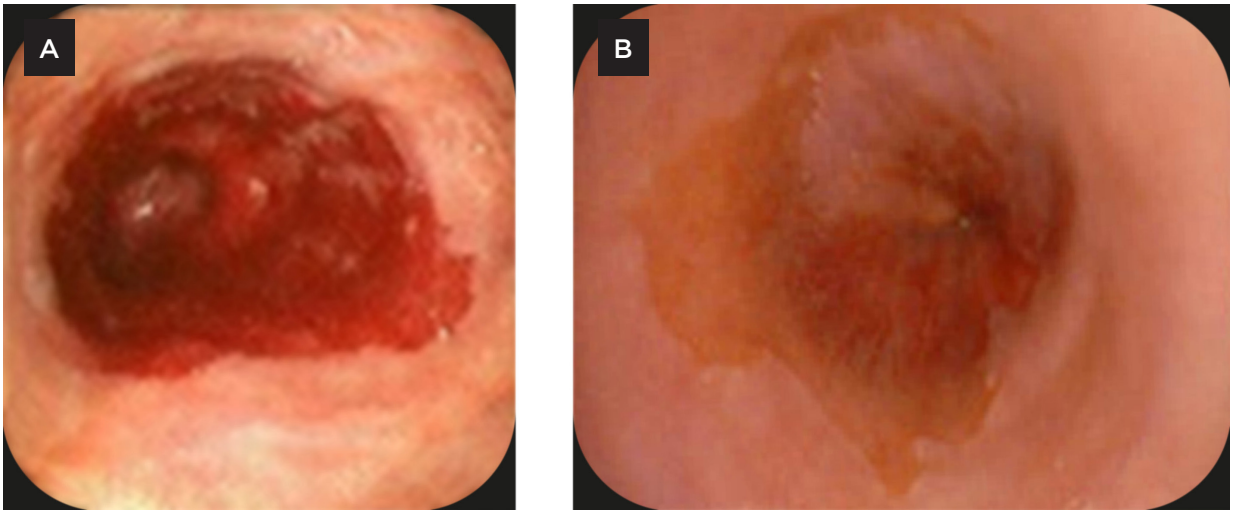

Figure 1: Endoscopic images of Barrett's oesophagus.
A) Great evidence of salmon-pink colour in metaplastic columnar epithelium; B) slight difference of staining between squamous and columnar epithelium.

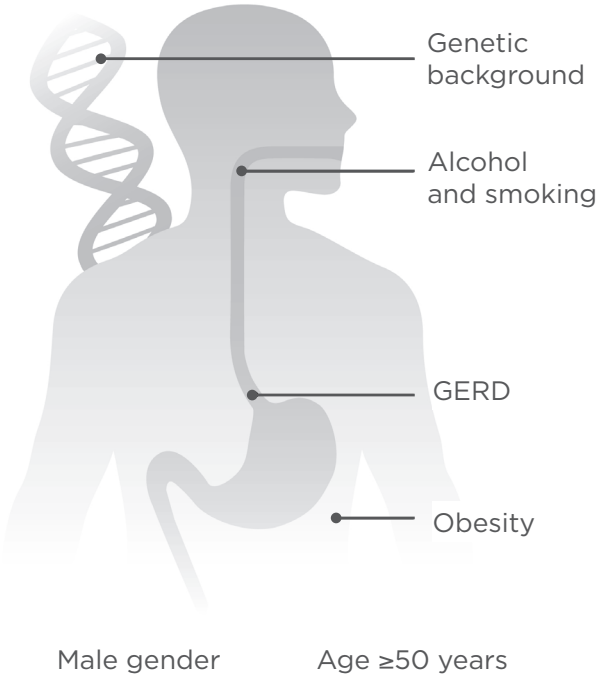

Figure 2: Some of the major risk factors for Barrett's oesophagus.
GERD: gastroesophageal reflux disease.

Among non-endoscopic strategies, we focus on a capsule sponge device (Cytosponge) that has been recently approved by the Medical Health Regulatory Agency in the UK;[17] it consists of a polyurethane sponge, contained within a gelatin capsule, which is attached to a string. To clearly distinguish Barrett's cells from normal cell population, the device is coupled with trefoil factor 3, an immunohistochemical diagnostic biomarker of BO.[17,18] Kadri et al.[19] demonstrated that the Cytosponge test is simple, safe, and well tolerated by patients; the sensitivity and specificity for BO segments of 1 cm or longer are 73.3% and 93.8%, respectively.[19]

Risk Factors

According to the latest guidelines the endoscopic screening for BO may be appropriate only for patients who have at least one risk factor for OAC, in addition to chronic GERD, including being 50 years old, male gender, Caucasian ethnicity, hiatal hernia, increased body mass index (BMI), intra-abdominal distribution of fat, nocturnal reflux symptoms, and tobacco use (Figure 2).[8,12,20,21]

GERD

GERD is the most important risk factor for BO, 5-10% of these subjects develop BO.[22] GERD is a chronic form of gastroesophageal reflux, characterised by regurgitation of stomach contents back into the oesophagus. Acid reflux can cause heartburn, a burning sensation in the midchest, behind the breastbone, or in the upper part of the abdomen, and damage the cells in the oesophagus, causing difficulty swallowing (though this is rare). The features of GERD are different according to short-segment BO (SSBO <3 cm) or long-segment BO (LSBO >3 cm). Approximately 50% of patients with SSBO do not show any GERD symptoms[5] or have symptoms for only a short duration. Conversely, patients with GERD in LSBO tend to have a longer duration of reflux symptoms; in addition 40% of OAC patients have no history of GERD.[23]

Obesity

A strong positive association between BMI and the risk of OAC has been reported;[24] a stronger association of OAC with central abdominal obesity than BMI alone, and a strong association between central obesity and BO has been reported too.[25,26] Central obesity may predispose to GERD by increasing intra-abdominal pressure, and obesity may alter circulating levels of pro-proliferative factors so as to promote oesophageal carcinogenesis.[27] Inflammatory cytokines attract infiltrating immune cells,

which will produce other cytokines, inducing chronic inflammation systematically.[28]

Alcohol and smoking

Different studies on smoking and BO/OAC have shown contradictory results: a greater number of smokers were identified in BO patients compared to the population-based controls; in addition, a dose-response effect linked to cigarette consumption was present.[29] Conversely, Smith et al.[30] found that smoking was associated with an increased risk of BO and BO with dysplasia, but no dose-response effect was found. Other small studies found no clear association.[31] BO studies have generally reported null findings for alcohol consumption; however, results among studies reporting beverage-specific effects have been conflicting. While some have reported an inverse association with wine consumption, others have found lower risk associated with beer, and some evidence for higher risk associated with liquor.[32] These contrasting findings may be due to measurement error; one study captured lifetime alcohol exposure, whilst others used recent alcohol exposure which may be affected by disease status in case–control studies. In one study only wine seemed to be protective[33,34] and perhaps constituents of wine may prevent metaplastic progression to cancer.[35]

Human papillomavirus (HPV)

HPV has been previously investigated in aetiology and progression of BO and OAC with either negative data or positive results of doubtful clinical/aetiological significance.[36,37] Recently, a discovery of a strong association of transcriptionally active high-risk HPV with Barrett's dysplastic tissue has been demonstrated; in addition, viral cancer protein activity was detected more frequently with disease progression. The results strongly indicate that HPV is a common denominator in a significant proportion of pre-malignant oesophageal tissue (Barrett's dysplasia [BD]) and oesophageal cancer.[38]

Genetic risk factors

Several genetic studies have been performed to identify different genomic regions or candidate genes associated with BO.[39-42] Genes related to inflammation, DNA repair, and xenobiotic metabolism have been associated with risk of BO.[43] In 2012, the first genome-wide association (GWA) study on BO was performed in the UK, comprising 1,852 cases and 5,172 controls in the discovery stage and 5,986 cases and 12,825 controls in the replication stage. This study identified two single nucleotide polymorphisms (SNPs) associated with BO: on chromosome 6p21 (rs9257809), within the major histocompatibility complex locus, and on chromosome 16q24 (rs9936833), a locus near the *FOXF1* gene that is involved in oesophageal development and structure.[44] In 2013, another group carried out, for the first time, a GWA of OAC together with the precancerous lesion BO: three new associated loci have been identified. The first, on chromosome 19p13 (rs10419226), is associated with oncogenic activity. The second, in *BARX1* gene, on chromosome 9q22 (rs11789015), encodes a homeobox transcription factor involved in oesophageal differentiation. Finally, the third, in *FOXP1* gene, on chromosome 3p14 (rs2687201), regulates the oesophageal development. The authors conclude that much of the genetic basis for OAC lies in the development of BO, rather than in its progression from a precancerous lesion to cancer.[45] Very recently, Ren and colleagues[46] identified three SNPs and one haplotype in the *CDK1* gene, as well as two SNPs in the *CDK2* gene associated with BO.

Protection Factors and Prevention

Helicobacter pylori

H. pylori infection as well as a 'healthy' diet may decrease the risk of developing BO.[47] Likely *H. pylori* infection decreases gastric acid secretion and thus prevents the development of GERD.[48] While the bacteria damages the stomach and the tissue in the duodenum, some researchers believe the bacteria can actually make the stomach contents less damaging to the oesophagus when GERD is present.

Chemoprevention

Two of the most important strategies to reduce the risk of conversion from BO to OAC are the acid suppression and the modulation of the proinflammatory mechanisms. A wide meta-analysis of 1,813 patients with OAC revealed a greater protective effect of aspirin compared with nonsteroidal anti-inflammatory drugs.[49] Furthermore, a protective role in progression to cancer has also been suggested for statins, and a synergistic role of statins and aspirin in reducing the incidence of OAC in patients with BO has been hypothesised.[50] The AspECT trial,[51] which will be completed in 2019, has recruited 2,500

patients to undergo treatment with aspirin and esomeprazole, a proton pump inhibitor (PPI). Up to now, the treatment appears to be well tolerated and without many side-effects.[51]

Endoscopic surveillance

Dysplasia remains the only validated marker for identifying BO patients at risk, and forms the basis of OAC surveillance. Gaddam et al.[52] recruited a large cohort of 1,401 patients with non-dysplastic BO who were followed-up for ~5 years; the risk of cancer decreased over time, with every subsequent endoscopy, from 0.32% in patients with only one surveillance to 0.11% for patients who had five endoscopies. The largest BO study in the world, the BOSS study,[53] is randomising 3,600 individuals with BO in the UK to evaluate the effectiveness of the surveillance endoscopy; the results are still ongoing.

Artificial Neural Networks and Genetic Predisposition to BO

Relatively little is known about the mechanisms that confer susceptibility to BO carcinogenesis, and the data available are rather controversial due to different methodological issues (e.g. inappropriate control group, lack of population-based DNA collections, small study size, etc.). These findings prompted us to carry out a genetic study.[54] 74 BO patients and 67 controls coming from 6 gastrointestinal (GI) Italian units were evaluated for 6 polymorphisms in 4 genes: *XPC*, *XPD nucleotide excision repair* (*NER*) genes, *XRCC1* (*BER* gene), and *glutathione S-transferase P1*.

Table 1: Some of the genes implicated in the development of Barrett's oesophagus.

Gene Symbol	Gene Name/Description	Expression
ACTA2	Actin, α2, smooth muscle, aorta	+
BMP4	Bone morphogenetic protein 4	+
CDX1	Caudal-type homeobox 1, transcription factor	+
CDX2	Caudal-type homeobox 2, transcription factor	+
COX2	Cyclooxygenase-2, prostaglandin synthesis	+
CCND1	Cyclin D1, cell cycle protein G1-to-S transition	+
COL5A2	Collagen, Type 5, α2, fibrillar collagen molecule	+
EGFR	Epidermal growth factor receptor, transmembrane glycoprotein kinase	+
GATA4	GATA binding protein 4	+
GATA6	GATA binding protein 4	+
HNF1α	Hepatocyte nuclear factor 1 α	+
HNF3 (α,β, γ)	Hepatocyte nuclear factor 3 α, β, γ	+
HNF4α	Hepatocyte nuclear factor 4 α	+
IL-1β	Interleukin 1β, cytokine produced by activated macrophages	+
KLF4	Kruppel-like factor 4, zinc finger-containing transcription factor	+
LGR5	Leucine-rich repeat-containing G protein-coupled receptor 5	+
POSTN	Periostin, osteoblast-specific factor	+
SHH	Sonic hedgehog	+
SOX9	SRY (sex-determining region Y) box 9	+
CDH1	E-cadherin	-
CDKN2A (p16)	Cyclin-dependent kinase inhibitor 2A	-
PAX9	Paried box gene 9	-
SOX2	SRY (sex-determining region Y) box 2	-
TP53	Tumour protein p53	-
TP63	Tumour protein p63, transcription factor	-

Smoking status was analysed together with the genetic data. Since the linear correlation among genetic variants distribution and BO diagnosis was extremely low, with no R-squared values higher than 0.02, we decided to employ for data analysis artificial neural networks, particularly suitable to handle non-linear relations among variables, rather than classical statistical tests. Using artificial neural networks, it was possible to explain two-thirds of the variance related to cases, and control difference through the adaptive selection on nine polymorphisms, with a sensitivity near to 80%.

Molecular Pathogenesis

The metaplastic conversion of SE to specialised columnar epithelium in the distal oesophagus may originate from two different mechanisms.[55] Transdifferentiation seems to be wrong, since new SE can develop after ablation treatment in which the BO epithelium has been completely removed.[56] The best pathogenic hypothesis regarding BO is likely the altered differentiation of stem cells.[57] Different experimental data support four potential origins of these altered metaplastic stem cells: SE, GEJ, the neck, and bone marrow.[58,59] In addition, acid and bile salts, alone or together, might also be involved in the pathogenesis through an increase in reactive oxygen species, causing oxidative stress that results in DNA damage and cell death.[60,61] Chen and colleagues[62] suggest that when gastroesophageal stem cells are stimulated by GERD, the squamous differentiation programme may be inactivated through a loss or downregulation of squamous transcription factors; at the same time the overexpression of the transcription factors related to intestinal development may be activated (Table 1).

Experimental Models

In recent years, different approaches have been used to find a model for BO, but as of yet, no one model offers an ideal system for the study of environmental exposure, genetic risk, and prevention strategies. Cell culture based methods lack the complexity of a multicell system and this aspect can be overcome through the use of organotypic culture that mimics the *in vivo* interplay between the epithelium and underlying stoma. However, animal models provide a better solution to study such a complex disease since they offer the opportunity to evaluate clinical and environmental risk factors in a controlled setting. Furthermore, since several genes and pathways have been implicated in the development of BO, genetic manipulation can also be applied. Mouse, rats, dogs, opossum, guinea pigs, baboons, and pigs have all been used to study BO; however, the lack of spontaneous development of BO in animals presents a strong limitation.[63]

Treatment

The target of treatment is the control of reflux symptoms in order to stop the impairment of the oesophageal lining. This goal could be achieved through a dietary change, removing foods that increase the risk of reflux (e.g. chocolate, coffee and tea, peppermint, orange juice). Alternatively, the use of acid-suppressing medications (PPIs, e.g. omeprazole, lansoprazole, pantoprazole) can be applied. Although the acid suppression is important, the dose to use is still controversial.[8,64] Recently, while continuous PPI therapy may be a symptomatic treatment at best, it could potentially promote dysplastic progression and adenocarcinoma, rather than prevent it.[65] A recent study observed an increased risk for developing HGD and adenocarcinoma in the oesophagus with long-term PPI usage. Therefore, PPI may not protect against malignant progression in BO patients and in selected high-risk patients, and clinicians may consider adding or replacing long-term medical treatment with other modalities.[66] Anti-reflux surgery (ARS) may be considered for people with GERD symptoms. This therapy seems to promote the resolution of BO metaplasia; a meta-analysis demonstrated that 15.4% of patients who had undergone ARS had a regression of BO, compared with 1.9% of patients who were medication treated.[67] In some papers the ARS is even associated to a lower cancer risk progression.[68,69] Dysplasia is the typical precursor of OAC in BO patients and some studies have demonstrated that surgical or endoscopic removal of the dysplastic tissue can prevent its progression to cancer.[8] In the recent years different endoscopic therapies have been established.

Endoscopic ablative therapies

The procedures most often used are photodynamic therapy (PDT) and radiofrequency ablation (RFA). Complications of PDT technique include stricture formation (nearly 40%)[70] and the risk of buried metaplasia, as a result of incomplete endoscopic ablation procedures that destroy only a superficial layer of Barrett mucosa.[71] RFA uses radiofrequency energy (10 J/s) to inflict a thermal injury which

destroys the mucosa of BO patients. RFA appears as the better treatment in eradicating dysplasia and cancer prevention, with greater simplicity management and fewer serious adverse effects compared with PDT.[7,72] The problems of RFA regarded the recurrence rate of intestinal metaplasia ranging from 0-9%[73,74] to 30%.[75,76] Both PDT and RFA have been proven to be superior to eradicate dysplastic BO compared to routine anti-reflux measures and pharmacological anti-reflux measures in randomised trials. Nevertheless, the relative efficacy and safety of the promising endoscopic ablation treatment modalities remain unclear, since no previous head-to-head comparison of PDT versus RFA exists. In a recent study, the two modalities were compared with regards to complete eradication of BO and BD, adverse events, and costs. Both resulted in successfully eradicating dysplasia in BO. However, the overall success rate of RFA was higher than PDT, and RFA was very well tolerated without any major complications and fewer side-effects.[77,78]

Endoscopic mucosal resection (EMR)

EMR is increasingly being utilised as an alternative to surgery in the management of high-grade intraepithelial neoplasia, intramucosal cancer of the GI tract, dysplasia, and some small, very early-stage cancers of the oesophagus. It is less invasive than surgery and, unlike ablative therapies, it provides tissue for histological assessment. EMR is a technique where a piece of the inner lining of the oesophagus is removed with instruments passed down the endoscope. The most common side-effect of EMR is bleeding in the oesophagus, which is usually not serious. Less common, but more serious, side-effects can include oesophageal strictures (areas of narrowing) that might need to be treated with dilation, and puncture (perforation) of the oesophagus wall.[79-81] Both ablative and mucosal resection are often combined in order to reach a better outcome.

Oesophagectomy

This procedure is associated with high morbidity and mortality and causes detrimental effects on the quality of life. Thus, it should be reserved only for patients in which ablation or resection eradication is not complete or durable, and only when endoscopic screening or surveillance revealed HGD. The risk of progression to cancer in BO patients with HGD is considered high enough to determine an intervention through endoscopic eradication therapy. This method includes the use of one or any combination of endoscopic strategies to remove all of the Barrett metaplasia - dysplastic or not.[8,12] Conversely, the low-grade dysplasia (LGD) data of management are contradictory. One study on 147 patients revealed a risk of neoplastic progression of 85%, whereas another one carried out on 210 patients, described a rate of progression to HGD or cancer of only 1.83% per year.[82,83] After this controversial evidence, the guidelines suggested either a more intensive programme of endoscopic surveillance or endoscopic ablation. In addition the diagnosis of LGD should be confirmed by at least two expert GI pathologists.[8,12] Despite the wide variability for cancer risk in the LGD patients, novel specific biomarkers (e.g. abnormal presence of p53 or a number of dysplastic glands) are able to recognise the patients at risk.[84]

CONCLUSIONS

Even though several efforts have been applied to shed light on this disease, we still lack the opportunity to precisely identify those factors allowing early detection of those patients who will develop cancer. In our experience, on a small number of tested subjects and variables, we successfully applied a different method to build up a model that is able to discriminate amongst cases and controls with 80% accuracy. This finding highlights the importance of new methodological and statistical approaches in handling the complexity inherent to chronic degenerative diseases, such as BO.

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