ELSEVIER

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SURGERY FOR OBESITY AND RELATED DISEASES

White paper

A pathway to endoscopic bariatric therapies

ASGE/ASMBS Task Force on Endoscopic Bariatric Therapy

Preamble The American Society for Gastrointestinal Endoscopy (ASGE) is dedicated to advancing patient care and digestive health by promoting excellence in gastrointestinal endoscopy. The American Society for Metabolic and Bariatric Surgery (ASMBS) is dedicated to improving public health and well-being by lessening the burden of the disease of obesity and related diseases. They are the largest professional societies for their respective specialties of gastrointestinal endoscopy and bariatric surgery in the world. The ASGE/ASMBS task force was developed to collaboratively address opportunities for endoscopic approaches to obesity, reflecting the strengths of our disciplines, to improve patient and societal outcomes. This white paper is intended to provide a framework for, and a pathway towards, the development, investigation, and adoption of safe and effective endoscopic bariatric therapies (EBT). (Surg Obes Relat Dis 2011;7:672–682.) © 2011 American Society for Metabolic and Bariatric Surgery and American Society for Gastrointestinal Endoscopy.

Introduction

Obesity is a complex metabolic disease of excessive fat accumulation associated with an increased risk to health. One measure of the degree of obesity is the body mass index (BMI), a person's weight (in kilograms) divided by the square of his or her height (in meters). A person with a BMI of 30 kg/m^2 or more is considered obese. Over the past few decades obesity has evolved into a global epidemic, and it is now more prevalent than malnutrition from hunger [2]. The World Health Organization projects that by 2015, approximately 2.3 billion adults will be overweight and >700 million will be obese [3]. Moreover, some 20 million children <5 years old were overweight globally in 2005. Once considered a problem only in the first world, obesity is now on the rise in low- and middle-income countries, particularly in urban settings [4].

In the United States, obesity is a major health problem that contributes to a host of maladies including heart disease, hypertension, dyslipidemia, type II diabetes, osteoarthritis, sleep apnea, certain malignancies, and all-cause mortality [5–10]. BMI is used to classify overweight (BMI 25.0–29.9 kg/m^2) and obese (BMI ≥30.0 kg/m^2) individuals, and to further categorize the severity of obesity as class I (BMI 30–34.9 kg/m^2), class II (BMI 35–39.9 kg/m^2), or class III (BMI >40 kg/m^2). Based on data obtained from the National Health and Nutrition Examination Survey 2007-2008, 68% of adults over the age of 20 years in the United States are overweight or obese; 33.8% are Class I or above. Worryingly, a significant proportion of adults are severely obese, with 14.3% having Class II and 5.7% have Class III obesity [11,12].

Current treatment modalities for obesity and associated metabolic co-morbidities include lifestyle modification, diet and pharmacologic agents. However, these have been shown to have limited effectiveness and durability, with high rates of attrition [13]. Surgical intervention is the most effective treatment to date, resulting in sustainable and significant weight loss along with resolution of metabolic co-morbidities in up to 80% [14,15]. Furthermore, bariatric surgery results in a significant decrease in overall mortality among obese patients compared to obese individuals who are untreated or managed non-operatively [16]. In recognition of the risks associated with obesity, and the evidence for risk reduction associated with weight loss, the National Institutes of Health has recommended weight loss surgery as an appropriate alternative to conventional treatment in

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carefully selected individuals with Class III obesity, or obesity Class II with co-morbid conditions when dietary and behavioral interventions have failed [17,18]. Currently, the most common bariatric procedures are laparoscopic Roux-en-Y gastric bypass (RYGB), adjustable gastric band, and sleeve gastrectomy. Efficacy varies with the type of procedure: operations such as RYGB result in greater weight loss and higher rates of remission from metabolic co-morbidities compared to gastric specific procedures such as gastric band and sleeve gastrectomy [14]. While effective, these laparoscopic and open surgical bariatric procedures have morbidity rates of 3% to 20% and mortality rates of 0.1 to 0.5% [19,20] In particular, cardiopulmonary events and anastomotic leaks are sources of severe morbidity [21]. For these and other reasons, including limited access to care, only 1 in 400 morbidly (Class III) obese individuals undergo bariatric surgery in the US [22].

Given that all current surgical procedures require general anesthesia and have procedure specific complications, there is a need for less invasive weight loss interventions to potentially reduce morbidity and improve access. A range of novel endoscopic modalities may fit this profile. Any new surgical, endoscopic or nonsurgical weight loss intervention should include a defined threshold of efficacy, balanced with risks of the intervention. EBT, performed entirely through the gastrointestinal (GI) tract using flexible endoscopes, offers the potential for ambulatory weight loss procedures with a superior safety and cost profile compared to bariatric surgery. Such benefits increase the appeal and acceptance of this therapy to patients [23]. If this approach is developed and shown to be feasible, safe, and effective, endoscopic therapy may be appropriate for intervention to individuals with lower classes of obesity (i.e. Class I).

Treatment Classification

Several EBTs are currently in different stages of development, and include a variety of methods to induce weight loss and reduce obesity-related co-morbidities. EBT technologies can be categorized broadly according to the intended mechanism of action: gastric restriction or manipulation, malabsorption, neuro-hormonal alterations, or some combination.

Restrictive or gastric specific procedures may induce early satiety by decreasing gastric capacity, [24] or modifying hormonal signals [25]. A classic example of a gastric specific surgical procedure is the adjustable gastric band (AGB), which is felt to work primarily by creating a feeling of fullness, through restricting food transit time through the band, [24] although the mechanism of weight loss is not fully defined [26–27]. Capacity of the proximal stomach is limited to the gastric volume above the band and patients feel uncomfortable if they overfill the small portion of proximal stomach. Several EBTs attempt to mimic this mechanism by decreasing effective stomach capacity. These technologies include space-occupying devices and those that alter gastric anatomy.

Space-occupying devices most commonly take the form of temporarily placed prosthetic balloons, which effectively restrict intake, thereby enhancing satiety and instigating weight loss [28]. These devices are placed perorally with endoscopic assistance, and are ultimately intended to be inserted and removed as outpatient procedures. Conceptually, the devices work on a mechanical basis, although other mechanisms of action may include delayed gastric emptying, hormonal modulation, neuronal effects, and behavior modification [29]. Other non-balloon space-occupying technologies being developed include polymer pills that expand and later degrade in the stomach thereby eliminating the need for endoscopic insertion and removal [30].

To address the limited durability of a temporary prosthesis, other endoscopic restrictive weight reduction technologies are based on permanently altering the anatomy of the stomach through either suturing or stapling. At present there are numerous devices under various stages of development. The current generation of endoscopic gastric volume restriction devices requires significant skill and time compared to implantable space-occupying procedures. Continued device development is aimed at addressing these short-comings, to increase the appeal and usability of these novel technologies. The mechanisms of action of endoscopic procedures such as gastric plication are also not fully understood, but may mimic bariatric surgical interventions such as the gastric band and sleeve gastrectomy [31,32].

Weight loss and improvements in metabolic co-morbidities after malabsorptive surgical procedures are more profound than after purely stomach altering restrictive operations, and have prompted the development of endoscopic devices to induce malabsorption. These therapies are designed to create a physical barrier between food, the intestinal wall and biliopancreatic secretions. One such device is the duodenal-jejunal barrier sleeve, which may be placed temporarily or left *in-situ* indefinitely. These impermeable fluoropolymer sleeves open at both ends, are placed endoscopically, and anchor in the proximal duodenum or at the gastroesophageal junction. They prevent chyme from contacting the proximal intestine while bile and pancreatic secretions pass along the outer wall of the liner and mix with chyme in the distal jejunum [33,34].

Other EBT, still in early stage development, aim to modulate satiety and food intake through neural-hormonal mechanisms. Evidence suggests that gut hormones act in conjunction with the complex enteric nervous system to coordinate and regulate gastrointestinal satiety signals, motility, and digestive processes. Novel endoscopic devices seek to take advantage of this interaction by manipulating neural-hormonal signals to induce satiety [35,36]. Their intended mechanism of action is to interfere with vagal signals between the brain and gastrointestinal tract, through a variety of techniques such as gastric stimulation or pacing, neuromodulation, and vagal resection [37–39].

Intent of endoluminal therapies

The primary goal of EBT is to induce enough weight loss to decrease obesity related metabolic co-morbidities and improve quality of life. To that end, relatively higher risk (i.e., comparable to current surgical interventions) EBTs are expected to yield substantial improvements in order to achieve a favorable risk/benefit profile; on the other hand, while a lower risk EBT must achieve this primary goal, its threshold for efficacy should be lower than a higher risk intervention. With this concept in mind, endoluminal therapies have many potential applications as primary, adjunctive, or revisional bariatric procedures. Specifically, the indications for EBT include primary therapy, early intervention/preemptive therapy, bridge therapy, and metabolic therapy. For each of these indications, we will consider the minimum threshold for efficacy, risk profile, durability and repeatability.

Potential indications for EBT

Primary therapy

The goal of primary EBT is to induce weight loss and improvement in medical co-morbidities, with a safety and efficacy profile similar to operative bariatric therapy. An EBT with morbidity and mortality comparable to laparoscopic adjustable gastric banding should hold similar efficacy, with the potential to achieve approximately 40 % excess weight loss [14,15]. Alternatively, lower efficacy is acceptable for an EBT with a lower risk profile. Such treatments would be considered for patients with severe obesity (Class II, III), with or without obesity related co-morbidities.

Early intervention/preemptive obesity therapy

Patients with Class I and II obesity are at risk for disease progression, have a higher cardiovascular risk profile, and have a substantially increased relative risk of all-cause mortality.6 There is evidence that patients with Class I obesity respond well to surgical intervention. Prospective trials of both sleeve gastrectomy and adjustable gastric banding in patients with Class I obesity have demonstrated significant weight loss and resultant improvement in or resolution of many obesity related co-morbidities [40,41]. Several other non-randomized studies have confirmed similar results [42–44]. As a result, the FDA has recently approved the use of gastric banding for patients with Class I obesity and at least one associated obesity related co-morbidity. Since the goal of 'Early Intervention/Preemptive Therapy' is to achieve modest weight loss, the risk/benefit profile of gastric banding should serve as baseline for any EBT proposed for this indication. In this category, the durability or repeatability of an EBT will be important. For a procedure to be repeatable, the patients' anatomy must have minimal permanent alteration and be amenable to future intervention.

Bridge therapy

The intent of 'Bridge Therapy' is to promote weight loss specifically to reduce the risk from a subsequent intervention, including bariatric surgery. Patients with Class III (BMI>50) obesity and those with metabolic co-morbidities present greater technical challenges and surgical risk than less obese, healthier patients [45–47] Furthermore, these effects are more pronounced in patients with BMI>60 where there is a greater risk of morbidity or mortality than patients with BMI [45–60] [48–51]. Examples of procedures that may benefit from preoperative weight loss include orthopedic, cardiovascular, organ transplant, and bariatric operations. Efficacy would be primarily measured by a reduction in post-operative morbidity and mortality following the intervention that required bridging. The magnitude of weight loss can be lower, since the primary objective is to significantly reduce the risk of a subsequent intervention. Similarly, durability is a less important feature.

Metabolic therapy

EBT may be justified in patients with less severe obesity (Class I), where improvement in metabolic illness is the primary concern. In particular, co-morbidities such as type II diabetes, hyperlipidemia, and hypertension, may improve or resolve with even modest weight loss [52–53]. Procedures which aim to effect metabolic disease should have a lower risk profile and greater durability compared to therapies which specifically aim to induce massive weight loss. Substantial weight loss may not be necessary in order to achieve metabolic benefits in less severely obese individuals. Obese patients who lose 5% of their total body weight benefit from significant reductions in diabetes and cardiovascular risk factors including hypertension and dyslipidemia [1]. Therefore, we advocate using 5% of total body weight lost as the absolute minimum threshold for any non-primary EBT (e.g., early intervention, bridging or metabolic therapy).

Grading the endpoints/outcomes of Endoluminal Interventions (Table 1)

1. ***Weight loss***

   The grading system for weight loss is based on percent excess weight loss (%EWL) and total body weight loss (TBW) attainable from an intervention

   \+ Equivalent to medical therapy, Minimal 5% TBW Change

   ++ Minimum of 20% EWL

   +++ Equivalent to Gastric Banding, Minimum of 25% EWL, but may be lower for low-risk procedures, depending on the primary indication for the intervention
2. ***Safety (SE)***

   This grading system compares EBT to other endoscopic procedures; for example those with minimal risk such as colonoscopy with polypectomy, or those

Table 1
Graded outcomes of endoluminal bariatric interventions†

	Weight Loss	Safety	Efficacy	Durability	Anatomy Altering
Early Intervention	+	+++	++	++	–
Bridge	+ *or* ++	++	+	+	–
Metabolic Disease	+	++	++	++	+
Endoluminal Bariatric Surgery	+++	+	+++	++ *or* +++	+

† The "+" symbols used in table 1 correspond to the definitions outlined below.

with potential for significant risk such as ERCP with sphincterotomy

+ Moderate Risk

++ Modest Risk

+++ Minimal Risk

3. ***Efficacy***

+ Achieves relative risk reduction by affording mild to moderate weight loss

++ Modest effect on weight loss or metabolic disease, without necessary substantial weight loss

+++ Profound effect on weight loss and metabolic illnesses

4. ***Durability***

+Rapid effect of therapy (weight loss or metabolic improvement) with short term duration (6 months)

++ Minimal effect of one year therapy is repeatable

+++ Sustained effect of therapy for of five years

5. ***Altered Anatomy***

− No permanent change in gastrointestinal anatomy

+ Permanent change in anatomy acceptable

Efficacy

Primary efficacy endpoints

Weight loss. It stands to reason that an intervention which promotes weight loss should result in weight loss. With the growing development of potential less invasive alternatives to bariatric surgery such as EBT for weight loss, it is critically important to define the minimum threshold that would define an endoscopic procedure as an effective therapy for the treatment of obesity.

Definitions for weight loss. Weight loss after bariatric surgery is often calculated as either changes in the baseline BMI or the percent of excess weight loss (%EWL). The %EWL is defined as:

$$\frac{\text{Amount of weight loss}}{[\text{Patient's initial weight} - \text{ideal body weight based on gender and height}]} \times 100$$

One's ideal body weight is most often obtained from the Metropolitan Life Insurance table, according to gender and using the middle weight of a medium frame person. A less common method for calculation of weight loss is measuring the change in BMI from the time of intervention. The majority of medical therapy trials use the percent of total body weight lost (%TBW) to define efficacy.

Comparison of weight loss between therapies. Weight loss after currently accepted interventions varies greatly (Table 2). Comparison of nonsurgical and operative interventions is limited by differences in the primary outcome measure: nonsurgical interventions typically use actual weight lost or % of total body weight, whereas operative therapies traditionally use %EWL. To put this into perspective, let us use an average height U.S. man (5'10") and woman (5'4") and ideal body weights from the Metropolitan life tables to illustrate the magnitude of weight loss observed in representative trials for lifestyle/diet, pharmacologic and selected operative interventions. In a comparison of various diet regimens, Sacks et al. reported an average weight loss of 4kg after two years in patients with class I obesity (average BMI 33) who completed the trial (20% dropout rate). For our representative Americans, this would translate into a %EWL of 12 (man) and 14 (woman). The FDA has approved orlistat for the pharmacological treatment of obesity. In a Cochrane meta-analysis, orlistat provided an additional 2.9kg of weight lost versus controls in patients with an average BMI of 36 after 12 months of follow-up [13]. Using an average height American, this translates into a %EWL of 7 (man) and 8 (woman). Rimonabant was slightly better in a similar patient population (average BMI 36), yielding 4.7kg of lost weight compared to controls; for average height men and women with a BMI of 36, this equates to a %EWL of 11% and 13%, respectively. Rimonabant was

Table 2
Reported weight loss at 12–24 months†

Intervention	Weight loss
Lifestyle Interventions (24 months) (Diet, counseling, exercise)[54]	4kg (2–9% total body weight)
Medical Therapy (12 months)[13]	3–5kg (2–9% total body weight)
Laparoscopic gastric banding (12 months)[36]	47.5% EWL
Gastroplasty (12 months)[14,15]	68% EWL
RYGB (12 months)[14,15]	62% EWL

† Values extrapolated from representative clinical trials of each intervention class.

approved in Europe, but removed from the market due to complications.

Actual weight lost can be a deceiving outcome measure, particularly among class II and III obese individuals. For an average height class I man (BMI 32.5), 5kg of weight lost would translate into a drop in weight from 227 to 216 pounds, or 16% EWL. However, the same man with class II (BMI 37.5) or III (42.5) obesity would drop from 262 to 251 (11% EWL) or from 297 to 286 (8% EWL), respectively.

The magnitude of average weight loss in operative interventions is significantly greater. In a meta-analysis published by Buchwald *et al*, RYGB achieves a mean excess weight loss of 68%, gastroplasty achieves 69%, and gastric banding 50% at varying follow-up time intervals [15]. If an EBT is expected to have a considerably lower risk profile than surgery, it may not be held to the same expected weight loss as a surgical intervention [55]. For example, a low risk EBT could be expected to have comparable efficacy to intensive lifestyle or pharmacotherapy.

Threshold for weight loss for endoscopic therapies. The weight loss threshold for the adoption of any new endoscopic procedures should be balanced against the risk of that procedure. Currently there are no thresholds established for endoscopic bariatric interventions. However, in general it is expected that endoscopic modalities should achieve weight loss superior to that anticipated with medical and intensive lifestyle interventions [55]. Pharmacologic agents such as orlistat have been FDA approved despite their modest effects because 1) lifestyle interventions have even lower efficacy and poor durability/compliance and 2) small amount of lost weight (5% of total body weight or less) can lead to significant reductions in obesity-related co-morbidities. Therefore, based on available evidence and expert opinion, the Taskforce recommends that an EBT intended as a primary obesity intervention achieve a mean minimum threshold of 25% EWL measured at 12 months. This goal will vary depending on the category or intent of endoscopic bariatric procedure.

EBT should be compared to a second treatment group, not necessarily a sham. Sham groups in comparative trials evaluating the efficacy of bariatric therapies have shown considerable variability in weight loss (3–13%EWL) [38,55,57–60]. In addition to the absolute threshold of weight loss, the mean %EWL difference between a 'Primary' EBT and control groups should be a minimum of 15% EWL, and be statistically significant. For other categories of EBT, the amount of EWL and durability of the effect may vary by type and intent of the EBT. As previously described, EBT may be performed for early intervention, bridge therapy, and as a metabolic therapy. In these instances, the primary endpoint may include, but not be limited too, an improvement or resolution in metabolic illness, decreasing the risks associated when performing another planned intervention, and preventing the progression to greater severity of obesity with its associated risks.

Study design

As a device is designed and modified to address a specific clinical need various types of studies are typically required as part of the regulatory process. Following rigorous preclinical evaluation, a feasibility study in humans is often the appropriate next step. The concept of such feasibility studies is well described in the FDA guidance documents. These are typically small studies performed in a limited number of subjects to confirm design and operating specifications. The emphasis is on technical feasibility and safety. Device modification is often necessary in this phase and flexibility is emphasized. There are typically no efficacy targets and the final results are generally used to calculate sample size and establish parameters for a larger pivotal trial.

The emphasis of the pivotal trial is device effectiveness and safety. Pivotal trial design should vary depending on the category and intention of the specific EBT. Efficacy in terms of weight loss or resolution of comorbidities is most accurately assessed by comparison to a control group. Randomized controlled trials provide the highest level of evidence and are the preferred design. Importantly, EBT may be best evaluated when compared to a second treatment group, rather than a sham group. Sham groups in bariatric trials have proven to be unreliable with considerable variability in weight loss (3–13%EWL) [39,56–59]. Sham procedures are primarily necessary when the major outcome measure is a subjective judgment and the evaluator needs to be deceived as to the treatment assignment [61]. Shams have led to confusion in previous trials. For example, the 1990 paper by Mathus-Vliegen showed no difference in a crossover sham balloon trial; however the design was potentially flawed by a balloon that was too small and by an unrealistic control diet instead of a standard diet control group [62]. In other studies, sham has been used as a proxy to influence the level of control diet/exercise interventions. However it is difficult to equate this group to non-intervention and difficult to find an adequate sham for true surgical intervention. Additionally, this type of design may put sham subjects at unnecessary risk. Thus the use of a sham arm is controversial. Studies must be designed to best evaluate the intended outcomes of the specific EBT, and the control group should be considered a reasonable alternative regarding potential risks and benefit. 'Primary' EBT that might be considered an alternative to traditional surgery should have an absolute threshold of weight loss that is established based on its particular risk profile. Additionally, the mean %EWL difference between this type of EBT and a medical control group should be a minimum of 15% EWL, and should be statistically significant. If a surgical control group is thought to be more relevant, a non-inferiority trial design comparing those two groups would be preferred. Similarly, for an 'early intervention' EBT a non-inferiority design with randomization to a medical control group may be optimal.

Intended duration of effect and study length will also

Table 3
Intensity level of EBT, with expected morbidity and mortality

EBT intensity*	Comparative procedure	Anesthesia	Mortality	Morbidity	Minimum expected benefit	Recovery setting
Low	Colonoscopy & polypectomy	Conscious sedation or MAC	0.003%-0.03%[74,97]	2.3%[74,97]	+	Outpatient
Moderate	ERCP & sphincterotomy	Deep sedation or MAC, possible intubation	0.33%[98]	3.5%[98]	++	Outpatient or ≤23 hour stay
High	Laparoscopic gastric banding	General anesthesia with intubation	0.5%[14]	20%[14]	+++	≥ 23 hours

* The "intensity" level reflects the technical complexity of the intervention, and the periprocedural care. MAC: monitored anesthesia care.

depend on the category of EBT being evaluated. 'Bridge' procedures should require a shorter interval (3–6 month) outcome assessment, since the objective is simply to reduce the risk of a downstream procedure. Similarly, some 'early interventions' that are low risk and easily repeated may require shorter trial durations, however, long term studies would likely be necessary for 'primary' EBT devices. For other devices, such as those in the 'metabolic' EBT category, weight loss may only be a secondary endpoint. Control groups for these trials would be very different, and may involve medical treatment of DM, or other related conditions.

We must be mindful of the various categories of EBT and their intended clinical applications when designing and evaluating clinical trials. It is important to remain flexible and consider risk-benefit ratio and optimal control group characteristics for each specific device.

Secondary efficacy.

Reduction in obesity-related co-morbidities. Clinical studies have shown that sustained moderate weight loss achieved through dietary and lifestyle intervention lowers blood pressure, improves glucose control, prevents diabetes, and improves dyslipidemia, hemostatic and fibrinolytic factors [63]. Obese patients who lose 5% of their total body weight benefit from significant reductions in diabetes and cardiovascular risk factors including hypertension and dyslipidemia [1]. Therefore, we advocate using 5% of total body weight lost as the absolute minimum threshold for any EBT intended for anything but a primary bariatric intervention (e.g., early intervention, bridging or metabolic therapy). Given that weight loss can improve comorbid disease, it is intuitive that EBT has the potential to induce significant metabolic effects; among them, an improvement in or resolution of obesity-related co-morbidities such as diabetes mellitus, hypertension, obstructive sleep apnea and nonalcoholic fatty liver disease (NAFLD). If an endoscopic intervention proves to have a significant impact on one or more of these co-morbidities with a negligible risk profile, the threshold for intervention may extend to Class I obese individuals (BMI 30–35 kg/m^2).

In addition to lowering the prevalence of co-existent obesity-related metabolic illnesses, there is potential for an EBT to primarily prevent these comorbidities by promoting weight loss in mildly obese individuals. In this population, it is important that improvement/resolution of comorbidities be significantly better for endoscopic therapies compared to that of control groups, given the risks associated with any intervention despite how minimal they may be. Improvement and resolution of comorbidities should be defined using objective and standardized criteria. For example, remission of diabetes is defined as [64]:

1. Fasting plasma glucose $<$ 7 mmol/L in the absence of medical treatment for at least 3 days.
2. A 2-hour plasma glucose $<$ 11.1 mmol/L following an oral glucose tolerance test (OGTT) as specified by the World Health Organization [65]
3. Glycosylated hemoglobin (HbA1c) $<$ 6% after 3 months of last hypoglycemic agent usage.

Improvement in diabetes may be similarly defined by reduction of fasting glucose level, or HbA1C level, with a reduction in use of antidiabetic medications.

Class III obesity and its metabolic sequelae present a significant dilemma for patients who require surgical intervention for other illnesses, whether these are related to an increased BMI or not. It has been demonstrated that class III individuals are at increased risk of postoperative morbidity after vascular, cardiac, orthopedic, transplant, and bariatric surgery [66–70] Evidence suggests that preoperative weight reduction as a 'bridge to safe surgery' may benefit these high-risk patients [71–75]. Even modest weight loss can result in prompt lowering of blood pressure, improved glucose tolerance, and reduction in thrombotic risk [71]. Further benefits of preoperative weight loss, particularly among patients with BMI $>$ 50, include shorter hospital stays, decreased intraoperative blood loss, decreased need to deviate from the standard surgical procedure, and decreased

risk of complications such as wound infection [72–75]. EBT has potential to play an important role in this setting. Where prompt but minimal weight loss is the primary goal, a low-risk EBT procedure may bridge that gap and permit safer surgery for these high-risk individuals.

Changes in quality of life. Weight loss can lead to a significant improvement in quality of life, anxiety and depression [76]. Furthermore, the short-term improvements in body dissatisfaction and mood can positively affect long-term weight loss [77]. Changes in quality of life, work productivity, and underlying psychological disorders represent important secondary endpoints in trials of EBT.

Safety The risk profile of EBT should be considered in the context of established medical and operative interventions. Surgical therapies are currently accepted as the most effective treatment for Class III/IIc obesity, given their favorable risk/benefit profile. In order for EBT to become accepted as a feasible primary therapeutic modality for obesity & metabolic disease, it's risk/benefit ratio must be at least comparable to surgical therapies. Firstly, the risk profile of EBT includes inherent risks of sedation/anesthesia. Compared to non-obese populations, Class II/III obese patients undergoing endoscopic procedures have an increased but acceptable sedation/anesthesia risk [78–80]. Secondly, EBT have procedure-specific risks akin to those of established therapeutic endoscopic procedures. Adverse events include perforation, hemorrhage, and septic sequelae, in addition to failure of the intervention to achieve the desired outcome [81–82]. The range of potential adverse events from EBTs should be considered relative to those of routinely performed endoscopic procedures, and perhaps expressed in terms of the intensity of the procedure (low, moderate, or high levels). This "intensity" level is intended to reflect the technical complexity of the intervention, and the periprocedural care (Table 3). The safety of an EBT at a low intensity level would be similar to the safety of colonoscopy with polypectomy, which is typically performed as an outpatient procedure under conscious sedation or monitored anesthesia care. Perforation and bleeding after colonoscopy and polypectomy occur infrequently (0.1 - 0.3% and 0.85 – 2.7% respectively), and more serious complications should be very uncommon [83–84]. The safety of an EBT at a moderate intensity level implies a higher incidence of bleeding, perforation and other complications, similar to that observed with interventional endoscopic procedure such as therapeutic ERCP with sphincterotomy [85]. Patients undergoing these procedures may be subject to deep sedation and monitored anesthesia care. The safety of EBT at a high intensity level would be similar to that seen perioperatively with low risk operative procedures such as the adjustable gastric band. They would typically employ general anesthesia (± endotracheal intubation) as well as extended observation periods.

Durability and Repeatability. The goal of primary bariatric surgical therapies is to induce substantial and sustainable weight loss with associated metabolic benefits. These same expectations apply to EBT, as a primary weight loss therapy. However, obesity is a complex disease and many individuals regain weight and comorbidities after initially effective interventions [86–88]. Diet and pharmacologic agents are classic examples of weight loss modalities with suboptimal durability. However, an EBT with reduced durability may be offset by repeatability of the intervention; EBT is particularly suited to this approach. Low risk EBT may be repeated at varying intervals to achieve durable effect, whilst remaining cost effective compared to surgical alternatives or a lengthy period of pharmacological agents and supervised lifestyle interventions. It is prudent to evaluate the cost-benefit ratio for a candidate endoscopic therapy, to determine what level of durability would be expected from its implementation. For anticipated "bridge therapy", EBT durability is not a critical issue. For example, a procedure for weight loss prior to liver transplantation would be considered effective if the patient lost enough weight to have the required surgery with a beneficial effect on co-morbid conditions in the perioperative period regardless of the durability of that weight loss (Table 4).

Adoption

EBT in the context of global patient care

Weight loss interventions have been demonstrated to achieve superior outcomes when the intervention is performed as part of a comprehensive, multidisciplinary treatment program [89–90]. EBT should also be performed in this context in order to achieve maximal benefit. Nutritional support, experienced nursing care, behavioral medicine specialists, and physicians experienced in the management of obese patients, are essential components of such programs [91]. In addition, the ability and availability of physicians and surgeons willing and able to manage potential complications in obese patients is advised.

Endoscopy unit considerations

Facilities to accommodate bariatric patients and their families must be thoughtfully developed. The goal of EBT is to be less invasive; however these patients often have multiple medical co-morbidities that require close peri-procedural observation. Prolonged sedation may require additional anesthetic support. The right sized facility with the appropriate equipment is essential to providing a safe environment for the patient and medical staff.

Table 4
Properties expected of EBT, according to the intent of the intervention

EBT category/intent	Repeatability	Expected durability
Primary (weight loss)	Unlikely	Long
Bridge therapy	Not necessary	Short
Early intervention	Yes	Intermediate
Metabolic disease	Yes	Long

Training/Credentialing

Evidence demonstrates that higher quality patient care is associated with high volume bariatric units. Recognition of this prompted the process of credentialing Centers of Excellence in bariatric surgery [92–94]. Training and skill acquisition with EBT techniques and technology are mandatory before clinical application is undertaken, and must include didactic as well as hands-on practical education. Importantly, any practitioner who is interested in performing an EBT should also be educated in the clinical management of obese patients. The duration and type of training is likely to depend on the complexity of a particular EBT. The ASGE Interactive Training & Technology center (ITT) and Masters Series courses represent appropriate venues for focused training in the procedural aspects of EBT. EBTs of greater complexity may also require proctoring during the first several clinical applications by a new practitioner. EBTs of the highest complexity may require a focused training program (i.e., "mini-fellowship"), or longer [95]. For all EBTs, early studies should evaluate its learning curve in order to guide the subsequent training and credentialing process. These procedures should be included as a part of a comprehensive obesity program and not performed in isolation.

Cost effectiveness

The costs of bariatric surgery and its associated complications may be offset by consequential reductions in weight and obesity-related co-morbidities. Health care consumption among the obese is significantly greater than non-obese individuals [96–98]. Overall health care expenditures related to obesity are estimated at $92.6 billion annually, or 9.1% of total U.S. health care costs [99]. Using a threshold of no more than $50,000/quality-adjusted life year (QALY), bariatric surgery appears to be a cost effective intervention and may actually *lower* overall costs [100–103]. The strongest evidence for cost effectiveness supports bariatric surgery for patients with class IIc and III obesity [104–105]. However, there are also data to support surgical intervention among class II and class I obese individuals with concomitant Type II diabetes [106–107]. Cost effectiveness studies in bariatric surgery are limited by a paucity of long term (> 10 year) weight loss data and impact of weight loss on quality of life, an important indirect cost outcome in cost effectiveness analyses.

A threshold of no more than $50,000/QALY corresponds with a cost effective intervention. Differences between an EBT and a surgical intervention or observation should be expressed as the Incremental Cost Effectiveness Ratio (ICER). We suggest that elements of a cost effectiveness analysis in EBT include the direct cost of a proposed device and the associated health care utilization required for its implementation (e.g., sedation requirements, time of hospitalization, physician fees). The durability and repeatability of an EBT must also be considered. However, an EBT which decreases obesity-related co-morbidities for a sustained period of time is likely to reduce long term healthcare consumption; therefore, accurate data on this secondary outcome are paramount. Additional measures of indirect costs include consequential improvements in quality of life and work productivity secondary to weight loss from an EBT. Therefore, cost effectiveness studies in EBT require long term data on weight loss, obesity-related co-morbidities, impact on quality-of-life, and the possible need for repeated EBT in order to sustain these outcome measures. For these reasons, studies evaluating the cost effectiveness of EBT are expected to be phase III or IV clinical trials.

Government and Industry Relations

The development of EBT should be done in collaboration with government regulating agencies (e.g. FDA) to establish thresholds for safety and efficacy (primary and secondary endpoints). While this is a complex process for new devices with widely different risk and efficacy profiles, a clear and transparent process is needed to stimulate development of innovative EBT. Inconsistent endpoints for device approval create uncertainty and confusion among device developers and investors in this field. This can result in reduced investment into EBT at a crucial time when societal needs support an increased effort in this field. This collaboration is essential to promote efficient use of physician, regulatory agency, and industry resources while protecting patients as we attempt to address and reverse the obesity epidemic. Failure to act responsibly and rapidly now will only result in stagnation of the development of new and innovative technologies that could reach a population of patients unwilling to undergo major surgical interventions for obesity, resulting in significant increases in future healthcare costs to us all.

Summary statements

- Obesity is a major health problem, is associated with substantial morbidity and cost and is increasing worldwide.
- Life-style and medical therapies for obesity have limited benefit.
- Operative therapy for obesity is effective but at considerable cost, limited patient applicability, and with substantial risks.
- EBTs may have various roles in the treatment of the obesity epidemic, including primary therapy, early intervention, bridge therapy, and metabolic therapy.
- EBTS will have varying degrees of intensity, durability, and repeatability and therefore should be evaluated based on intent of therapy and their overall risk/benefit.

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