Laparoscopic Anti-Reflux Surgery Promotes Regression or Disappearance of Barrett’s Esophagus, but does not Eliminate the Risk of Esophageal Adenocarcinoma

Cirurgia Anti-Refluxo Promove a Regressão ou Desaparecimento do Esôfago de Barrett, mas não Elimina o Risco de Adenocarcinoma de Esôfago

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ABSTRACT
Background: Barrett’s Esophagus (BE) is a complication of gastroesophageal reflux disease (GERD) and can be a pre-malignant condition. Nevertheless, there is no consensus about the effectiveness of surgery in preventing malignant transformation in patients with BE. The impact of Laparoscopic Anti-Reflux Surgery (LARS) on those suffering from BE is still not understood. The objective of this study is to prospectively evaluate clinical, endoscopic and histopathological results after LARS in patients with BE.

Methods: 372 patients suffering from GERD underwent Laparoscopic Nissen Fundoplication (LapNissen). Among them, 95 (25.5%) presented BE. Follow-up using endoscopic biopsy was performed in all patients. The average follow-up was 59.8 months. Results: The control of symptoms was effective in 92 patients. Three patients remained symptomatic, and BE remained unaltered in these patients. Regression of BE occurred in 58 patients (63.9%). Of these, 26 (28.9%) showed no further signs of BE in endoscopic or histopathological examinations. In one patient, who remained asymptomatic after surgery, the degree of dysplasia increased to high-grade dysplasia, and another asymptomatic patient developed adenocarcinoma. Both underwent endoscopic mucosectomy of the BE area. Conclusions: LapNissen is safe and effective in the control of symptoms in a significant number of patients with BE. In spite of the control of GERD attained by most patients and regression occurring in a high percentage of the patients who underwent LARS, the development of high-grade dysplasia and adenocarcinoma is not fully prevented by anti-reflux surgery. Routine endoscopy follow-up with biopsy is recommended for all patients with BE after LARS.

Key words: Barrett’s esophagus, laparoscopy, Nissen fundoplication, dysplasia, cancer.

1. INTRODUCTION

In 1950, Norman Barrett mistakenly believed that he was observing a congenitally short esophagus and an intra-thoracic stomach. However, in 1953, Phillip Allison after examining esophagectomy specimens concluded that what was observed by Barrett was the tubular esophagus lined with columnar epithelium. Barrett’s esophagus (BE) is known to be an acquired condition in which the normal squamous epithelium of the distal esophagus is replaced by an abnormal columnar mucosa containing intestinal metaplasia. Endoscopic studies have shown that 5–15% of patients with gastroesophageal reflux disease
(GERD) can develop BE. The high incidence and the correlation with the esophageal adenocarcinoma make BE as an important public health problem.3

The treatment of patients with BE, especially those with long segment of columnar epithelium, is difficult, mainly for those who present a more serious GERD, typically associated with a large hiatal hernia, shortened esophagus, or because they have lesions considered premalignant.4

With the introduction of minimally invasive surgeries through laparoscopy, interventions which once were associated with high morbidity and mortality have been replaced with safer procedures. Anti-reflux surgery, which previously required a thoracotomy or a laparotomy, today is performed efficiently by a laparoscopic procedure, with lower rates of infections and other complications, shorter hospital stays, and lower costs. Patients recuperate faster and are able to return to work and other activities sooner.5

In patients with Barrett’s Esophagus, the results of the anti-reflux medical therapy have not been satisfactory. Laparoscopic anti-reflux surgery (LARS) is becoming a more popular procedure, with increasingly good results, with multiple reports showing regression of the pre-malignant columnar epithelium.1-11

However, the real impact of surgical anti-reflux procedures in patients with Barrett’s Esophagus has not been completely elucidated. The objective of this study is to show that LARS has the potential to considerably reduce GERD symptoms and to promote the regression of Barrett’s Esophagus, or at least to reduce the likelihood of – or at least slow – progression of pre-malignant BE to malignancy.3-6

2. MATERIALS AND METHODS

2.1 Study Population

From January 2000 to January 2009, 372 patients who presented with GERD were subjected to LARS, by the same surgeon (GLC). Pre-operatively all patients were evaluated with upper endoscopy with biopsy and manometry. Of the 372, 95 (25.53%) were found have Barrett’s Esophagus. Patients received a diagnosis of BE when they were found to have specialized intestinal metaplasia in the esophagus with columnar epithelium.1 Patients without evident histological evidence of intestinal metaplasia in the specimens of the biopsy of the gastroesophageal junction were excluded from further analysis, as were patients with histopathologic evidence of invasive carcinoma. The median age was 50.5 years (range: 14 to 82). 74 (78%) patients were men, 21 women.

2.2 Surgical Technique

All patients underwent laparoscopic Nissen fundoplication; none required conversion to open surgery. The positioning of the surgical team, patient, and trocars is illustrated in figure 1. The pneumoperitoneum was performed by open technique at the umbilical site where a 10-mm trocar was inserted and maintained at an intra-abdominal pressure of 8–12 mmHg throughout the procedure. After the pneumoperitoneum was established, a 30°/10 mm scope was inserted through the umbilical trocar. Four other trocars were inserted. After hepatic retraction, the diaphragmatic hiatus was evaluated. The surgery proceeded with the sectioning of the short gastric vessels to create a window behind the esophagus. After the sectioning of the gastric–hepatic and phrenic ligaments, the esophagus was isolated and traction applied using a latex catheter. The diaphragmatic hiatus was repaired by interrupted sutures of polyester 2-0 (Ethibond 2-0-Ethicon), maintaining an intra-esophageal bulgie as a mold (Figure 2). Next, the 360 degree fundoplication was made short and floppy. Intraoperatively, upper endoscopy was done to confirm the correct positioning of the fundoplication; if

Figure 1 - Positions of the patient, surgical team, and trocars.
necessary, the fundoplication was redone. The trocars were removed and the orifices were closed, ending the procedure.

2.3 Upper Endoscopy and Histopathology
All patients underwent upper endoscopy with biopsy before and after the surgery. A transoperative endoscopy without biopsy was also performed confirming the correct positioning of the fundoplication. A columnar-lined esophagus was visually identified when the squamocolumnar junction or any part of its circumference extended above the gastroesophageal junction, and its presence was confirmed by a biopsy.

The presence of intestinal metaplasia and dysplasia was determined according to conventional histopathologic criteria. The condition was considered to have regressed or progressed if two consecutive biopsy samples at least six months apart showed a significant change in the mucosal characteristics as assessed by two pathologists. The endoscopic criteria were combined with histopathologic criteria and regression of the Barrett’s Esophagus was classified as: total regression, partial regression or no regression.

2.4 Esophageal Manometry
The manometric study was carried out after an overnight fasting with the patient in the supine position. A structurally defective sphincter was defined by a resting pressure of less than 6 mmHg, overall sphincter length of less than 2 cm, abdominal length of less than 1 cm, or a combination of these.

Manometry was performed one month before the surgery, six months after, one year after the procedure, and in some cases five years after the surgery.

3. RESULTS

3.1 Clinical Results
The average follow-up was 59.8 months. There were no conversions from the laparoscopic to the open technique. Most patients were discharged within 24 hours; three were observed for 48 hours. Only three patients, among our first ten BE patients, had no symptomatic relief, and are still in treatment with proton pump inhibitors. In these cases, the BE persists unaltered.

3.2 Endoscopy and Histopathologic Examination
After the endoscopy and biopsy, the Barrett’s Esophagus of 32 patients (33.7%) was found to be unaltered. Fifty eight patients (63.9%) presented regression of the intestinal metaplasia; 27 (28.9%) of these 58 patients had a total regression (disappearance) of the BE disease, and 31 (32.5%) had a partial regression of BE. In one patient who remained asymptomatic after surgery, the degree of dysplasia increased from medium-grade to high-grade dysplasia six months after surgery). An endoscopic mucosectomy of the BE area was performed and two years after the procedure there were no signs of BE. Another patient developed adenocarcinoma two
months after surgery, and also underwent endoscopic mucosectomy of the BE area, and continues to be monitored with periodic endoscopic surveillance.

4. DISCUSSION

There are four aims of therapy for patients with BE and they should be the same for both surgical or nonsurgical treatments: provide long-term relief from the symptoms; allow healing of the esophageal mucosa injury; prevent progression to more advanced mucosal injury or dysplastic changes; and establish the conditions which permit regression of dysplastic to nondysplastic Barrett’s, or of intestinalized to nonintestinalized columnar epithelium.1

In spite of several controversies that exist about the use of clinical or surgical therapy, several recent studies have demonstrated the effectiveness of LARS in these patients. DEMEESTER et al.1 showed that after LARS, the patients presented an improvement in reflux symptoms; all patients were considered improved or cured. In 14% of the patients the intestinal metaplasia disappeared. Adenocarcinoma and high-grade dysplasia were prevented from developing in almost all of them. In our study, intestinal metaplasia disappeared in 28.9% of the 95 patients. Nevertheless, although BE regressed or disappeared in most cases, one patient developed high grade dysplasia and another developed adenocarcinoma. The duration of follow-up did not make these data statistically significant. ABBAS4 reported that of 49 patients with BE who underwent LARS, the functional results were classified as excellent in 69% patients, good in 19%, regular in 10%, and poor in 2%. They also demonstrated that LARS is effective in the control of symptoms in most of the patients with BE, and that disappearance of columnar epithelium could happen in some cases, but that the risk of evolution adenocarcinoma was reduced, but not eliminated, with the procedure.4 In our data, only three (3.6%) of patients did not obtain satisfactory symptomatic control, and most patients stopped taking medications for symptoms of reflux.

In those patients who lesions evolved and developed into high grade dysplasia and adenocarcinoma, several therapeutic options exist. We believe that mucosectomy is the preferred option as it removes the abnormal tissue and also provides ample tissue for histopathology, which is not possible (except for small biopsies) when argon plasma laser, or other techniques that treat by destroying the BE are used. Not much is known about the evolution and the pathophysiology involved in the emergence of esophageal adenocarcinoma. JAMIESON has raised some doubts about the origin of adenocarcinoma,3 asserting that Barrett’s mucosa alone does not clearly provoke esophageal adenocarcinoma, since most patients with BE do not develop cancer. Adding support to Jamieson’s questioning is the curious observation that the incidence ratios for white males versus white females, for reflux disease, is approximately 1:1, and 1:1 for the development of Barrett’s mucosa, and yet the incidence ratio for adenocarcinoma of the esophagus is about 10:1. Jamieson also notes that in any surgical series of esophagectomy for adenocarcinoma, Barrett’s mucosa is found in only about half of the patients, leading him to pose the following questions: “Is Barrett’s mucosa really so important in the development of adenocarcinoma, other than as a marker of severe reflux disease? Does our persistent concentration on it divert our attention from finding an as yet unidentified, but much more important, cause of adenocarcinoma involving the esophagus?” Our answers are: We still do not know.

CSENDES et al.2 performed a study accompanying 78 patients for more than five years. The radical anti-reflux procedure performed by the surgical team combined vagotomy, antrectomy, and Roux-en-Y gastrointestinal reconstruction. BE regressed in approximately 60%; however, the results obtained were similar to the Nissen fundoplication in the patients with short segment BE. The radical procedure is a more invasive surgery with greater morbi-mortality without benefits superior to simpler procedures such as the LapNissen.2

ROSSI et al.6 published a prospective study comparing Nissen fundoplication with medical therapy and considering the regression of BE, observed a statistically significant difference ($p < 0.03$), favoring the surgical treatment (93.8%) over medical management (63.2%). This study also suggested that surgery can be more effective than the medical management in modifying the natural history of the low-grade dysplasia, in the 35 patients with BE. Chang et al.7 performed a systematic review of MEDLINE literature in order to compare the effectiveness of the surgical therapy against medical therapy. They found surgical treatment to be superior to medical management in patients with BE. The probability of progression was 2.9% (95% CI: 1.2%–5.5%) in surgical patients, and 6.8% (95% CI: 2.6%–12.1%) for medical patients ($p=0.054$). They also found a
more compelling difference in the probability of regression of BE with 15.4% (95% CI: 6.1%–31.4%) in surgical patients and 1.9% (95% CI: 0.4%–7.3%) in medical patients ($p=0.004$). However, evidence suggesting that surgery reduces the incidence of adenocarcinoma in these patients was not found.

These results suggest that the control of the acid reflux alone probably does not have the capacity to halt or reverse the dysplastic transformation. Considering that the concomitant control of biliopancreatic reflux – which is also achieved by anti-reflux surgery – may be important, there is support for the hypothesis that combined reflux is part of the etiology of the BE dysplasia. In spite of studies with good results using proton pump inhibitors – presenting partial regression in the form of squamous islands – medical therapy does not act where the origin of the dysplasia was thought to be located. Based on these findings, surgical procedures can be considered more effective than medical management for BE.$^{8,9}$

Some technical aspects of LARS warrant mention because they can partly explain the better therapeutic response of our patients who underwent anti-reflux surgery. These include: 1) the use of a bulgie during the construction of the fundoplication (Figure 2), and 2) intraoperative upper endoscopy, which is done in all patients. The intraoperative endoscopy is done to ensure that the fundoplication would not hide the Barrett metaplasia, and would allow an effective post-operative evaluation to assess regression. This assessment is especially important in patients with dysplasia, who face the possibility of progression of the dysplasia and development of a malignant process. These precautions aim to make sure the fundoplication does not twist the esophagus – which could conceal the Barrett’s Esophagus – ensuring that any regression is a real change in the esophageal epithelium made possible by the suppression of noxious stimulation.

The advent of new laparoscopic surgical procedures has aroused great interest on the part of both surgeons and patients seeking better treatment options for Barrett’s Esophagus. Superior results of the surgical therapeutics when compared with medical management of BE can be attributed to the fact that surgical procedures which once were quite invasive, can now be performed with minimally invasive surgery, with better aesthetic results, shorter hospitalizations, less post-operative pain. These characteristics have made LARS the best option for the treatment of the patients with Barrett’s Esophagus.$^{10,11}$

5. CONCLUSIONS

LapNissen is safe and effective in the control of symptoms in a significant number of patients with BE. In spite of regression occurring at a high percentage level in patients operated and the control of GERD attained by most patients, the development of high-grade dysplasia and adenocarcinoma is not fully prevented by anti-reflux surgery. Periodic surveillance with endoscopy with biopsy is highly recommended for all patients with BE after LARS.

RESUMO
Introdução: O Esôfago de Barrett (EB) é uma complicação da doença do refluxo gastroesofágico (DRGE) e pode ser considerada como uma condição pré-maligna. Contudo, ainda não existe consenso acerca da eficácia da cirurgia anti-reflux laroposcópica (CARL) na prevenção da transformação maligna do epitélio esofagiano em pacientes com EB, ademais, o impacto da CARL em portadores de EB ainda não é bem compreendida. O objetivo deste estudo é avaliar, prospectivamente, a evolução e os resultados clínicos, endoscópicos e histopatológicos de pacientes com EB submetidos a CARL. Métodos: 372 pacientes portadores de DRGE foram submetidas a CARL. Destes, 95(25,53%) apresentaram Esôfago de Barrett. Biópsia endoscópica foi realizada em todos os pacientes durante todo o acompanhamento o qual teve duração média de 59.8 meses. Resultados: O controle dos sintomas foi efetivo em 92 pacientes. 3 pacientes permaneceram sintomáticos e sem regressão do EB. A regressão do EB ocorreu em 58 (63,85%) dos pacientes. Destes, 26 (28,91%) não demonstraram aumento das lesões metaplásicas em exames endoscópicos e histopatológicos. Em um paciente, assintomático após a cirurgia, ocorreu aumento para displasia de auto grau e em outro, também assintomático, houve evolução para adenocarcinoma. Ambos foram tratados por mucosectomia endoscópica nas áreas de lesões. Conclusão: CARL é segura e efetiva no controle dos sintomas em significante número de pacientes portadores de EB. Apesar da regressão ocorrida em percentual elevado de pacientes operados e do controle da sintomatologia da DRGE na maioria dos pacientes, não houve total impedimento do desenvolvimento de displasia de alto grau e nem de adenocarcinoma esofagiano. A Endoscopia de rotina com biópsia é altamente recomendado para todos os pacientes com EB submetidos a CARL.

Palavras-chave: Esôfago de Barrett; Laparoscopia; Fundoplicatura à Nissen; Displasia; Câncer.
6. REFERENCES


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