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Toupet fundoplication to prevent progression of scleroderma-associated interstitial lung damage: a study protocol

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Summary

Background Systemic sclerosis (SSc) is a rare autoimmune and multiorgan disorder. Hallmarks of the disease include inflammation, endothelial dysfunction, and dysregulation of fibroblasts leading to fibrosis of the skin and internal organs. The esophagus is often involved, with up to 80% of patients developing gastroesophageal reflux disease (GERD). Reflux can be associated with hiatal hernia and several complications such as erosive esophagitis, peptic stricture, Barrett's esophagus, aspiration pneumonia, and chronic microaspiration. Silent aspiration can lead to interstitial lung disease (ILD) in up to 50% of patients with scleroderma and accounts for up to 40% of mortality. Treatment of GERD in patients with SSc is challenging. Proton pump inhibitors (PPI) have been shown effective in relieving typical GERD symptoms, but up to 40% of patients are non-responders. Various antireflux surgical procedures have been proposed to treat GERD and to modify the natural course of the disease by preventing lung damage in these patients. However, current algorithms consider only the degree of esophageal dilation as a marker of disease severity/progression, and results of antireflux surgery remain controversial.

Methods We propose a feasibility, observational, multicenter, single-arm trial including adult patients diagnosed with SSc. Criteria for inclusion are individuals with GERD symptoms refractory to PPI, absence of peptic stricture at baseline endoscopy, high-resolution computed tomography (HRCT) scan showing no or less than 10% lung fibrosis, forced vital capac-

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ity at least 40% of the predicted value, and diffusing capacity of lung for carbon monoxide 30–89% of the predicted value. A laparoscopic partial posterior fundoplication according to the Toupet technique will be performed. Primary study outcome is the efficacy of fundoplication to reduce reflux exposure measured with a pH-impedance study or 4-day wireless pH recording. Secondary outcomes include endoscopic, HRCT, and respiratory function tests findings as well as quality of life at 12-month follow-up.
Conclusions The expected reduction of reflux burden in SSc patients selected for Toupet fundoplication may improve GERD symptoms/complications, pulmonary function, and quality of life, and may be associated with a reduced risk for lung transplant.

Keywords Gastroesophageal reflux disease · Hiatal hernia · Connective tissue disease · Pulmonary fibrosis · Antireflux surgery

Abbreviations

BRAVO system	4-Day wireless pH recording system
DLCO	Diffusing capacity of lung for carbon monoxide
EGDS	Esophagogastroduodenoscopy
EndoFLIP	Functional luminal imaging probe
FEV1	Forced expiratory volume in one second
FEV1/FVC	Forced expiratory volume in one second/forced vital capacity ratio
FVC	Forced vital capacity
GERD	Gastroesophageal reflux disease
GERD-HRQL	Gastroesophageal reflux disease health-related quality of life
HRCT	High-resolution CT scan
HRM	High-resolution manometry
ILD	Interstitial lung disease
PFT	Pulmonary function tests
PPI	Proton pump inhibitors
QOLRAD	Quality of Life in Reflux and Dyspepsia
RSI	Respiratory symptom index
SGRQ	St. George Respiratory Questionnaire
SSc	Systemic sclerosis
SySQ	Systemic sclerosis questionnaire
TLC	Total lung capacity
VC	Vital capacity

Highlights

- There is a need for an objective assessment of gastroesophageal reflux burden in scleroderma patients in order to define the severity of reflux and the risk of lung damage.
- Satisfactory outcomes of fundoplication for end-stage scleroderma-associated interstitial lung disease have been reported in lung transplant recipients at risk for allograft dysfunction.
- It is possible that early partial fundoplication performed on select fit patients without evidence of lung damage or with limited interstitial lung disease may protect from ongoing pulmonary deterioration and even reduce the risk of lung transplant.
- An observational multicenter trial of standardized laparoscopic partial fundoplication may contribute to fill the gap of knowledge and improve current treatment algorithms for scleroderma patients with no or minimal interstitial lung disease.

Background

Systemic sclerosis (SSc) is a rare and heterogeneous autoimmune connective tissue disease. It is characterized by inflammatory changes, microvascular involvement, immune dysregulation, and connective tissue fibrosis. A considerable variability of disease phenotypes and progression has been reported, but multidisciplinary consensus on diagnosis and treatment is still lacking and SSc remains an “orphan” disease with a high unmet medical need [1]. Gastrointestinal tract involvement is common, with the esophagus being affected in up to 80% of patients. Esophageal dysfunction consists of reduced lower esophageal sphincter pressure and loss of peristalsis in the lower two thirds of the esophagus (Fig. 1).

Disruption of the antireflux barrier in combination with loss of peristalsis, impaired salivary production, and gastroparesis can promote the progression of gastroesophageal reflux disease (GERD) and the development of SSc-associated interstitial lung disease (ILD). Up to 80% of patients with SSc present with symptoms of heartburn, regurgitation, and dysphagia. Severe GERD can result in complications such as erosive esophagitis, peptic stricture, and Barrett’s esophagus, which occur in 65%, 30%, and 37% of patients, respectively [2, 3]. Furthermore, GERD may cause recurrent episodes of aspiration pneumonitis and chronic lung damage secondary to microaspiration contributing to the onset/progression of ILD [4–7] and to the risk of lung transplant. Despite sharing common profibrotic pathways and pathophysiological characteristics at presentation, SSc-associated ILD and idiopathic pulmonary fibrosis are distinct clinical entities [8]. Pulmonary involvement may be found in patients with either limited or diffuse SSc. Overall, the prognosis of SSc-associated ILD remains poor, with a 10-year mortality rate of 20% [9] and a 2.5–3.5-fold increased risk for death compared with patients with SSc without pulmonary involvement [10]. Immunosuppressive drugs including mycophenolate and cyclophosphamide are most commonly used as first-line medical treatments. A recent randomized trial with patients with SSc-associated ILD has shown that nintedanib, a tyrosine kinase inhibitor, decreased by 44% the annual rate of decline in forced vital capacity compared to placebo, and no clinical benefit was observed for other manifestations of SSc [11].

First-line management of GERD consists of lifestyle modifications, dietary interventions, and gastric acid

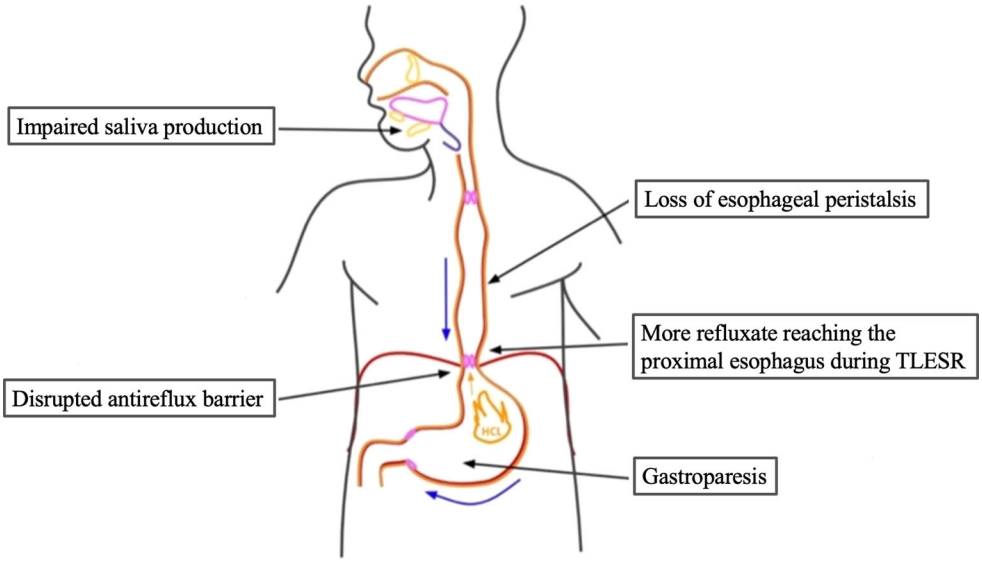


Fig. 1 Esophageal-related alterations in patients with systemic sclerosis. *TLESR* transient lower esophageal sphincter relaxation

suppression with proton pump inhibitors (PPIs; [12]). While the efficacy of PPI therapy in the overall GERD population is well documented, up to 40% of the patients present with symptoms refractory to PPI. Conceivably, PPI resistance in the SSc population may increase due to extreme deterioration of LES pressure, concomitant loss of esophageal body peristalsis, and coexisting hiatal hernia. In addition, long-term pharmacologic acid suppression does not effectively relieve symptoms related to weakly acidic/nonacidic reflux and can lead to side effects, such as small intestinal bacterial overgrowth and nutritional deficiencies that may further impair patients' quality of life. A prospective study investigated 40 patients with SSc who underwent chest high-resolution computed tomography (HRCT) and 24-h impedance pH monitoring [13]. The esophageal acid exposure, the number of acid reflux episodes, and the number of acid and nonacid reflux episodes reaching the proximal esophagus were higher in patients with ILD compared to patients with normal lungs ($p < 0.01$), and the total number of reflux episodes correlated with the degree of pulmonary fibrosis.

A recent systematic review found limited and heterogeneous case series reporting surgical treatment of GERD in SSc patients ([14]; Table 1). Symptomatic improvement and significant reduction of acid exposure time have been reported after Nissen fundoplication, but 71% of patients complained of postoperative dysphagia. Goldberg et al. reported the outcomes of different types of partial and total fundoplication (Toupet, Dor, Nissen) in 34 patients with GERD and esophageal hypomotility. Overall, 38% of patients had a scleroderma-like esophagus and 10 were diagnosed with SSc. Improvement or resolution of GERD was recorded in 97% of patients, with acceptable postoperative dysphagia rates [25]. Similarly, Watson et al. reported effective GERD improvement in patients with aperistaltic esophagus and SSc using Dor fundoplication [26]. One recent study reported data for Toupet fundoplication and Roux-en-Y laparoscopic gastric bypass [21]. Although short-limb gastric bypass may be more effective than fundoplication, the potential morbidity including anastomotic leak, small-bowel dysmotility, and restrictive/malabsorptive effects should be considered in SSc patients. Finally, caution is necessary in interpreting these studies because of the limited sample size, the retrospective study design, the different length of follow-up, and the heterogeneity of surgical techniques. In patients with GERD and ineffective esophageal motility, the Toupet fundoplication has been demonstrated to be safe and associated with improvement of typical symptoms and low rates of dysphagia and gas bloating. Given these encouraging results, Toupet fundoplication has been recommended also for SSc patients [18, 21].

Methods

This is a feasibility, exploratory/descriptive, single-arm, observational, and multicenter prospective study with the intent to evaluate the efficacy of laparoscopic Toupet fundoplication in controlling reflux symptoms and improve quality of life in patients without or with limited SSc-associated ILD. We hypothesize that this study can provide data in support of early antireflux surgery to improve GERD-related and respiratory symptoms as well as quality of life.

Study objectives and endpoints

The objective of this study is to assess the efficacy and safety of laparoscopic Toupet fundoplication in decreasing GERD-related symptoms and complications through reduction of esophageal exposure to acid/weakly acidic/non-acidic reflux. The study will also evaluate the effect of this procedure on the incidence

Table 1 Evidence from published data

Author, year	Study design	No. of patients	Surgical therapy
Orringer et al., 1981 [15]	Ret, single center	37	Collis–Nissen ($n=20$), Collis–Belsey ($n=17$)
Mansour et al., 1988 [16]	Ret, single center	11	Belsey ($n=6$), Collis–Belsey ($n=2$), Nissen ($n=2$), Collis–Nissen ($n=1$)
Poirer et al., 1994 [17]	Ret, single center	14	Nissen ($n=10$), Collis–Nissen ($n=2$), Collis–Belsey ($n=1$), antrectomy, vagotomy, and R-Y reconstruction ($n=1$)
Kent et al., 2007 [18]	Ret, single center	23	Laparoscopic RYGB ($n=8$), laparoscopic Nissen ($n=5$), laparoscopic Collis–Nissen ($n=3$), laparoscopic Collis–Toupet ($n=1$), laparoscopic Toupet ($n=1$), minimally invasive esophagectomy ($n=3$), open transhiatal esophagectomy ($n=2$)
Yekeler et al., 2008 [19]	Case report	1	Ivor–Lewis esophagectomy
Andrade et al., 2017 [20]	Case report	1	Robotic Dor
Yan et al., 2018 [21]	Ret, single center	14	Laparoscopic RYGB ($n=7$), laparoscopic Nissen ($n=2$), laparoscopic Collis–Toupet ($n=2$), laparoscopic Toupet ($n=1$), open Toupet ($n=1$), robotic Dor ($n=1$)
Perez Rivera et al., 2019 [22]	Case report	1	Laparoscopic total gastrectomy
Loganathan et al., 2021 [23]	Ret, single center	5	Robotic Dor ($n=5$)
Hii et al., 2022 [24]	Ret, single center, PS	17	Laparoscopic Lortat–Jacob ($n=4$), laparoscopic Lind ($n=12$), laparoscopic Toupet ($n=1$)

Ret retrospective, *PS* propensity score matching

of postoperative dysphagia and in preventing the onset/progression of SSc-associated ILD.

Primary outcome: Assessment of pre- and postoperative esophageal reflux exposure with pH-impedance study or Bravo ™ (Medtronic, Minneapolis, MN, USA) off PPI. Specifically, the DeMeester score, the % acid exposure time (%AET), and the total number of reflux episodes will be analyzed according to the Lyon 2.0 consensus [27].

Secondary outcomes: Assessment of esophageal motility with esophageal high-resolution manometry (HRM), endoscopic findings, pulmonary function tests, HRCT, and patient-reported outcomes assessed with the GERD Health-Related Quality of Life (GERD-HRQL), Reflux Symptom Index (RSI), Quality of Life in Reflux and Dyspepsia (QOLRAD), Systemic Sclerosis Questionnaire (SySQ), and St. George's Respiratory Questionnaire (SGRQ).

Assessment of symptoms will be performed using validated questionnaires for GERD (GERD-HRQL, RSI, QOLRAD), SySQ, and respiratory disease (SGRQ). All patients will be investigated preoperatively with objective tests including upper gastrointestinal endoscopy, 36-channel esophageal HRM, 24-h pH-impedance study or 96-h wireless esophageal pH test, HRCT chest scan, and pulmonary function tests with measurement of TLC, VC, FEV_1, FVC, DLCO, and FEV_1/FVC. In order to test our hypothesis, we aim to specifically analyze primary and secondary endpoints. We will assess these outcomes preoperatively and at the pre-defined endpoint of 12-month follow-up.

Inclusion criteria

The following inclusion criteria will be applied: adult patients (≥ 18 years) diagnosed with SSc; presence of pathologic GERD confirmed by 24-h pH-impedance test or 4-day wireless pH recording; intolerance to PPI or refractory GERD symptoms (incomplete symptom relief or symptom recurrence after an 8-week full-dose PPIs trial).

Exclusion criteria

The following exclusion criteria will be applied: previous esophago-gastric surgery; patients with documented gastroparesis; patients unfit for surgery due to reduced exercise tolerance and/or need of for supplemental oxygen; fibrosis affecting more than 10% of the lungs at HRCT; FVC < 40% of predicted value; DLCO < 30% of the predicted value; patients with clinically significant pulmonary hypertension; patients taking immunosuppressants and high-dose steroids (Fig. 2).

Participating surgeons and hospitals

The indications for antireflux surgery will be discussed during periodical multidisciplinary board meetings and the recruited patients will sign an appropriate informed consent for the study. In Italy, the project will be conducted at the IRCCS Ospedale Galeazzi-Sant'Ambrogio and IRCCS Policlinico San Donato, both teaching and research hospitals and high-volume referral centers for upper gastrointestinal surgery devoting special attention to multidisciplinary GERD management. The centers include a dedicated digestive endoscopy service and an outpatient esophageal pathophysiology laboratory. Other involved facilities for patient recruitment and investigation will be Ospedale Gaetano Pini, Ospedale San Paolo, Ospedale San Giuseppe, and IRCCS Ospedale Maggiore Policlinico di Milano (Cà Granda). All these facilities will contribute to the multidisciplinary management of these patients and will provide expertise in gastroenterology, rheumatology, pneumology, and radiology.

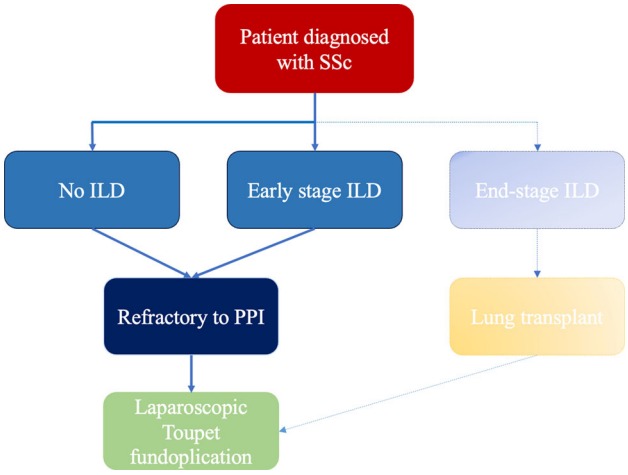


Fig. 2 Study flowchart. *SSc* systemic sclerosis, *ILD* interstitial lung disease, *PPI* proton pump inhibitors

Surgical technique

The operation will be performed through a minimally invasive laparoscopic approach. The EndoFLIP technology will be used intraoperatively to standardize the procedure by measuring the distensibility index at crural closure at values of $>3.5\,mm^2/mm\,Hg$ (40 mL fill) to prevent postoperative dysphagia. The standardized technique of posterior Toupet fundoplication has been described in detail [28]. Briefly, standard crural repair without mesh, mediastinal dissection, and 270° posterior fundoplication are performed through a laparoscopic approach. The gastrohepatic ligament is opened and the anterior aspect of the esophagogastric junction and the angle of His are exposed. Dissection is done circumferentially around the esophagus, thus creating a retroesophageal window to accommodate the fundoplication. The hernia sac is completely excised and at least 3 cm of esophageal mobilization is achieved below the diaphragm.

Follow-up

The follow-up plan includes repeat investigation with upper gastrointestinal endoscopy, high-resolution esophageal manometry, 24-h pH-impedance or 96-hour Bravo™ (Medtronic, Minneapolis, MN, USA) test, pulmonary function tests, and chest HRCT. Finally, the GERD-HRQL, RSI, QOLRAD, SySQ, and SGRQ questionnaires will be also completed (Fig. 3).

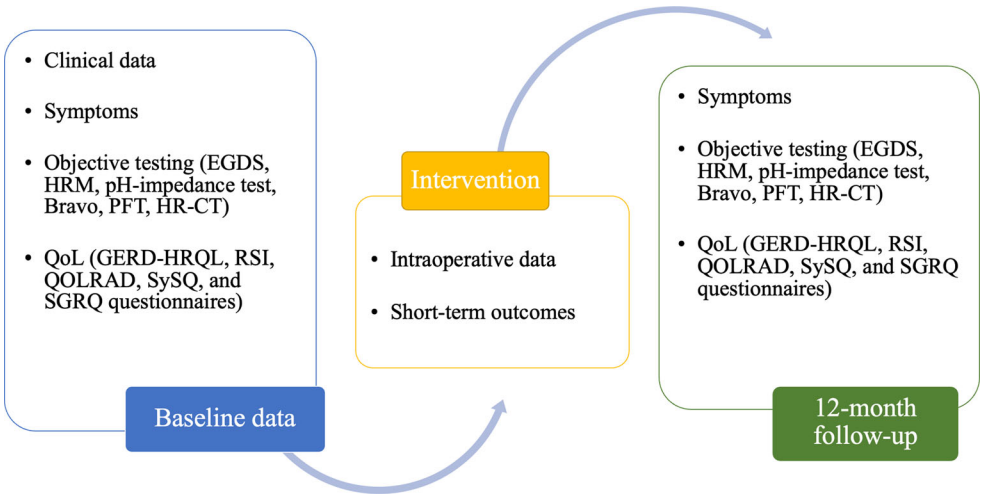
Statistical analysis and sample size calculation

Baseline and 1-year follow-up data will be compared using parametric or nonparametric statistical tests, as appropriate. The tests will be applied to previously determined continuous and binary outcomes. Confidence intervals for the effect measures will be computed. The SPSS software (IBM, https://www.ibm.com/de-de) will be used for statistical analysis. Data analysis will be managed by an expert statistician (GB). A sample of 30–35 is considered sufficient in feasibility studies to ensure a normal distribution of participants [29, 30]. Based on the rarity of the disease, study resources, multicenter design, and timelines, recruitment of a target sample of up to 30 participants over a 12-month is estimated.

Dissemination plan

Dissemination activities will ensure maximal visibility, accessibility, and impact of the GERD-SSc project activities. The GERD-SSc project is endorsed by two national, non-profit associations that will maximize social media communication: *Associazione Italiana Lotta alla Sclerodermia* (AILS) and *Associazione Italiana Ricerca Esofago* (AIRES). This multicenter protocol will be shared with other Italian and European centers under the patronage of the European Foregut Society (https://euro-fs.org).

Fig. 3 Data collection and follow-up scheme



Discussion

Gastroesophageal reflux is still regarded a comorbidity in SSc patients rather than part of the disease. Although some evidence suggests a correlation between GERD and SSc-associated ILD, causality has not been firmly established and immunosuppressive therapy remains the focus of most guidelines. As a consequence, the role and timing of antireflux surgery remain a controversial issue in the current literature [9, 31]. Data on the effect of PPIs on the progression of SSC-associated ILD are lacking, although a registry-based study suggested an improved 5-year overall and progression-free survival [32]. The current paradigm is that GERD is more prevalent in lung-transplant recipients because of postsurgical vagal denervation that increases the detrimental effects of pre-existing GERD and microaspiration [33, 34]. Most previous studies have reported the outcomes of posttransplant fundoplication in patients with end-stage SSc-associated ILD who experience worsening GERD and progress toward bronchiolitis obliterans syndrome and chronic allograft dysfunction [5, 35]. Some of these studies found that early posttransplant fundoplication may protect against further GERD-induced lung damage through reduction of the proinflammatory environment before the bronchiolitis obliterans syndrome develops.

Of note, about 50% of patients with SSc will develop clinically significant ILD within the first 5 years of the diagnosis. Therefore, a timely diagnosis of SSc-associated ILD is important for monitoring progression of the disease and informing therapeutic decision-making [36]. This requires a multidisciplinary patient management and combined expertise across the multifaceted clinical manifestations of SSc to mitigate the triggers and to stabilize/improve the respiratory function. Alternatively, it is possible that a well-standardized laparoscopic antireflux procedure performed in the early disease stages may provide safer and near-optimal reflux control by repairing the hiatal hernia and augmenting the LES pressure [37–41]. This may in turn halt the progression of interstitial lung damage and avoid later lung transplantation. Previous studies have shown that fundoplication may stabilize end-stage lung disease before lung transplantation and may even lead to withdrawal from the transplantation list [42].

The choice of a partial fundoplication to control GERD seems adequate with respect to the clinical scenario of defective esophageal motility in patients with SSc. In fact, in addition to providing a viable antireflux barrier, Toupet fundoplication has been shown to minimize postoperative dysphagia and gas bloat symptoms compared to total fundoplication, especially in patients with defective esophageal motility [26, 43]. To the best of our knowledge, this is the first study aimed at evaluating the efficacy of Toupet fundoplication through objective physiologic testing, patient-reported outcomes, and quality-of-life measurements using validated questionnaires.

This study may represent a further step toward standardization of antireflux surgery in SSc patients. The protocol that we propose has the potential to improve patients' symptoms and quality of life while reducing esophageal acid exposure, daily PPI use, and chronic microaspiration. We believe that fundoplication should play a major role before the onset or at very early stages of ILD to protect the lungs from ongoing deterioration and to reduce the risk of future lung transplantation.

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Author Contribution All authors contributed to the study protocol conception and design. All authors read and approved the final manuscript.

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Declarations

Conflict of interest A. Aiolfi, D. Bona, M. Manara, C. Ogliari, C. Baldessari, M. Resta, N. Del Papa, S. Cirri, A. Baisi, G. Bonitta, L. Sconfienza, S. Harari, M. Nosotti, M. Vecchi, S.F. Schoppmann and L. Bonavina declare that they have no competing interests.

Ethical standards All procedures will be in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. Informed consent will be obtained from all patients for being included in the study.

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