Study Protocol

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BACKGROUND

Laparoscopic sleeve gastrectomy (LSG) is currently the most frequent primary bariatric procedure performed worldwide. LSG is safe and effective in terms of excess weight loss. It is a powerful metabolic operation that activates significant hormonal pathways that lead to changes in eating behavior, glycemic control and intestinal functions. LSG can be a faster procedure for its technical aspects (any need for intestinal anastomosis, being limited to the stomach transection). The most frequent and sometimes dangerous complications are leaking, hemorrhage, splenic injury, stenosis and Gastroesophageal Reflux Disease (GERD)(1). Despite its established efficacy and safety, dispute still exists on optimal operative technique for LSG: bougie size, distance of resection margin from the pylorus, the shape of section at the gastroesophageal junction, staple line reinforcement and intraoperative leak testing are among the most controversial issues (2). Indeed, different Authors have adopted a resection distance from the pylorus between 2 and 6–7 cm with various reasons (3). In favor of resections more distant to the pylorus, Authors argue that it seems to improve gastric emptying, prevent distal stenosis and reduce intraluminal pressure, potentially leading to a lower incidence of fistula and/or reflux. On the other hand, resections close to the pylorus seems to reduce more the gastric distensibility and increase intragastric pressure, potentially leading to a better satiation with less oral intake (4, 5). However, only few studies have investigated the differences between these two approaches (3). Thus, the primary aim of this randomized monocentric study is to evaluate variations in percentage of excess weight loss (%EWL) at 1 and 2 years follow-up after LSG in subject with a gastric resection starting from 2 cm from the pylorus (wide antrectomy) compared to those with a gastric resection starting from 6 cm from the pylorus (small antrectomy). Secondary aim-points are represented by evaluation of differences in morbidity, mortality, tolerance to food, incidence of reflux symptoms and GERD Health-Related Quality-of-Life (GERD-HRQL) score between the two groups.

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Material and Methods

This study was conducted from January 2015 to November 2017 in the Department of General and Emergency Surgery of "A. Rizzoli" Hospital in Lacco Ameno (Naples, Italy). All the procedures were

performed by the same surgeon. Morbid obesity was preoperatively diagnosed according to the International Federation for Surgery of Obesity (IFSO) guidelines (1). Patients were randomized into 2 groups: Group A (dissection starts at 2 cm proximally to the pylorus and continued along the greater curvature to the left crus) and Group B (dissection starts at 6 cm proximally to the pylorus and continued along the greater curvature to the left crus). Results were obtained at 1 and 2 years follow-up.

Pre-operative evaluation

Preoperative evaluation included anthropometric measurements (height in cm, weight in kg, Body Mass Index(BMI) in kg/m2), comorbidity evaluation [Glycated Hemoglobin(A1c), C-peptide, stimulated C-peptide, Electrocardiography (ECG), echocardiography, lower limbs US color-doppler study, thyroid function profile]. All patients were evaluated for the presence/absence of GERD before surgery. All patients were surveyed about the presence of heartburn and/or regurgitation with a specific questionnaire GERD HRQL questionnaire (6). Each of the 10 questions were rated from 0 (absence of symptoms) to 5 (severe symptoms) for a total score that may range from 0 to 50. Symptoms were defined as absent when patients reported a GERD-HRQL score of 0, mild from 1 to 15, moderate from 16 to 24, and severe from 25 to 50. Patients with GERD-HRQL score >16 was considered positive for GERD;(7). Atypical symptoms were also recorded. All patients underwent upper endoscopy (UE) after 20 days proton pump inhibitors (PPIs) or H2 blockers off, with Helicobacter Pylori(HP) test. When present, HP was eradicated according to Maastricht consensus(8). At UE, esophagitis presence was graded according Los Angeles Classification (9). PPI assumption and symptoms relief was also measured. In case of atypical symptoms and PPI refractoriness, pH-monitoring was indicated to confirm or exclude GERD diagnosis.

2.2 Study Design

The study is designed as a randomized controlled trial. Primary outcome was the evaluation of %EWL between 2 groups. Secondary outcomes were evaluation of morbidity, mortality, incidence of reflux symptoms and Quality of Life score between the Groups.From January 2015 to November 2017, a series of 218 consecutive patients suffering from morbid obesity and scheduled for LSG were included; informed consent was obtained from each participant before surgery.

Inclusion criteria were morbid obesity defined as BMI 40 kg/m2 and age between 25–50 years old. Obesity-related comorbidities included Type 2 Mellitus Diabetes (T2MD), hypertension, hyperlipidemia, bronchial asthma, osteoarthritis and degenerative joint disease.

Exclusion criteria

Patients with previous bariatric surgical procedures, endocrine disorders causing obesity (as hypothyroidism and Cushing disease), pregnancy or lactation, psychiatric illness, or recent diagnosis of malignancy, inflammatory bowel disease, Barrett's esophagus, and GERD with esophagitis scored as or greater than grade B, a large hiatal hernia (>3 cm) were excluded from the study. In case of absence or grade A esophagitis, GERD was also considered as severe with GERD-HRQL> 30 and when interfering with daily activities or inducing dietary restriction despite, also these were excluded.

One hundred-fifty patients were considered eligible and randomized in two Group (Group A n = 75, Group B n=75). All patients underwent elective laparoscopic LSG. In the case of conversion to open surgery, patients were excluded. Details of enrollment procedure are shown in Fig. 1.

Randomization

Participants were randomly assigned to one of the two groups using computer-generated permuted blocks (www.randomization.com). Outpatient clinic controls were done by surgeons/surgical residents/GP blinded for the groups. Patients were randomized into 2 groups based on the distance to pylorus of resection: Group A (n=75) at 2 cm, Group B(n=75) at 6 cm. Results were obtained at 1 and 2 years follow-up. The randomization scheme was generated using the web site Randomization.com ⟨http://www.randomization.com⟩.

Blinding Process

Patients, care providers, staff collecting data, and those assessing the endpoints were all blinded to treatment allocation. Patients were blinded to the surgical procedure performed until the final assessment of the study endpoints. Because the blinding of the operating surgeons was not feasible, they were not involved in the data collection and outcome assessment. Physicians in charge of patients' management were not involved in the operating room and were blinded to the surgical procedure. Data were collected and analyzed by physicians who were not involved in the patient's management during the whole RCT. For all patients enrolled in the study, a detailed letter of the protocol was sent to general practitioners, with a detailed calendar of clinical and/or instrumental follow-up data to be performed at the bariatric surgery center.

Surgical Technique

The patient is placed in a split leg position with the surgeon located in between the patient's legs. Closed pneumoperitoneum was established using our standard technique of Veres needle insufflation in Palmer site and optical insertion of a 12-mm port at a supraumbilical site (10-15 cm from umbilicus) Two further 15-mm and 12-mm ports were placed respectively in the left and right ipocondrum as working ports. A subxiphoid track was created using a 5-mm port for placement of a liver retractor. CO_2 is insufflated up to 15 mmHg. In patients with higher body mass index who have severe visceral obesity, additional trocars can be added for retraction of the omentum or big fatty livers, to optimize the exposure to reach the left crus. Once the left crus is reached, an optimal exposure of the hiatus is mandatory to find incidental hiatal hernias and a complete dissection of the left crus performed to prevent retained fundus. The greater omentum was opened close to the stomach wall in some part in between the fundus and the antrum to have greater curvature completely detached from the stomach; this dissection starts at 2 cm proximal to the pylorus and continued along the greater curvature to the left crus in Group A with Blunt Tip (Medtronic Inc., Dublin, Ireland), and at 6 cm proximal to the pylorus in Group B. Posterior adhesions if present, were carefully divided. The left gastrophrenic ligament was divided to expose the angle of His to identify the complete hiatus and fundus. A bougie was positioned before starting resection of the stomach. We use a 36Fr bougie The starting point from the pylorus to begin the gastrectomy was 2 cm in Group A and 6 cm in Group B. To perform gastrectomy, we used a Medtronic Tri-Staple® SIGNA (Medtronic Inc., Dublin, Ireland) with GORE®SEAMGUARD® Bioabsorbable Staple Line Reinforcement. we have chosen cartridges Black at the antrum level and finished with a purple cartridge. We always checked the posterior wall before firing. Once we have reached the proximal stomach, the stapler has to be positioned 1 cm lateral to the left of the angle of His to avoid inclusion of esophageal tissue. Methylene blue test is performed routinely.

2.5 Post-operative evaluation

All patients were actively clinical followed up regularly at 3, 6, 12 and 24, included GERD-HRQL. UE was performed in all patients at 12 or 24 months. Significant vomiting and food intolerance were evaluated at 6, 12 and 24 months follow-up. Vomiting was considered significant when occurring at least three times a week and food intolerance was defined as vomiting occurring almost each day. Esophageal biopsies were performed only in case of esophagitis $\geq$ B (9).

Weight loss parameters were recorded at 3, 6, 12 and 24 months after the LSG : BMI (in kg/m2), %EWL and percentage total weight loss %TWL from baseline. The secondary endpoints were GERD and esophagitis studied with Upper endoscoy and GERD score

2.6 Statistical Analysis

Statistical analysis was performed using Graphpad Quick Calcs (GraphPad version 6.04 for Windows, GraphPad Software, La Jolla California USA). Baseline comparisons were performed using chi-square tests and T-tests. Continuous variables are expressed as mean ± standard deviation (SD). Differences between preoperative and postoperative parameters were compared by Wilcoxon paired rank test. For all tests, a two-sided $p<0.05$ was considered statistically significant.

Sample size

THIS IS A CONTROLLED RANDOMIZED STUDY OF BINARY NON-INFERIORITY OUTCOME IN PARALLEL GROUPS. IF THERE IS TRULY NO DIFFERENCE BETWEEN THE STANDARD AND EXPERIMENTAL TREATMENT, THEN 138 PATIENTS ARE REQUIRED TO BE 90% SURE THAT THE LOWER LIMIT OF A ONE-SIDED 95% CONFIDENCE INTERVAL (OR EQUIVALENTLY A 90% TWO-SIDED CONFIDENCE INTERVAL) WILL BE ABOVE THE NON-INFERIORITY LIMIT OF -10. SAMPLE SIZE WAS CALCULATED WITH SEALED ENVELOPE LTD. 2012.

Appendix 2

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Study Protocol

Results summarized in the table:

Table 1 :Preoperative demographics data

Table 2: Weight, Body mass index, and the percentage of excess body weight loss and the Percentage Total Weight loss of the two groups at follow-up 3-6-12-24-months

Table 3: GERD Health-Related Quality-of-Life (GERD-HRQL) Score preoperative and postoperative scores follow-up 3-6-12-24 months

Table 4: Endoscopy Preoperative and at 1 and 2 years follow-up into two Groups

Table 1 Preoperative demographics data

Patients	Total	Group A (n=75)	Group B(n=75)
Age	33.6 ± 14	32.2 ± 8	34.2 ± 9
Male	39%	35%	38%
Female	61%	63%	62%
Height	151.2 ± 22	150.1 ± 23	152.8 ± 33
Weight kg	121.9 ± 21.7	124.5 ± 26.7	125.3 ± 23.5
BMI	44.23 ± 6.32	43 ± 8 (40–57)	44 ± 4(40–55)
ASA(I-II)(%)	65%	64%	66%
ASA(III-IV)(%)	35%	36%	34%
T2MD(%)	12(8.%)	7(9.3%)	5(6.6%)
Chronic obstructive pulmonary disease(%)	7(4.6%)	2(2.6%)	3(4%)
Heart Ischemia	1	0	0
Hypertension(%)	95(63%)	55(73.3%)	40(53.4%)

BMI body mass index, %EWL percentage excess weight loss, %TWL percentage total weight loss, Type 2 Mellitus Diabetes (T2MD)

Table 2: Weight, Body mass index, and the percentage of excess body weight loss and the Percentage Total Weight loss of the two groups at follow-up

Patients	3 months follow-up 145/150		p	6 months follow-up 141/150		p	12 months follow-up 136/150		p	24 months follow-up 131/150		p
	Group A (n=72)	Group B(n=73)	*p>0.05*	*Group A(n=70)*	*Group B(n=71)*	*P<0.05*	*Group A(n=67)*	*Group B(n=69)*	*p*	*Group A(n=65)*	*Group B(n=66)*	*p>0.05*
BMI	30.9 ± 5.32	34.7 ± 4.18	*P<0.05*	26.13 ± 7.32	31.06 ± 3.12	*P<0.05*	24.2 ± 3.4	27.5 ± 4.3	P<0.05	25.2 ± 4.4	26.2 ± 3.3	*p>0.05*
EBWL%	40.9 ± 8.1	31.60± 8.7	*P<0.05*	54.1±11.3	48.20±12.5	*P<0.05*	63.7±14.1	59.6±12.5	P<0.05	62.8±13.1	61.6±10.5	*p>0.05*

Results

Table 3 GERD Health-Related Quality-of-Life (GERD-HRQL) Score preoperative and postoperative scores

Patients	Preoperative 150/150		3 months follow-up 145/150			6 months follow-up 141/150			12 months follow-up 136/150			24 months follow-up 131/150		
	Group A (n=75)	Group B(n=75)	Group A (n=72)	Group B(n=73)	*p>0.05*	*Group A(n=70)*	*Group B(n=71)*	*P<0.05*	*Group A(n=67)*	*Group B(n=69)*	*P<0.05*	*Group A(n=65)*	*Group B(n=66)*	*p>0.05*
GERD HRQL Score<15			38(52.7%)	57(78%)	P<0.05	36(51.4%)	56(78.8%)	P<0.05	47(70.4%)	55(79.7%)	P<0.05	49(75.3%)	55(83.3%)	P<0.05
GERD HRQL Score >16<30	7(9.3%)	9(12%)	29(40%)	15(20.5%)	P<0.05	30(42.8%)	14(19.7%)	P<0.05	16(23.8%)	13(18.8%)	P>0.05	14(21.5%)	10(15.1%)	P>0.05
GERD HRQL Score >31	-	-	5(6.9%)	1(1.3%)	P<0.05	4(5.7%)	1(1.4%)	P<0.05	4(5.9%)	1(1.4%)	P<0.05	1(1.5%)	0	P<0.05
Significant Vomit	-	-	11(15,3%)	3(4.1%)	P<0.05	6(8.6%)	2(2.8%)	P<0.05	6(8.9%)	2(2.9%)	P<0.05	2(3.1%)	1(1.5%)	P<0.05
Intolerance to food	-	-	2(2.7%)	0	P<0.05	1(1.4%)	0	*p>0.05*	0	0	*p>0.05*	0	0	*p>0.05*

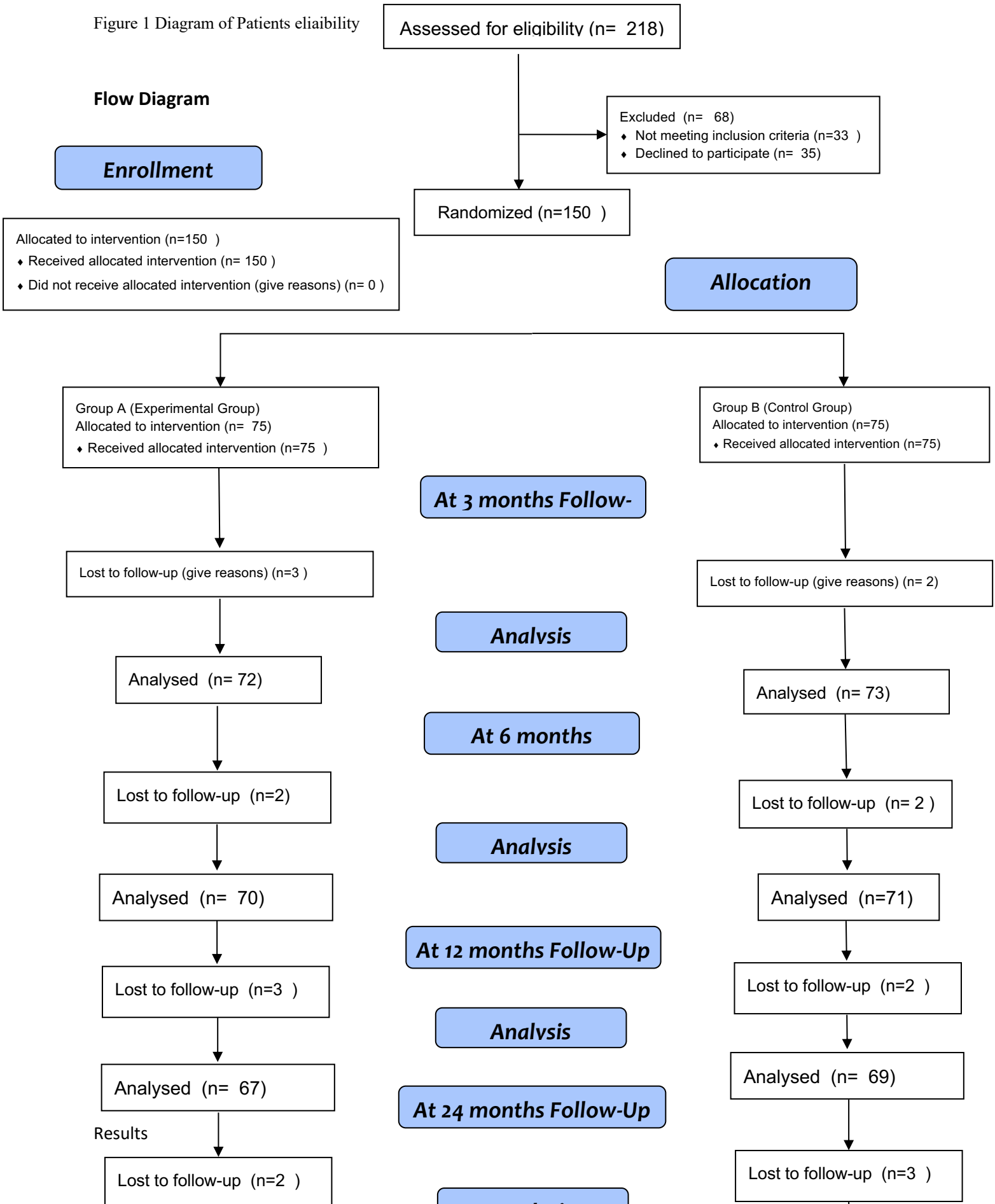
Results

Table 4: Endoscopy Preoperative and at 1 and 2 years follow-up into two Groups

	Preoperative Patients 150		1 year follow-up Patients 108/150(72%)		2 years follow-up Patients 105/150(70%)	
	Group A 75	Group B 75	Group A 53	Group B 55	Group A 52	Group B 53
Esophagitis						
A	4(5.3%)	5(6.7%)	9(16.9%)	7(12.7%)	5(9.6%)	5(9.4%)
B	-	-	11(20.7%)	5(9%)	9(17.3%)	3(5.6%)
C	-	-	2(3.8%)	0	1(1.9%)	0
D	-	-				
Esophageal biopsy						
Metaplasia	-	-	0	0	0	0
Helicobacter Pylori	9(12%)	7(9.3%)				
Hiatal Hernia< 5 cm	1(1.3%)	2(2.7%)	-	-	-	-

Results

Figure 1 Diagram of Patients eliaibility



Results