ISSN 1948-9366 (online)

World Journal of *Gastrointestinal Surgery*

World J Gastrointest Surg 2017 April 27; 9(4): 97-117

Published by Baishideng Publishing Group Inc

WJGS World Journal of Gastrointestinal Surgery

A peer-reviewed, online, open-access journal of gastrointestinal surgery

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2016-2019

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World Journal of Gastrointestinal Surgery

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AIM AND SCOPE

World Journal of Gastrointestinal Surgery (*World J Gastrointest Surg*, *WJGS*, online ISSN 1948-9366, DOI: 10.4240) is a peer-reviewed open access academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

WJGS covers topics concerning micro-invasive surgery; laparoscopy; hepatic, biliary, pancreatic and splenic surgery; surgical nutrition; portal hypertension, as well as associated subjects. The current columns of *WJGS* include editorial, frontier, diagnostic advances, therapeutics advances, field of vision, mini-reviews, review, topic highlight, medical ethics, original articles, case report, clinical case conference (Clinicopathological conference), and autobiography. Priority publication will be given to articles concerning diagnosis and treatment of gastrointestinal surgery diseases. The following aspects are covered: Clinical diagnosis, laboratory diagnosis, differential diagnosis, imaging tests, pathological diagnosis, molecular biological diagnosis, immunological diagnosis, genetic diagnosis, functional diagnostics, and physical diagnosis; and comprehensive therapy, drug therapy, surgical therapy, interventional treatment, minimally invasive therapy, and robot-assisted therapy.

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INDEXING/ABSTRACTING

World Journal of Gastrointestinal Surgery is now indexed in Emerging Sources Citation Index (Web of Science), PubMed, and PubMed Central.

NAME OF JOURNAL
World Journal of Gastrointestinal Surgery

ISSN
ISSN 1948-9366 (online)

LAUNCH DATE
November 30, 2009

FREQUENCY
Monthly

World Journal of Gastrointestinal Surgery
Baishideng Publishing Group Inc
7901 Stoneridge Drive, Suite 501, Pleasanton, CA 94588, USA
Telephone: +1-925-2238242
Fax: +1-925-2238243
E-mail: editorialoffice@wjgnet.com
Help Desk: http://www.f6publishing.com/helpdesk
http://www.wjgnet.com

PUBLISHER
Baishideng Publishing Group Inc
7901 Stoneridge Drive, Suite 501,
Pleasanton, CA 94588, USA
Telephone: +1-925-2238242
Fax: +1-925-2238243
E-mail: bpgoffice@wjgnet.com
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PUBLICATION DATE
April 27, 2017

World Journal of Gastrointestinal Surgery

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World J Gastrointest Surg 2017 April 27; 9(4): 97-102

DOI: 10.4240/wjgs.v9.i4.97

ISSN 1948-9366 (online)

ORIGINAL ARTICLE

Retrospective Study

Trends with neoadjuvant radiotherapy and clinical staging for those with rectal malignancies

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Author contributions: Reddy SS designed, performed the research, and wrote the paper; Handorf B performed the statistical analysis; Farma JM and Sigurdson ER edited and supervised the project.

Institutional review board statement: This study was reviewed and approved by the institution.

Informed consent statement: Patients were not required to give informed consent to the study because the analysis used anonymous clinical data that was obtained from a national cancer database.

Conflict-of-interest statement: The authors have no financial relationships to disclose.

Data sharing statement: There is a potential risk of confidentiality loss during the study. The following steps will be taken to protect the confidentiality of the information obtained throughout the study: All protected information will be de-identified at the start of the research project; all original documents will be maintained on a computerized system in their original format. Data points will be maintained on a locked file in the office of Beth Handorf; only the investigators will have access to the electronic medical records; all investigators are HIPAA and NIH trained with regard to the protection of human research participants.

Manuscript source: Invited manuscript

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Received: September 30, 2016
Peer-review started: October 10, 2016
First decision: November 10, 2016
Revised: January 3, 2017
Accepted: February 18, 2017
Article in press: February 20, 2017
Published online: April 27, 2017

Abstract

AIM

To see how patterns of care changed over time, and how institution type effected these decisions.

METHODS

A retrospective analysis was performed using the National Cancer Database, looking at all patients that were diagnosed with rectal cancer from 1998 to 2011. We tested differences in rates of treatment and stage migration using χ^2 tests and logistic regression models.

RESULTS

A review of ninety thousand five hundred and ninety four subjects underwent multimodality therapy for cancer of the rectum. Staging and response to treatment varied greatly between centers. Forty-six percent of the time staging was missing in academic practices, *vs* fifty-four percent of the time in community centers (P < 0.001). As a result, twenty-percent were down-staged and eight percent up-staged in academia, whereas only fifteen percent were down-staged and 8% up-staged in community practices (P < 0.001). Forty-two percent of individuals underwent radiation before surgery in 1998.

Within two years this increased to fifty-three percent. This increased to eighty-six percent by 2011 ($P < 0.001$). Institution specific treatment varied greatly. Fifty-one percent received therapy before surgery in academic centers in 1998. Thirty-nine percent followed this pattern in the same year in the community ($P < 0.001$). By 2011, ninety-one percent received radiation before their procedure in academic centers, *vs* eighty-four percent in the community ($P < 0.001$). Rates of adoption were better in academia, although an increase was seen in both center types.

CONCLUSION

From the study dates of 1998 to 2011, preoperative treatment with radiation has been on the rise. There is certainly an increased rate of use of radiation in academia, however, this trend is also seen in the community. Practice patterns have evolved over time, although rates of assigning clinical stage are grossly underreported prior to initiation of preoperative therapy.

Key words: Neoadjuvant therapy; Community; Rectal cancer; Academic

Core tip: This paper serves to show how changes in practice patterns evolve over time. The adoption of these practice patterns differ across institution type, and the role of appropriate clinical staging is often not included. In order for proper treatments to be initiated, we not only need data substantiated by level one evidence, but we also need proper clinical staging so we can ensure appropriate therapies are delivered to these patients.

Reddy SS, Handorf B, Farma JM, Sigurdson ER. Trends with neoadjuvant radiotherapy and clinical staging for those with rectal malignancies. *World J Gastrointest Surg* 2017; 9(4): 97-102 Available from: URL: http://www.wjgnet.com/1948-9366/full/v9/i4/97.htm DOI: http://dx.doi.org/10.4240/wjgs.v9.i4.97

INTRODUCTION

The implementation of radiotherapy for rectal cancer has seen many adaptations over time, particularly when comparing adoption in community *vs* academic centers in the United States. Surgical resection with sound oncologic technique is a critical component. Various series report local regional recurrence rates anywhere between 50%-60% in patients undergoing surgery for rectal adenocarcinoma[1-3]. Histological grade, primary tumor invasion, and length of the lesion, have all been found to influence rates of local recurrence[1,2,4]. Another important correlate for local recurrence are those subset of patient found to have positive nodal disease[4]. Local recurrence rates, in addition to overall survival, were both adversely affected when any of these criteria were met.

The use of radiotherapy was initially met with skepticism, as many believed that surgery, which included a total mesorectal excision (TME), offered superior results. Heald *et al*[5] surmised that patients with low tumors did no worse than those with high tumors when treated by anterior resection, provided that the mesorectum is excised intact with the cancer. Karanjia *et al*[6] and Heald *et al*[7] went as far as to suggest that less margins may not increase recurrence or effect survival, as long as a good TME was performed. As surgical techniques for rectal cancer improved, innovations regarding the selective use of radiotherapy were also being explored. Despite this, many continue to argue that a technically sound TME may eliminate radiation[8,9].

The addition of radiotherapy to surgical resection has been an evolving process, and several randomized controlled trials have compared various regimens to surgery alone. Many of these trials were done in an academic institution, and although validated by randomized trials, adoption into the community initially lagged. The Colorectal Cancer Collaborative Group reviewed twenty eight randomized trials, and found a decreased risk of recurrence when preoperative therapy was given[10]. The Dutch group implemented short course radiation and TME, and found lower recurrence rates then when TME was done by itself[11]. Implementation of chemoradiotherapy (CRT) was widely adopted in the 1990's, when two trials were completed. These compared pre and postoperative therapy.

Despite prospective data showing the success of radiation, its adoption within the community seems limited, and could partially be a result of inaccurate initial staging. Using the National Cancer Database (NCDB) we looked to see how patterns of care changed over time, and how institution type effected these decisions. We also looked to see if clinical staging was lacking, and if so, how this effected the adoption of neoadjuvant therapies.

MATERIALS AND METHODS

A retrospective review was performed using the NCDB. All patients diagnosed with rectal cancer from 1998 to 2011 were included. Patients were stratified by those who underwent surgery as initial treatment, *vs* those who underwent neoadjuvant radiotherapy. Of these patients, clinical staging was reviewed, and compared between academic and community centers. Clinical stage was further divided into node positive and node negative disease, and tumor response by induction therapy was determined by final pathological stage. Differences in rates of treatment and stage migration were tested using χ^2 tests and Cochran-Armitage tests for trend.

RESULTS

A review of ninety-thousand five hundred and ninety four subjects underwent multimodality therapy for cancer of the rectum. The total cohort included 62%

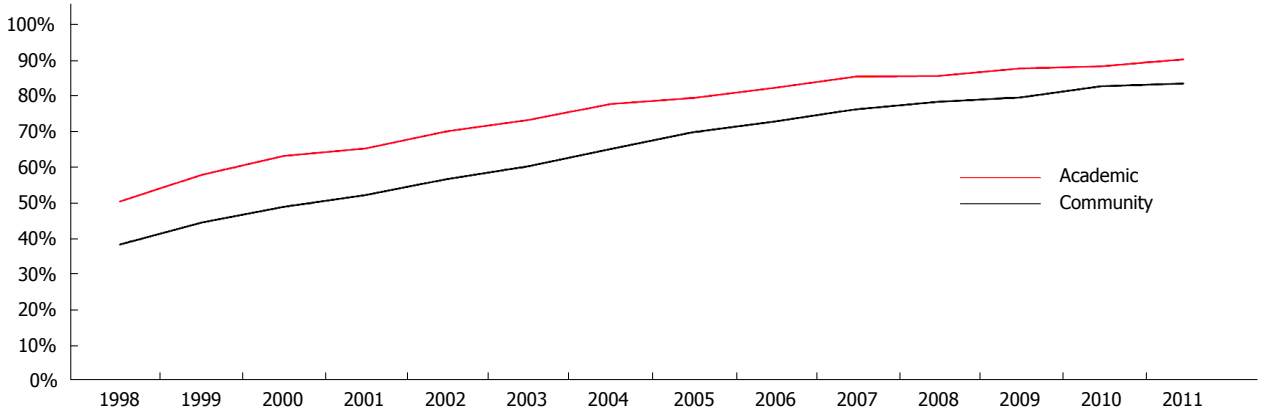

Figure 1 Trends in the adoption of neoadjuvant therapy. Graphical interpretation of the adoption of neoadjuvant therapy over time when comparing academic and community institutions.

Table 1 Patient demographics

Demographics (%)	
Gender	
Male	62
Female	38
Age	
< 50	18
51-70	54
> 70	28
Race	
Caucasian	88
African American	8
Other	4
Insurance	50
Private	43
Medicare/Medicaid	
None	4
Other	3

males and 38% female. Fifty-four percent of patients were between the ages of 51-70. The overwhelming majority of patients were Caucasian, at 88%. Patient's insurance status was 50% privately insured, and 43% with Medicare/Medicaid (Table 1).

Forty-two percent of individuals underwent radiation before surgery in 1998. Within five years, this proportion had increased to 64%, and over the course of the study period we saw a 33% increase in adoption of radiotherapy. By 2011, 86% received induction radiotherapy prior to surgery ($P < 0.001$). In 1998, 51% of patients underwent induction radiotherapy when seen in an academic center *vs* 39% when seen in the community. Within five years there was a rise in the routine application of radiotherapy at 74% and 61%, respectively. By 2011, 91% of academic centers, and 84% of community centers routinely used induction radiotherapy in the treatment of rectal cancers ($P < 0.001$). Adoption was better in academia overall, but an increase was seen in both center types (Figure 1).

Across the cohort of patients who received neoadjuvant radiotherapy, 21% did not have a clinical stage recorded, 25% had no pathological stage, and 6% had neither recorded. When assessing staging differences between academic and community centers, clinical stage was unknown in 17% *vs* 23%, respectively ($P < 0.001$). Pathological staging was not recorded 24% of the time in academic centers, and 26% of the time in the community ($P < 0.001$). Neither stage was recorded in 5% and 6% of the time in academic *vs* community centers, respectively ($P < 0.001$). Overall, staging was incomplete 46% of the time in academic centers, and 55% of the time within the community ($P < 0.001$) (Table 2).

Overall response to treatment showed that seventeen percent were down-staged, eight percent up-staged, and twenty-four percent had no change. Within academic centers, twenty percent were down-staged, eight percent up-staged, and twenty-six percent had no changes. Down-staging in the community occurred fifteen percent of the time, up-staging eight percent, and no changes in twenty-three percent. Patients at academic centers were down-staged more often after neoadjuvant therapy than when in the community ($P < 0.001$) (Table 3). Patients were also stratified by T-stage and nodal status. Fifty-four percent with clinically negative nodes had node negative disease on final pathology. Twenty-two percent of patients without palpable nodes were found to be node positive. Thirty-seven percent were down-staged to node negative status.

DISSCUSION

The use of neoadjuvant radiation has increased over time. Unfortunately evidence-based medicine remains difficult to enforce[12]. In our review, adoption of these practices seems to be initially lower within the community compared to academics; however, trends suggest a steady increase in its implementation. One explanation for this is the non-uniform anatomic definition of rectal cancer, and as a result, the lack of appropriate clinical staging done. In a systematic review searching for national and international guidelines, no consensus concerning a definition was found[13]. Four guidelines used fifteen centimeters from the anus as the anatomic rectum, and

Table 2 Institutional staging

Unknown staging	%
Overall unknown	
Path stage	25
Clinical stage	21
Both stages	5
Academic unknown	
Path stage	24
Clinical stage	17
Both stages	5
Community unknown	
Path stage	26
Clinical stage	23
Both stages	6

Table 3 Trends in staging

Unknown staging	%
Overall	
Up-stage	8
Down-stage	17
No change	24
Academic	
Up-stage	8
Down-stage	20
No change	26
Community	
Up-stage	8
Down-stage	15
No change	23

two used twelve centimeters[13]. In addition to this, how measurements were made varied between consensus guidelines; some used proctoscopy, others flexible endoscopy, and some MRI. The lack of a universal definition could be attributing to the lack of compliance in undergoing appropriate staging studies and thus assigning clinical stage, and subsequent delivery of care.

Staging modalities

Standardized treatment would not be possible without appropriate staging modalities. Proper disease staging will determine whether or not induction therapy would be of value. Imaging options include endorectal ultrasound, computerized tomography, and magnetic resonance imaging[14]. We found that 21% of patients that underwent neoadjuvant therapy had no clinical stage recorded. Although clinical staging seems to occur less within the community, it is difficult to tell if this is a result of improper data collection, or reflective of the institution itself. Similarly, pathological staging was unavailable more often within community centers than in academic places. Charlton *et al*[15] demonstrated that fellowship trained surgeons more often ordered endorectal ultrasounds and MRI's. They were also more likely to refer for neoadjuvant treatments[15]. Although not certain, this could be suggestive that this trend would hold in academic centers, as opposed to the community based practices. In our review, in patients with data available for staging, it seemed as though academic institutions had improved rates of down staging tumors, when compared to the community. This could be correlated to the difference in clinical stage recorded amongst these centers. However, a flaw in our work is that we do not know whether clinical staging was done or simply not recorded.

TME

The use of TME challenged implementation of radiotherapy in the treatment algorithm. Since its inception, reductions in local recurrence, improved survival, and sphincter preservation have been noted. The main issue with this surgical approach is that it is operator dependent. Whether or not the surgeon has been properly instructed in the technique ultimately plays a role in recurrence patterns. Unfortunately, whether or not a TME was implemented at the time of surgical resection in our study is not known. One could argue that surgeons practicing in academic centers have had extra training in TME's, and this again supports the lack of adoption of evidence-based practices within the community. When properly performed, a TME provides excellent local control. Heald *et al*[5] found a recurrence rate of 7.2%. Several years later this was 3.5%[16]. Macfarlane *et al*[17] confirmed recurrence rates of 5% with TME, 25% with conventional surgery and radiotherapy, and 13.5% with conventional surgery and CRT. Enker *et al*[9] reports recurrence in 7.3%. Nodal involvement and perineural invasion were statistically significant risk factors.

Use of radiotherapy

In terms of neoadjuvant radiotherapy, the German group looked to challenge the recommended standard therapy of postoperative CRT. After randomization, 6% recurred locally in the preoperative group, *vs* 13% in the postoperative arm[18]. Despite strong evidence, there remains a subset of clinicians that challenge this, and advocate a selective approach to induction therapy. In a single center, retrospective cohort study, Williamson and colleagues supported an individual approach to when CRT was used. The mention a 5-year recurrence rate of 6.5% in the treatment group, *vs* 0% when surgery was done by itself[19]. Patients receiving treatment were selected on the basis of an involved circumferential margin. This explains the variation in recurrence between these arms. However, this represents a prime example of how treatments patterns differ across institutions. To elaborate on this further, the PROSPECT trial initially evaluated patients who were candidates for a low anterior resection with TME, and were given six cycles of FOLFOX[20]. If disease was stable or progressed, then they would proceed to preoperative CRT, if they were responders, then they would go straight to surgery. The pilot study by Schrag *et al*[20] demonstrated that those who had chemotherapy had complete pathologic response rates of 25%, and a 0% four-year local recurrence rate.

SEER data by Fitzgerald *et al*[12], the use of radio-

therapy was 17% in 1998, which increased to 51% in 2007. In our review, 42% of patients received induction radiotherapy, which increased to 64% in five years. By 2011, 85% of patients seen received neoadjuvant radiotherapy for rectal cancer ($P < 0.001$). Similar trends were noted by Jobsen *et al*[21], finding a steady increase in the utilization of neoadjuvant radiotherapy from 1997-2008. It remains evident that a trend for the routine use of neoadjuvant radiotherapy is there. However, factors such as volume and facility type certainly play a role[22,23]. Stewart *et al*[22] surmised that hospitals where teaching was a priority, increased the likelihood of receiving neoadjuvant treatments ($P < 0.0001$). In our review, fifty-one percent of those treated in academia underwent preoperative therapy *vs* 39% when seen in the community. By 2011, 91% of academic centers, and 84% of community centers, routinely used radiotherapy ($P < 0.001$).

Caring for those with of locally advanced rectal cancer has evolved over the decades. Advances in surgical technique with TME revolutionized the field of rectal surgery, and offered patients superior local control than when compared to conventional surgery alone. Several studies have suggested this benefit, attributing higher local recurrence rates to inadequate TME's[24-26]. As clinical trial accrual escalated, the implementation of radiotherapy to the treatment algorithm was the next logical step. The Dutch group found that preoperative therapy was safe in patients, even if they were to undergo surgery[27]. Despite this, adoption of the routine use of neoadjuvant radiotherapy was a difficult undertaking. The data shows a trend favoring the influence of evidence-based medicine, which in turn affects the way in which we practice medicine. In order for this to continue, we must work on improving recording of clinical stage, so that patients are not only eligible for potential clinical trials, but receive the current standard of care. Although smaller discrepancies continue to exist between academic and community centers in terms of its usage of neoadjuvant therapy, the overall trends are on the rise.

COMMENTS

Background

The implementation of radiotherapy for rectal cancer has seen many adaptations over time, particularly when comparing adoption in community *vs* academic centers in the United State. Surgical resection with total mesorectal excision is a critical component. Various series report local regional recurrence rates anywhere between 50%-60% in patients undergoing surgery for rectal adenocarcinoma. The addition of radiotherapy to surgical resection has been an evolving process, and several randomized controlled trials have compared various regimens to surgery alone. Many of these trials were done in an academic institution, and although validated by randomized trials, adoption into the community initially lagged.

Research frontiers

The adoption of radiotherapy for this disease has altered the way in which we treat this disease. As with any new therapy, there are always experiments being conducted to see if the authors again can change their practicing treatment plan.

Innovations and breakthroughs

In this study the authors looked to see how patterns of treatment changed over time. Differences between the types of facility administering care were reviewed, and whether appropriate clinical staging was assigned was critiqued.

Applications

This study suggests that radiotherapy had slow adoption into mainstream practice, but over time, practice patterns changed.

Terminology

Radiation: This is the emission or transmission of energy in the form of waves or particles. The use of radiation in clinical practice has greatly changed the way the authors treat disease in the modern era.

Peer-review

The paper is interesting.

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P- Reviewer: da Rocha JJR, Seo A, Wilkins S **S- Editor**: Song XX
L- Editor: A **E- Editor**: Lu YJ

World Journal of Gastrointestinal Surgery

Submit a Manuscript: http://www.f6publishing.com

World J Gastrointest Surg 2017 April 27; 9(4): 103-108

DOI: 10.4240/wjgs.v9.i4.103

ISSN 1948-9366 (online)

ORIGINAL ARTICLE

Observational Study

Feasibility of pancreatectomy following high-dose proton therapy for unresectable pancreatic cancer

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Author contributions: Hitchcock KE, Nichols RC and Rutenberg MS wrote the manuscript; Bose D, Hughes SJ, Stauffer JA, Celinski SA, Johnson EA, Zaiden RA and Mendenhall NP reviewed the manuscript; Morris CG performed statistical analysis; Bose D, Hughes SJ, Stauffer JA, Celinski SA, Johnson EA and Zaiden RA provided patient care.

Institutional review board statement: The University of Florida Health Proton Therapy Institute's PC-O1 and outcomes-tracking study were approved by an institutional review board at the University of Florida College of Medicine in Jacksonville, FL.

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

Conflict-of-interest statement: The authors of this current series have no conflicts of interested to disclose.

Data sharing statement: No additional data are available.

Manuscript source: Invited manuscript

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Received: November 17, 2016
Peer-review started: November 23, 2016
First decision: December 29, 2016
Revised: January 28, 2017
Accepted: March 12, 2017
Article in press: March 13, 2017
Published online: April 27, 2017

Abstract

AIM

To review surgical outcomes for patients undergoing pancreatectomy after proton therapy with concomitant capecitabine for initially unresectable pancreatic adenocarcinoma.

METHODS

From April 2010 to September 2013, 15 patients with initially unresectable pancreatic cancer were treated with

proton therapy with concomitant capecitabine at 1000 mg orally twice daily. All patients received 59.40 Gy (RBE) to the gross disease and 1 patient received 50.40 Gy (RBE) to high-risk nodal targets. There were no treatment interruptions and no chemotherapy dose reductions. Six patients achieved a radiographic response sufficient to justify surgical exploration, of whom 1 was identified as having intraperitoneal dissemination at the time of surgery and the planned pancreatectomy was aborted. Five patients underwent resection. Procedures included: Laparoscopic standard pancreaticoduodenectomy (n = 3), open pyloris-sparing pancreaticoduodenectomy (n = 1), and open distal pancreatectomy with irreversible electroporation (IRE) of a pancreatic head mass (n = 1).

RESULTS

The median patient age was 60 years (range, 51-67). The median duration of surgery was 419 min (range, 290-484), with a median estimated blood loss of 850 cm^3 (range, 300-2000), median ICU stay of 1 d (range, 0-2), and median hospital stay of 10 d (range, 5-14). Three patients were re-admitted to a hospital within 30 d after discharge for wound infection (n = 1), delayed gastric emptying (n = 1), and ischemic gastritis (n = 1). Two patients underwent R0 resections and demonstrated minimal residual disease in the final pathology specimen. One patient, after negative pancreatic head biopsies, underwent IRE followed by distal pancreatectomy with no tumor seen in the specimen. Two patients underwent R2 resections. Only 1 patient demonstrated ultimate local progression at the primary site. Median survival for the 5 resected patients was 24 mo (range, 10-30).

CONCLUSION

Pancreatic resection for patients with initially unresectable cancers is feasible after high-dose [59.4 Gy (RBE)] proton radiotherapy with a high rate of local control, acceptable surgical morbidity, and a median survival of 24 mo.

Key words: Pancreatic cancer; Pancreatectomy; Pancreas; Proton therapy; Radiotherapy

Core tip: Patients undergoing pancreatectomy for resectable pancreas cancers have a significant risk of local and regional recurrence. That risk could be reduced if patients received moderate-dose preoperative radiotherapy. Many surgeons, however, are concerned that conventional X-ray-based radiotherapy could complicate what is already a complicated operation. The current series documents the surgical outcomes for 15 patients with initially unresectable pancreatic cancers who underwent pancreatectomy after high-dose [59.40 Gy (RBE)] proton-based radiotherapy. The lack of increased surgical toxicity suggests that proton radiotherapy may represent an optimal vehicle for the delivery of moderate dose neoadjuvant radiotherapy in the setting of resectable disease.

Hitchcock KE, Nichols RC, Morris CG, Bose D, Hughes SJ, Stauffer JA, Celinski SA, Johnson EA, Zaiden RA, Mendenhall NP, Rutenberg MS. Feasibility of pancreatectomy following high-dose proton therapy for unresectable pancreatic cancer. *World J Gastrointest Surg* 2017; 9(4): 103-108 Available from: URL: http://www.wjgnet.com/1948-9366/full/v9/i4/103.htm DOI: http://dx.doi.org/10.4240/wjgs.v9.i4.103

INTRODUCTION

Patients undergoing pancreatectomy for tumors which are believed to be resectable by preoperative imaging experience high rates of lymph node positivity, margin positivity and local/regional recurrence[1-6]. In spite of this, many surgeons are reluctant to recommend neoadjuvant radiotherapy which might have the potential to sterilize microscopic disease in the operative bed and reduce the incidence of these events. This reluctance is presumably due to concerns that even moderate dose radiotherapy in the range of 50.40 Gy might complicate what is already a lengthy and complicated operation.

The current series reviews the surgical outcomes for a group of patients with initially unresectable disease who, after high-dose proton radiotherapy [59.40 Gy (RBE)] and chemotherapy (oral capecitabine, 1000 mg, twice a day), achieved enough of a radiographic response to justify surgical exploration. The favorable physical characteristics of proton radiotherapy are demonstrated in Figures 1 and 2. Specific attention is paid to the surgical metrics of: Duration of surgery; estimated blood loss; and hospital length of stay which are compared to benchmark studies in the surgical literature.

MATERIALS AND METHODS

This is a retrospective single-institution study of patients enrolled on either the University of Florida Health Proton Therapy Institute PC-01 trial for patients with unresectable disease or the University of Florida Health Proton Therapy Institute outcomes-tracking study. The statistical methods of this study were reviewed by Christopher G Morris from the Department of Radiation Oncology, University of Florida College of Medicine.

From April 20, 2010 to September 30, 2013, 15 patients with initially unresectable pancreatic cancer were treated with full-dose proton therapy with concomitant capecitabine at 1000 mg taken orally twice a day. All patients received 59.40 Gy (RBE) to the gross disease, and 1 patient also received 50.40 Gy (RBE) to the high-risk nodal targets. There were no treatment interruptions or chemotherapy dose reductions. Patient details can be found in Table 1.

The technical details for the delivery of proton radiation therapy have been described previously[7,8]. In summary, optimized 2- or 3-field 3-dimensional conformal passive-scatter proton plans were created in which 95% of the

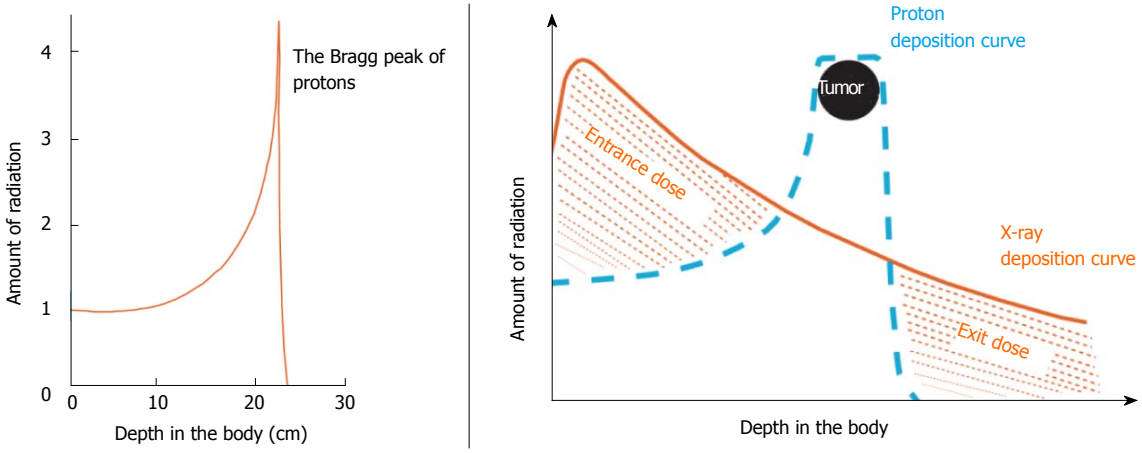

Figure 1 Favorable physical characteristics of proton radiotherapy are demonstrated. A: Charged particles such as protons travel a finite distance into tissue, as determined by their energy, and then release that energy within a tightly defined region called the "Bragg peak"; B: By delivering a range of energies toward the tumor target, several Bragg peaks can be formed to create a "spread-out Bragg peak" that conforms to the depth and position of the tumor target.

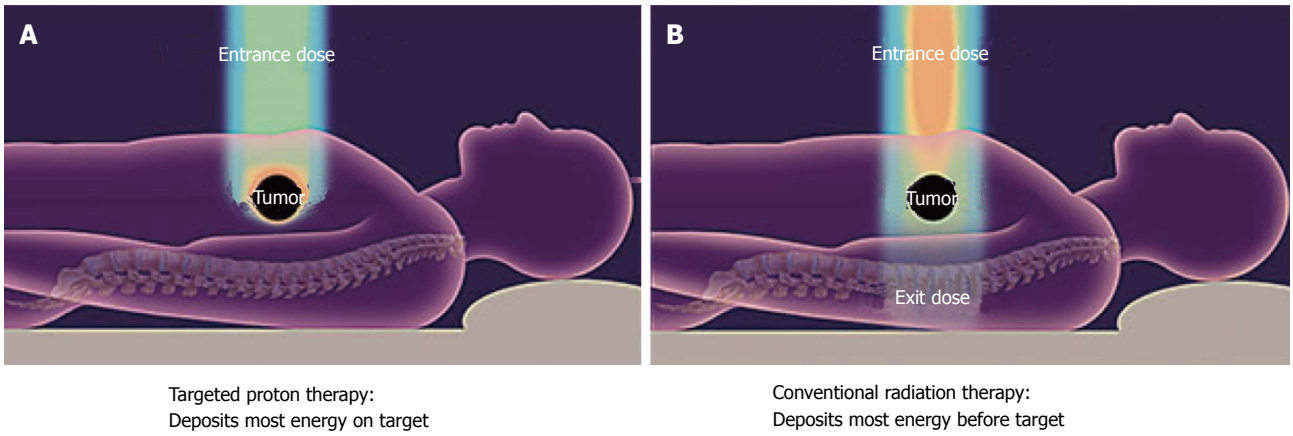

Figure 2 Conventional radiotherapy. With conventional radiotherapy (A) using X-rays (photons), the highest dose is deposited where the beam enters the patient. The dose at the tumor target is significantly less than the entry dose. Also, an exit dose is delivered beyond the tumor target. With protons (B), the entry dose is low. The highest dose is deposited at the depth of the tumor target, and there is no exit dose beyond the target.

planning target volumes received 100% of the prescribed dose, and 100% of the planning target volumes received at least 95% of the prescribed dose. Normal-tissue constraints included the following: Spinal cord, < 46 Gy; right kidney, V18 < 70%; left kidney, V18 < 30%; liver, V30 < 60%; and small bowel (including duodenum) and stomach, V20 < 50%, V45 < 15%, V50 < 10%, and V54 < 5%. These target coverage goals and normal-tissue limits were met for all patients with minor patient-specific adjustments. A typical proton therapy plan is shown in Figure 3.

To document surgical outcomes, we used treatment records to verify the type and extent of resection, procedure duration, blood volume lost during the procedure, length of hospital stay, number of days spent in intensive care, readmission for surgical complications, pathologic assessment of the surgical specimens, local disease control, distant disease control, and overall survival.

RESULTS

Six patients achieved a radiographic response sufficient to justify surgical exploration. Of these, 1 patient was identified as having intraperitoneal dissemination at the time of surgery and the planned pancreatectomy was aborted. Five patients underwent resection. Procedures included laparoscopic standard pancreaticoduodenectomy (n = 3), open pyloris-sparing pancreaticoduodenectomy (n = 1), and open distal pancreatectomy with irreversible electroporation of a pancreatic head mass (n = 1). Median age was 60 years (range, 51-67). These patients had been initially designated as having unresectable disease based on superior mesenteric artery and celiac artery encasement (n = 2), inferior vena cava encasement with invasion of the posterior abdominal wall (n = 1), biopsy-positive regional nodal metastasis (n = 1), or mesenteric root involvement with abutment of the celiac and hepatic arteries (n = 1).

Two patients underwent gross total (R0) resections and subsequent pathology showed minimal residual disease. Two patients had gross subtotal (R2) resections. One patient, who after negative pancreatic head biopsies underwent distal pancreatectomy and irreversible

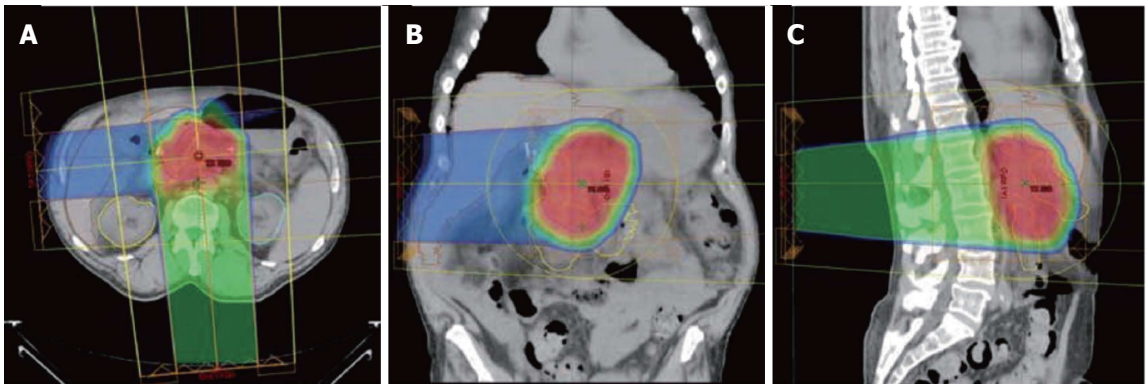

Figure 3 Typical proton dose distributions used to treat pancreatic cancers. Shown in the axial (A), coronal (B), and sagittal (C) projections. A heavily weighted (75% of the target dose) posterior or posterior oblique field is combined with a more lightly weighted (25% of the target dose) right lateral oblique field. Because protons are associated with a low entry dose and no exit dose compared with X-rays, there is significant sparing of small bowel and stomach tissue, which are highly sensitive to radiation damage. This normal-tissue sparing explains the low incidence of gastrointestinal toxicity when protons are used to deliver upper abdominal radiotherapy.

Table 1 Patient details

Patient	1	2	3	4	5
Age	55	60	51	68	67
Stage	T3 N1	T4 N0	T4 N0	T4 N0	T4 N0
Comorbidities	None	Colon cancer	Unintentional weight loss	None	Unintentional weight loss
Resection type	Laparoscopic	Laparoscopic	Laparoscopic	Open	Open
Surgery duration (min)	339	465	419	290	484
Estimated blood loss (mL)	300	800	850	2000	1000
Intensive care stay (d)	1	1	0	2	0
Total hospital stay (d)	5	11	6	10	14
Complications	Wound infection	Delayed gastric emptying	None	None	Delayed gastric emptying and gastritis
Readmission within 30 d	4 d for wound infection	2 d for nausea and vomiting	None	None	2 d for gastritis

electroporation of the pancreatic head mass, had no identifiable malignancy in the surgical specimen. In none of the 5 cases did the surgeon document any complaint regarding the texture of tissue around the resection, exceptional bleeding, difficulty with closure, postoperative wound complications, or any other issue that could be attributed to the irradiated state of the tumor and surrounding tissues.

The median duration of the surgical procedures was 419 min (range, 290-484 min). Estimated blood loss (EBL) ranged from 300 to 2000 cm^3 with a median of 850 cm^3. The median intensive-care stay for these patients was one day (range, 0-2) and median hospital stay (LOS) was 10 d (range, 5-14). Three patients were readmitted to a hospital within 30 d after discharge: The first was a patient discharged on postoperative day 5 who was then readmitted for wound infection on day 9. The second was discharged on postoperative day 11 who was then readmitted the next day with the primary complaint of delayed gastric emptying. The third was a readmission on postoperative day 19 for ischemic gastritis following discharge on postoperative day 10.

Only 1 patient demonstrated ultimate local progression at the primary site, which occurred 7 mo after surgery in 1 of the patients who underwent an R0 resection. The median survival for the 5 resected patients was 24 mo (range, 10-30); the 4 patients with locally controlled disease ultimately developed distant metastases.

DISCUSSION

The above surgical metrics for patients with initially unresectable disease who received dose escalated radiotherapy to 59.4 Gy (RBE) compare favorably to those observed in four published studies that, for the most part, involved surgery for resectable patients who had not received neoadjuvant radiotherapy (Table 2): (1) Tseng *et al*[9] published a series analyzing 650 procedures performed by experienced surgeons at the MD Anderson Cancer Center (Houston, TX). The mean operative time was 513 min. The mean EBL was 725 cc and the average LOS was 13 d. The authors acknowledge that some patients underwent preoperative radiation therapy or chemotherapy but these numbers were not reported; (2) Speicher *et al*[10] reported an average procedure length of 431 min in a series of 140 pancreaticoduodenectomies performed by experienced surgeons in which 40% were performed laparoscopically. Patients experienced a mean

Table 2 Surgical metrics for pancreatectomy - A comparison of the published studies

Published study	Operating room time (min)	Estimated blood loss (cc)	Length of hospital stay (d)
Tseng[9]	513	725	13
Speicher[10] open	NA	500	NA
Speicher[10] laparoscopic	NA	200	NA
Speicher[10] total	431	NA	10
Asbun[11] open	401	1032	12.4
Asbun[11] laparoscopic	541	195	8
Florida Agency for Healthcare Administration	NA	NA	11
Current series	419	850	10

NA: Not applicable.

EBL of 200 mL when a laparoscopic approach was used, and 500 mL with hybrid or open procedures. The mean LOS was 10 d with a 37% readmission rate. There is no mention of neoadjuvant therapy in these cases; (3) Asbun and Stauffer[11] at the Mayo Clinic reported similar metrics. For 215 open and 53 laparoscopic pancreaticoduodenectomies, the EBL averaged 1032 cm^3 and 195 cm^3, mean LOS was 12.4 d and 8 d, and average operating room time was 401 and 541 min, respectively. The authors did not record whether these patients had been irradiated before surgery; and (4) The Florida Agency for Healthcare Administration database[12] reported the statewide median length of stay following pancreatectomy in the years from 2010 to 2012 to be 11 d (mean ± SD, 14 ± 11.5).

It is an accepted precept of oncology that patients with solid tumors cannot be cured if local and regional tumor control cannot be achieved. For patients with nonmetastatic pancreatic cancer, it is also generally accepted that local control cannot be achieved without extirpative surgery. As such, surgery represents a necessary condition for cure. Nevertheless, because surgery alone is associated with a high local and regional failure rate, it is rarely a sufficient condition for cure. Patients undergoing pancreaticoduodenectomy with negative lymph nodes and negative surgical margins will experience a 50%-80% chance of local-regional tumor recurrence if adjuvant therapies are not offered[1,2]. Even when postoperative chemotherapy and radiotherapy are delivered, the local-regional failure rates range from 28% in the Radiation Therapy Oncology Group 97-04 trial[3] to 36% in the Massachusetts General Hospital (Boston, MA) experience[4]. Although its methodological and statistical flaws have been well-described[13], the results of the European Study Group for Pancreatic Cancer-1 trial suggest that postoperative X-ray-based radiation therapy not only fails to improve patient survival but may be associated with a nominal survival decrement, presumably due to radiation therapy toxicity[14,15].

The failure of postoperative radiation therapy to even reliably sterilize microscopic disease in the postoperative setting might be explained in two ways: First, to allow for postoperative recovery after pancreaticoduodenectomy, upper abdominal radiation therapy cannot be delivered until 10 or 12 wk have elapsed. This time interval potentially allows for the progression of malignant cells in a hypoxic tumor bed. Second, because a large volume of small bowel is transposed into the postoperative radiation therapy field, it is generally not possible to deliver X-ray doses over 50 Gy, which may be inadequate to eradicate even microscopic disease growing in such a hypoxic environment.

While it is recognized that patients undergoing pancreatic resection have a high local-regional failure rate-even in the setting of negative surgical margins and negative lymph nodes-contemporary data from two high-volume institutions suggest that margin-negative, lymph node-negative pancreatectomies are relatively uncommon. The series published by investigators at Johns Hopkins University (Baltimore, MD) on 905 patients undergoing pancreaticoduodenectomy between 1995 and 2005 indicated a 41% margin-positivity rate and a 79% node-positivity rate[5]. The series from investigators at Memorial Sloan-Kettering Cancer Center (New York, NY) on 625 resections conducted between 2000 and 2009 indicated a 16% margin-positivity rate and a 70% node-positivity rate[6]. Based on these data, as well as the low likelihood of reliably sterilizing microscopic disease in the postoperative tumor bed with radiotherapy, it is likely that even "resectable" patients could benefit from preoperative radiation therapy, perhaps with fields that could cover regional lymph nodes. With the current series showing no increase in surgical morbidity after high dose proton radiotherapy, it is arguable that protons allow for the safe delivery of this oncologically rational intervention.

The surgical duration, EBL, and LOS for pancreatectomy following high-dose [59.40 Gy (RBE)] proton radiotherapy for patients with initially unresectable disease in this series are comparable to those observed in studies that, for the most part, involved surgery for resectable patients who had not received neoadjuvant radiotherapy. These data strongly suggest that standard dose [50.40 Gy (RBE)] neoadjuvant proton radiotherapy should not increase the difficulty of pancreatectomy in patients with resectable disease.

COMMENTS

Background

Nearly every patient cured of adenocarcinoma of the pancreas has had complete surgical resection of the tumor. Because this malignancy is initially

asymptomatic, tumors are often very locally advanced at diagnosis and may not be resectable without removing vital tissues such as the major abdominal arteries. For many years chemotherapy and photon radiotherapy have been used to shrink advanced tumors in an attempt to make them resectable. Proton therapy has not previously been used for this purpose but is promising because it can be carefully shaped to spare the normal tissues of the abdomen such as the stomach, duodenum, spinal cord, and kidneys from radiation. This new treatment option will only be acceptable if it does not increase the rate of complications at the time of resection of the tumor.

Research frontiers

Proton radiotherapy has been used in the treatment of cancer for many decades but has only recently become widely available. Much meticulous research must be done to show whether proton treatment offers advantages over standard treatments for each type of cancer. The first step in each line of inquiry is to demonstrate that proton radiotherapy is safe, and then efficacy can be addressed.

Innovations and breakthroughs

In the current work the authors have shown for the first time that proton radiotherapy given prior to attempted resection of initially unresectable pancreas cancers does not result in increased rates of surgical complications.

Applications

In the large fraction of patients with pancreatic cancer who have an unresectable tumor at the time of diagnosis, proton radiotherapy offers one safe option for neoadjuvant treatment intended to downstage the tumor and make surgical resection possible.

Terminology

One patient in this study was treated with irreversible electroporation. This is an emerging technology in which the surgeon disrupts the integrity of tumor cell membranes using a high voltage, high frequency electrical field, leading to eventual cell death.

Peer-review

This paper is very interesting and suitable for publication in this journal.

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P- Reviewer: Engelholm SA, Hotta T, Rausei S **S- Editor**: Qi Y
L- Editor: A **E- Editor**: Lu YJ

World Journal of Gastrointestinal Surgery

Submit a Manuscript: http://www.f6publishing.com

World J Gastrointest Surg 2017 April 27; 9(4): 109-117

DOI: 10.4240/wjgs.v9.i4.109

ISSN 1948-9366 (online)

ORIGINAL ARTICLE

Prospective Study

Five-year outcomes of laparoscopic sleeve gastrectomy as a primary procedure for morbid obesity: A prospective study

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Author contributions: Hoyuela C designed the study, collected and analyzed the data, wrote the paper and revised the manuscript for final submission.

Institutional review board statement: This study was reviewed and approved by the Hospital Plató Institutional Review Board.

Clinical trial registration statement: This study is registered at www.researchregistry.com. The registration identification is researchregistry1580.

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrolment.

Conflict-of-interest statement: The authors have no commercial associations that might be a conflict of interest in relation to this article.

Data sharing statement: There is no additional data are available.

Manuscript source: Invited manuscript

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Received: August 31, 2016
Peer-review started: September 2, 2016
First decision: October 20, 2016
Revised: December 11, 2016
Accepted: February 8, 2017
Article in press: February 13, 2017
Published online: April 27, 2017

Abstract

AIM

To prospectively evaluate the postoperative morbi-mortality and weight loss evolution of patients who underwent a laparoscopic sleeve gastrectomy (LSG) as a primary bariatric procedure during 5 years of follow-up.

METHODS

Since 2006, data from patients undergoing a highly restrictive primary LSG have been prospectively registered in a database and analysed. Preoperative co-morbid conditions, operating time, hospital stay, early and late complications rate and evolution of weight loss after 5 years of follow-up were analysed.

RESULTS

A total of 156 patients were included, 74.3% of whom were women. The mean age was 43.2 ± 13.1 years and the mean body mass index (BMI) was 41.5 ± 7.9 kg/m^2. Seventy patients (44.8%) presented a BMI under 40 kg/m^2. The mortality rate was 0%. The leakage rate was 1.2%, and the total 30-d morbidity rate was 5.1% (8/156). With a mean follow-up of 32.7 ± 28.5 (range 6-112) mo, the mean percent of excess of weight loss (%EWL) was 82.0 ± 18.8 at 1 year, 76.7 ± 21.3 at 3 years and 60.3 ± 28.9 at 5 years. The mean percent of excess of BMI loss (%EBMIL) was 94.9 ± 22.4 at 1 year, 89.4 ± 27.4 at 3 years and 74.8 ± 29.4 at 5 years. Patients with preoperative BMI less than 40 kg/m^2 achieved greater

weight loss than did the overall study population. Diabetes remitted in 75% of the patients and HTA improved in 71.7%. CPAP masks were withdrawn in all patients with obstructive sleep apnoea.

CONCLUSION

LSG built with a narrow 34 F bougie and starting 3 cm from the pylorus proved to be safe and highly effective in terms of weight loss as a stand-alone procedure, particularly in patients with a preoperative BMI lower than 40 kg/m^2.

Key words: Sleeve gastrectomy; Morbid obesity; Bariatric surgery; Obesity surgery; Laparoscopy; Long-term results; 5-year results

Core tip: The number of laparoscopic sleeve gastrectomies (LSGs) performed worldwide as a primary bariatric procedure has grown exponentially in recent years, given the simplicity of the technique, the low complication rate and the good short- and mid-term results regarding weight loss and the resolution of co-morbidities. However, there are a limited data from long-term studies. In this study, a standardized LSG proved to be safe (no mortality and a leakage rate of 1.2%) and highly effective in terms of weight loss after 5-year of follow-up, particularly in patients with a low preoperative body mass index. This manuscript provides additional evidence supporting the role of laparoscopic sleeve gastrectomy as a stand-alone procedure for selected morbidly obese patients.

Hoyuela C. Five-year outcomes of laparoscopic sleeve gastrectomy as a primary procedure for morbid obesity: A prospective study. *World J Gastrointest Surg* 2017; 9(4): 109-117 Available from: URL: http://www.wjgnet.com/1948-9366/full/v9/i4/109.htm DOI: http://dx.doi.org/10.4240/wjgs.v9.i4.109

INTRODUCTION

The laparoscopic bariatric procedure commonly referred to as "sleeve gastrectomy" (LSG) is a left partial gastrectomy of the fundus and body to create a long tubular gastric conduit constructed along the lesser curve of the stomach[1].

LSG was initially proposed as a first-stage procedure to reduce the mortality and postoperative morbidity of more complex bariatric procedures in higher-risk patients[2], such as the duodenal switch, to complete the biliopancreatic diversion or the Roux-en-Y gastric bypass (RYGB) in a second stage. Soon, it was noted that many patients frequently lost sufficient weight such that a second-stage operation became unnecessary[3]. LSG is not merely a restrictive procedure. LSG provokes a rapid gastric emptying of solid food, accelerates intestinal transit and induces a favourable change in the gut hormones, thereby facilitating weight loss through restriction and appetite suppression, given the reduction in the ghrelin levels after resection of the gastric fundus[3-7]. Since then, LSG has been performed as a primary and definitive bariatric procedure in patients whose weight and medical condition are not sufficiently severe to require a complex bariatric operation, moving to a second stage only in those selected patients in which weight loss was inadequate[8]. Eventually, LSG was performed in some patients with special conditions in which the usual bariatric operations might be too aggressive[9].

The number of LSGs performed worldwide has grown exponentially over the last decade, because it appears to be an easier and safer technique[10-13]. Many surgeons now perform LSG as their standard bariatric operation[3]. The advantages of the LSG include its technical simplicity, shorter operative time, maintenance of bowel integrity and preservation of the pylorus[3,10]. The long-term problems associated with other complex bariatric procedures, including internal hernias and small bowel obstruction are avoided with LSG. In addition, patients who underwent LSG had fewer nutritional deficiencies than that did patients who underwent RYGB or biliopancreatic diversion[14]. The LSG can later be modified by a laparoscopic approach if required, to a more complex procedure (such as RYGB or duodenal switch) in patients who develop severe gastroesophageal reflux symptoms or those who regain weight.

LSG has proven highly effective at achieving durable weight loss and co-morbidity reduction over the short and intermediate terms and is comparable in some aspects to RYGB, the current gold standard in bariatric surgery[7,15-18]. However, some questions must be answered regarding the long-term results of LSG because there are a limited data from long-term studies and because of the variability in both the reported follow-up among series and the rate of patients lost to follow-up.

The aim of this study was to assess the safety and outcomes of patients who underwent a LSG as a primary bariatric procedure in analysing mortality, postoperative morbidity rate, late complications and evolution of weight loss after 5 years of follow-up.

MATERIALS AND METHODS

Patients selection and study design

From 2006 to January 2016, data from patients who underwent a LSG as a single procedure treating morbid obesity were collected in an electronic database (Microsoft Access 2003 Microsoft Corporation, Redmond, QA, United States) for analysis. All study participants, or their legal guardian, provided informed written consent prior to study enrolment. The study was officially registered under the identification number researchregistry 1580 on researchregistry.com.

The indications for LSG included patients with body mass index (BMI) less than 45 kg/m^2, primary

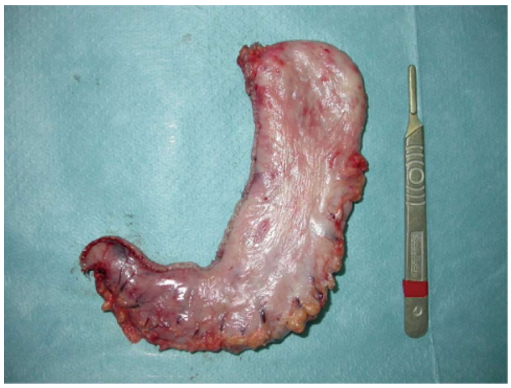

Figure 1 Specimen after sleeve gastrectomy. The whole fundus had to be removed. Stapler firings must be properly aligned to avoid excessive narrowing of the sleeve and functional obstruction due to rotation.

procedure in super-obese patients as the initial stage of a two-staged approach for weight loss (RYGB or BPD in 2 stages), adolescents (under 18 years old of age) with morbid obesity and obese patients with impaired medical conditions or other important co-morbidities such as liver cirrhosis.

The first endpoint of this study was to assess the safety of the procedure by analysing the 30-d mortality and early postoperative complications: Suture leak rate, haemorrhages, wound infection rate, deep venous thrombosis, pulmonary embolism and cardiac and pulmonary complications.

The second endpoint was to evaluate the outcome of LSG in terms of weight loss 5 years after the procedure. Weight loss was measured using BMI evolution and the percentage of excess weight loss (%EWL). Given the variability of %EWL depending on the definition of ideal body weight, we also used the percentage of excess body mass index loss (%EBMIL)[19]. Excessive BMI itself was defined as initial BMI minus 25. Values are reported as the mean ± standard deviation.

The following variables were also evaluated: Resolution of preoperative co-morbid conditions [diabetes, hypertension, obstructive sleep apnoea syndrome (OSA)], length of hospital stay and late complications (stricture, functional obstruction, gastroesophageal reflux, trocar-site hernia rate).

Surgical technique

Under general anaesthesia the patients were placed in the reverse Trendelenburg position with the surgeon standing between the legs. All patients received intravenous antibiotic prophylaxis with 2 g of cefazoline. Compression stockings were used during the operation to prevent deep vein thrombosis and thromboembolism.

The procedure was performed using 4 or 5 ports (two or three 12-mm trocars and two 5-mm trocars). The greater curvature of the stomach was completely freed starting from the antrum (3 cm proximal to pylorus) until the left pillar of the diaphragm and the gastroesophageal junction were completely exposed. If a hiatal hernia is identified, dissection should be carried posteriorly to achieve appropriate closure of the crus. If a hernia is found, it should be repaired[10]. A harmonic scalpel (Ultracision®, Ethicon Endo-Surgery Inc., Johnson and Johnson, Cincinnati, OH, United States) was used to divide the gastroepiploic and the short gastric vessels. Then, the adhesions of the posterior side of the stomach were dissected to achieve an appropriate sleeved stomach. The LSG was performed by sequentially firing an articulating linear stapler (Echelon Flex™ Endopath, Ethicon Endo-Surgery Inc., Johnson and Johnson, Cincinnati, OH, United States). The gastric division started at 3 cm proximal to the pylorus. Two 60-mm green staple cartridges (open height = 4.1 mm) were usually used to transect the antrum, and gold (3.8 mm) and blue loads (3.6 mm) were later applied at the gastric corpus and fundus. The whole fundus had to be removed. Special attention was required at that point to avoid rotation and functional obstruction of the sleeve by ensuring equal (and not excessive) traction on both walls of the stomach. It is of utmost importance to align the stapler firings properly to avoid excessive narrowing, especially at the level of the *incisura angularis* (Figure 1).

The calibration of the LSG was obtained using a 34 F oral gastric tube (1.13 cm). The gastric stapled line was always oversewn with a 2/0 absorbable running suture (Monoplus®, B. Braun, Melsungen, Germany) in the 125 initial cases. A bovine pericardial strip (BPS-Peristrip) was used in 5 patients. Since 2014, bioabsorbable membranes (Gore Seamguard® from WL Gore and Associates, Newark, DE, United States) were used instead of the reinforcement suture to achieve better hemostasis and reduce the suture leakage rate[15]. Intraoperative leak testing using methylene blue dye was routinely performed. A suction Blake or Jackson-Pratt drain was placed along the suture line. Finally, the gastric specimen was withdrawn through the right 12-mm port. All 12-mm wounds were closed with Monoplus® or Monomax® 2/0 sutures (B. Braun, Melsungen, Germany) using an Endoclose™ trocar-site closure device (Covidien Products, Medtronic, Minneapolis, MN, United States).

Patients started to walk 8 to 12 h after the procedure. A liquid diet was initiated on the first postoperative day and was implemented for two weeks. The patients were usually discharged on the second or third postoperative day. The treatment included oral analgesia, proton-pump inhibitors (PPI) and low molecular weight heparin against deep vein thrombosis for 30 d.

Postoperative follow-up

The first follow-up control was scheduled at the medical office eight days after the procedure. Follow-up data were obtained at the medical office after 15 d, 1, 3, 6 mo, 1 year and semi-annually thereafter by the surgeon who performed the procedure and by a nutritionist. All data were prospectively collected.

RESULTS

Data from 156 patients who underwent LSG until January 2016 were analysed. Of the patients, 116 (74.4%) were

Table 1 Patients' characteristics and general data of the series

Number of patients	156
Age[1] (yr)	43.2 ± 13.2 (16-71)
Gender (Female/male)	116 / 40
BMI[1] (kg/m^2)	41.5 ± 7.9
BMI < 40 kg/m^2	70 (44.9)
BMI 40-50 kg/m^2	71 (45.5)
BMI > 50 kg/m^2	15 (9.6)
Comorbidity	
HTA	39 (25)
Diabetes	12 (7.6)
Obstructive sleep apnea (with CPAP)	21 (13.4)
Other	67 (42.9)
Operating time[1] (min)	95 ± 14.1 (65-155)
Hospital stay[1] (d)	3.5 ± 0.7 (1-18)
Follow-up[1] (mo)	32.7 ± 28.5 (6-112)

[1]Data are frequency counts (percentage of total) or the mean ± SD plus range in parentheses. BMI: Body mass index; HTA: Arterial hypertension; CPAP: Continuous positive airway pressure.

Table 2 Mortality, early and late complications after laparoscopic sleeve gastrectomy *n* (%)

Mortality	0
Total 30-d complications	8 (5.1)
Staple line leakage	2 (1.2)
Staple line haemorrhage	1 (0.6)
Wound infection	2 (1.2)
Pneumonia	1 (0.6)
Cutaneous rash	1 (0.6)
Urethral bleeding	1 (0.6)
Late complications	
Symptomatic gastroesophageal reflux	24 (15.3)
Hiatal hernia needing laparoscopic repair	1 (0.6)
Gastric stricture – conversion to gastric by-pass	1 (0.6)
Symptomatic cholelithiasis	7 (4.4)

Data are frequency counts (percentage of total).

women, and 40 (25.6%) were men; overall, the mean age was 43.2 ± 13.1 (range 16-71) years, and the mean BMI was 41.5 ± 7.9 (range 34-76) kg/m^2. Seventy patients (44.9%) presented BMI under 40 kg/m^2, and only 15 patients (9.6%) were super-obese (BMI greater than 50 kg/m^2). All the procedures were performed laparoscopically by the same surgeon. The mean hospital stay was 3.5 ± 0.7 d (range: 1-18). All patients completed the 6-mo outpatient follow-up at the medical office. The mean follow-up was 32.7 ± 28.5 mo (Table 1).

The mean operating time was 95 ± 14.1 min. Conversion to laparotomy was necessary in 2 patients (1.2%) due to intraoperative haemorrhage. One patient was a woman suffering from a cavernous transformation of the portal vein and the other required a lateral segmentectomy to remove a bleeding 8-cm liver haemangioma.

Morbidity and mortality

No mortality was observed in this series. The total 30-d postoperative complication rate was 5.1% (8/156 patients). The type and severity of complications are listed in Table 2. A leakage in the staple-line was detected in 2 women (1.2%). The first woman (after oversewing the staple line) healed successfully with medical management 14 d after. The second (Peristrips® reinforcement) required a laparoscopic reoperation to drain a subphrenic abscess secondary to a leak at the angle of His. No endoprosthesis or self-expanded wall-stent was needed. There was no relationship between leakage and patients' BMI, age or technical difficulties during the sleeve gastrectomy procedure. Intraoperative leak testing was not predictive of the later development of staple line leaks. No patients presented with deep vein thrombosis or pulmonary embolism.

Regarding late complications, one patient (without symptoms of previous staple-line leak) developed a gastric stricture 10 mo after the LSG and submitted to a laparoscopic gastric bypass (0.6%). Twenty-four patients (15.3%) referred to new-onset symptoms suggesting gastroesophageal reflux requiring daily low-dose of PPI. One of these patients developed a hiatal hernia and underwent laparoscopic hiatoplasty and a Hill gastropexy with good outcomes. To date, three patients (1.9%) have developed a trocar-site hernia. Cholecystectomy due to symptomatic gallstones was performed during the follow-up in 7 patients (4.4%); 2 of them presented with acute pancreatitis. There were no data on the cholelithiasis rate in asymptomatic patients.

Weight loss

The mean follow-up was 32.7 ± 28.5 mo (range 6-112). There were 140 patients with at least 1 year of follow-up. Fifty-one patients reached more than 5 years of follow-up.

The mean initial BMI was 41.5 ± 7.9 kg/m^2 (range 34.2-76.0), and the mean initial percentage of excess of weight (%EW) was 83.1 ± 18.1%. The preoperative BMI of 72 patients (44.9%) was less than 40 kg/m^2. Marked weight loss was observed during the first year in all patients, achieving a mean BMI of 26.4 kg/m^2, with a mean %EWL of 82.0 ± 18.8 and a mean %EBMIL of 94.9 ± 22.4 after the 1-year follow-up. However, weight loss dropped progressively during the follow-up with remarkable differences among the patients (Figure 2). The mean %EBMIL was 89.4 ± 27.4 at 3 years and 74.8 ± 29.4 (range: 27.2-119.0) at 5 years. The evolution of mean BMI, %EWL and %EBMIL at different follow-up points is shown in Figure 2 and Table 3.

The overall success rate, defined when %EWL is > 50%, was 96.1% of the patients after 1 year, 95.1% after 2 years, 89.5% after 3 years, 82.1% after 4 years and 73.0% after 5 years. It must be highlighted that the patients with a lower initial BMI, especially those with initial BMI under 40 kg/m^2, achieve excellent results in terms of %EWL and %EBMIL (Figure 3).

Revisional surgery

During postoperative follow-up, re-operation because of weight regain from %EWL > 50% to %EWL < 30% was necessary in 4 patients (2.5%), all of them beyond

Table 3 Weight loss results of laparoscopic sleeve gastrectomy over time

Follow-up	Preoperative	1 yr	2 yr	3 yr	4 yr	5 yr
n	156	140	99	66	56	51
BMI[1]	41.5 ± 7.9	26.6 ± 4.4	26.3 ± 3.7	27.2 ± 5.8	28.7 ± 5.5	30.1 ± 6.1
%EWL[1]		82.0 ± 18.8	86.1 ± 28.9	76.7 ± 21.3	72.8 ± 22.6	60.3 ± 28.9
%EBMIL[1]		94.9 ± 22.4	93.7 ± 23.5	89.4 ± 27.4	81.1 ± 28.3	74.8 ± 29.4

[1]Data are frequency counts (total) or the mean ± SD. BMI: Body mass index; %EWL: Percentage of excess weight loss; %EBMIL: Percentage of excess body mass index loss.

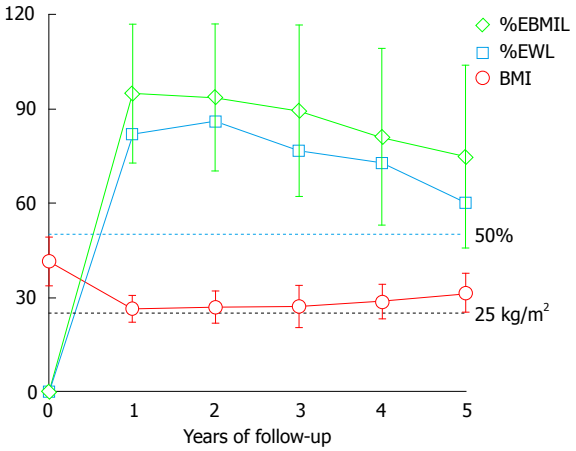

Figure 2 Evolution of body mass index, excess weight loss and excess body mass index loss during the follow-up. BMI: Body mass index; %EWL: Percent of excess weight loss; %EBMIL: Percent of excess body mass index loss.

the fourth year of follow-up. A 70-year-old woman received a laparoscopic re-sleeve, one patient underwent a SADI's and two received a laparoscopic RYGB.

Resolution of co-morbidities

After the first postoperative year, the rate of remission or improvement of hypertension was 71.7% (total remission in 25 patients and improvement in 3). CPAP was withdrawn in all patients with obstructive sleep apnoea (OSA). Complete remission of type 2 diabetes (T2DM) was observed in 75% (9/12) of preoperative diabetic patients (remission was considered when anti-diabetic medication was discontinued and blood glucose level was under 120 mg/mL). One patient receiving preoperative insulin improved and now receives per-oral anti-diabetic medication.

DISCUSSION

The first endpoint of this study was to assess the safety of LSG as a primary bariatric procedure. LSG has gained popularity in recent years given its theoretical technical simplicity and low rate of complications[10,11,15]. However, LSG can be a very difficult procedure even for laparoscopic surgeons with advanced skills. The surgeon's experience and some technical aspects, such as the bougie size (less than 40 F) and the distance to the pylorus being less than 4 cm from the first stapling, have been previously reported as risk factors for the development of complications after a LSG[13].

The mortality rate in this series was nil and the rate of 30-d severe complications related to the procedure was 1.9% (Table 1). The rate of staple-line leak and fistula, which is the most feared postoperative complication after LSG, was low in this series (1.2%), even when using a thin bougie to calibrate the stomach and sectioning the stomach at a short distance from the pylorus. According to the International Sleeve Gastrectomy Expert Panel[10], the average leak rate is 1.06% ± 1.13%. There is currently no consensus on the most effective measures to prevent the leakage and fistula, but we share the concept that reinforcing the staple line (with sutures or buttressing material) during LSG can significantly reduce the leakage rate[7,15,20]. The method for doing so is still a matter of debate[21]. Some reports showed no differences between oversewing of the staple line and the use of buttresses[22-24]. However, a systematic review of 88 included studies representing 8920 patients[15] found that the leak rate in LSG was significantly lower using absorbable membrane (Seamguard®) staple-line reinforcement (1.1%) than was oversewing (2.0%), bovine pericardial strip (BPS-Peristrips®) reinforcement (3.3%), or no reinforcement (2.6%). We observed one leak after oversewing of the staple line and another after the use of Peristrips®. No leaks were observed in the Seamguard® subgroup but the small number of patients in this series does not allow further analysis. It must be noted that the significantly highest incidence of leaks was reported when using both sutures and buttressing material (3.6%); consequently, this approach should always be avoided[24].

The second endpoint was to evaluate the evolution of weight loss after LSG as a primary bariatric procedure. The overall results of this study reinforce the evidence that LSG was effective at achieving a significant weight loss over short- and mid-term follow-up. Comparable outcomes in terms of weight loss over a 5-year period were reported at the 3rd International Summit of Sleeve Gastrectomy[3], with a mean percentage of excess weight loss of 62.7%, 64.7%, 64.0%, 57.3%, and 60.0% after 1, 2, 3, 4, and 5 years, respectively. These data are all consistent with other studies published to date[16,25-38] (Table 4). LSG outcomes are comparable to the gold standard procedure in bariatric surgery, the RYGB[6], thus

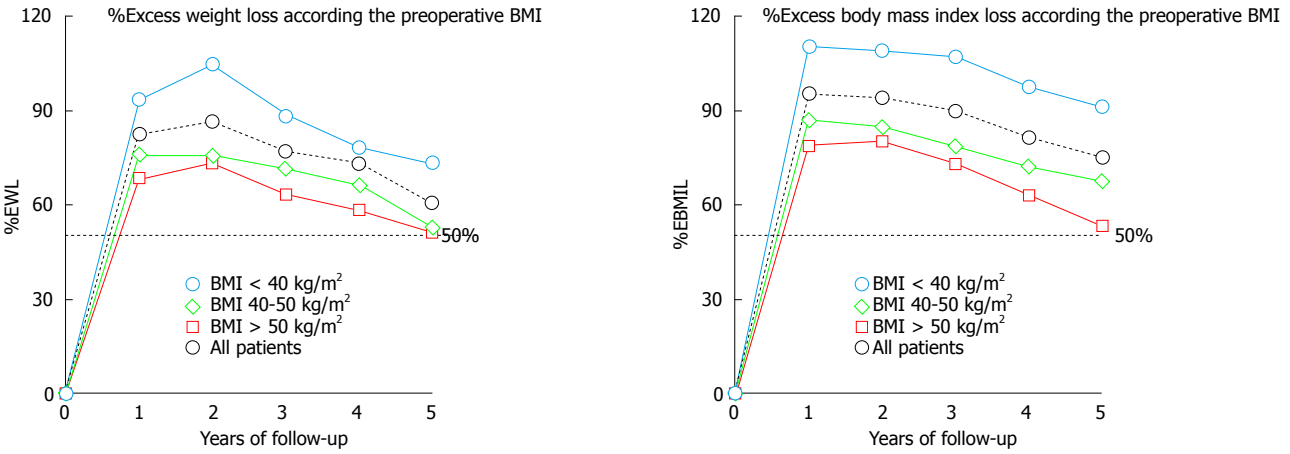

Figure 3 Excess weight loss evolution and excess body mass index loss evolution according to preoperative body mass index. Patients with a preoperative BMI under 40 kg/m^2 achieve better results after 5-year of follow-up. BMI: Body mass index; %EWL: Percent of excess weight loss; %EBMIL: Percent of excess body mass index loss.

Table 4 Long-term weight loss outcome of laparoscopic sleeve gastrectomy for morbid obesity

Author	Year	Patients with 5-yr follow-up	Mean initial BMI (kg/m^2)	%EWL 1 yr	%EWL 5 yr	%EBMIL 1 yr	%EBMIL 5 yr
Bohdjalian[26]	2010	26	48.2 ± 1.3	57.5 ± 4.5	55.0 ± 6.8		
Himpens[27]	2010	30	39		53.3		
D'Hondt[28]	2011	83	39.3	78.5	54.4		
Braghetto[29]	2012	60	38.4 ± 5.1	57.3	57.3		
Sarela[30]	2012	13	45.9	76	69 (8 yr)		
Rawlins[31]	2013	49	65	56	85.8		91
Sieber[32]	2014	62	43.0 ± 8.0			61.5 ± 23.4	57.4 ± 24.7
Boza[33]	2014	112	34.9	88	62.9		
Liu[34]	2015	44	41.0 ± 7.0	70.5	57.2		
Lemanu[35]	2015	55	50.7	56	40		
Pok[36]	2015	61	37.3 ± 8.1	76.5	72.6		
Alexandrou[37]	2015	30	55.5 ± 1.7	65.2 ± 6.1	56.4 ± 5.8		
Perrone[38]	2016	162	47.4 ± 4.2			75.1 ± 18.9	78.8 ± 23.5
Hoyuela	2016	51	41.5 ± 7.9	82.0 ± 18.8	60.3 ± 28.9	94.9 ± 22.4	74.8 ± 29.4

BMI: Body mass index; %EWL: Percentage of excess weight loss; %EBMIL: Percentage of excess body mass index loss.

supporting the role of LSG as a stand-alone bariatric operation for morbid obesity.

However, a significant amount of patients may regain weight over time after LSG. Long-term results of LSG still are an ongoing concern, and 10-year follow-up data are actually scarce. Furthermore, a high rate of patients lost to long-term follow-up is not uncommon in previously reported series. Although weight regain was evident with time, data from our series and some long-term observational studies indicate that a significant number of patients maintained good weight loss beyond 5 years of follow-up (Table 4). A recent systematic review of 16 long-term studies including 492 patients revealed the %EWL to be 62.3%, 53.8%, 43% and 54.8% at 5, 6, 7 and 8 or more years of follow-up, respectively[25]. Arman *et al*[39] reported a mean %EBMIL of 62.5% in patients who kept the simple sleeve construction (74.6% overall-study series) after a mean follow-up of 11.7 years.

It is still unclear why LSG ceases to be effective over time in terms of weight loss in some patients, but several reasons could be involved, including dilation of the gastric tube, insufficient gastric fundus resection (where ghrelin is produced) or hyperactivity of previously silent ghrelin-producing cells and other hormonal changes[6,26,39,40]. Inadequate adherence to aftercare changes in eating behaviour and lack of physical activity could play a role of paramount importance in patients with poorer maintenance of weight loss. A recent systematic review by Karmali *et al*[41] concluded that the underlying causes leading to weight regain are multi-factorial and related to patient- and procedure-specific factors.

Our data showed better results regarding weight loss when the initial BMI was lower. Patients with an initial BMI less than 40 kg/m^2 registered excellent results (73% of EWL and 90.8% of EBMIL at 5 years) compared with the overall study population (Figure 3). Age > 60 years, pre-existing co-morbidities and BMI superior to 50 kg/m^2 were identified as prognostic factors of poorer outcome after LSG. Super-obese patients also had poorer weight loss results in this series. These results allow us to suggest that LSG could be routinely used as a sole bariatric technique for patients whose BMI was less than

40 kg/m^2.

However, we observed high variability among patients regarding weight loss maintenance over time, even in patients with similar characteristics. No other significant differences were found between subgroups of patients probably due to the small sample of patients with 5 years of follow-up. Identifying preoperative predictive factors of success might be useful for developing strategies to improve bariatric surgery outcomes and patient selection. Further long-term follow-up randomized studies that include a larger number of patients are needed to identify which patients would benefit the most from LSG.

The last endpoint was to analyse the resolution of preoperative co-morbidities in the patients who underwent a LSG. LSG allowed CPAP to be withdrawn in all patients in the series with preoperative OSA and achieved the resolution of hypertension and T2DM in more than 70%. The improvement of T2DM occurred soon after surgery, even without significant weight loss yet being achieved, and this fact could be attributed to hormonal changes, such as increased GLP-1 secretion or decreased ghrelin[6]. The long-term effects of LSG on T2DM evolution are under continuous evaluation, and Aminian *et al*[42] recently reported a 44% of long-term relapse of T2DM after initial remission and continuous complete remission for $\geqslant$ 5 years ("cure") was achieved in only 3% of the patients. LSG and RYGB showed comparable remission rates of T2DM in a long-term observational study[18], but a meta-analysis including 6526 patients confirmed that RYGB achieved a higher diabetes remission rate (HR = 1.49, 95%CI: 1.04-2.12)[16]. Current data suggesting the long-term superiority of RYGB over LSG in the metabolic control of T2DM could be accounted for by the greater weight loss and by a larger contribution of weight-loss-independent mechanisms[43-45].

In our opinion, the main limitations of this study are the sample size of the series and the heterogeneity of the patients included in the series, precluding to discover significant differences between subgroups of patients (for example, only 15 super-obese patients are included in this series). In addition, only 32% (51/156) of patients reached 5-years of follow-up. The lack of adherence to follow-up was reported previously, and it can be related to several issues, including the distance to the medical office and a lack of trust or rapport with the surgeon or the medical team[46]. However, the most relevant strength of this study is that all patients underwent a standardized LSG operative technique, first, because surgeon expertise is a key issue to lower the complications rate[13,24] and second, because there were no technical differences that may influence the weight loss results. We always tried to perform a more restrictive LSG by using a thinner bougie and beginning the dissection 3 cm from the pylorus to achieve greater weight loss, as suggested by Baltasar *et al*[8,31]. In addition, the long-term follow-up of the patients was always carried out by the same surgeon who performed the procedure.

In conclusion, a LSG built with a narrow 34 F bougie and starting 3 cm from the pylorus, proved to be safe and highly effective in terms of weight loss as a stand-alone procedure, especially in patients with preoperative BMI lower than 40 kg/m^2. In our opinion, LSG could be accepted as the first stand-alone procedure for morbidly obese patients with low BMI. Prospective randomized trials analysing long-term results (beyond ten years of follow-up) will help elucidate whether LSG is comparable to more aggressive techniques.

ACKNOWLEDGMENTS

The unselfish support of Eric Herrero, MD and Fernando Carvajal, MD is highly acknowledged.

COMMENTS

Background

The number of laparoscopic sleeve gastrectomies (LSGs) performed worldwide as a primary bariatric procedure has grown exponentially in recent years, given the simplicity of the technique, the low complication rate and the good short- and mid-term results regarding weight loss and the resolution of co-morbidities. However, the long-term results of LSG still are an ongoing concern because a significant amount of patients may regain weight over time after LSG.

Research frontiers

Bariatric surgery is safe and efficient and allows not only to lose weight but treat conditions such diabetes, hypertension and sleep apnoea in morbidly obese people. Probably, the indications of bariatric and metabolic surgery will increase in the future treating such comorbidities, given its good results and low morbi-mortality.

Innovations and breakthroughs

The current prospective study suggests that LSG could be the procedure of choice for those morbid patients with a low preoperative body mass index (BMI) and without severe comorbidities. However, strict nutritional and behavioural monitoring and follow-up by the surgical team seem to be of paramount importance.

Applications

This study provides additional evidence supporting the role of LSG as a stand-alone procedure for morbidly obese patients, particularly in patients with a low preoperative BMI.

Terminology

Sleeve gastrectomy: Is a left partial gastrectomy of the fundus and body to create a long tubular gastric conduit constructed along the lesser curve of the stomach. The body mass index (BMI) is the main parameter to assess morbid obesity and is defined as the body mass (weight in kilograms) divided by the square of the body height and is universally expressed in units of kg/m^2. The changes in weight and BMI expressed by means of percentage of excess weight loss and percentage of excess of BMI loss help to evaluate the success of bariatric surgery.

Peer-review

The article addresses an important entity and many newly qualified surgeons may find this article interesting.

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P- Reviewer: Fogli L, Maleki AR, Mann O **S- Editor**: Song XX
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