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SURGICAL ENDOSCOPY
and Other Interventional Techniques

Laparoscopic esophagectomy in the palliative treatment of advanced esophageal cancer after radiochemotherapy

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Abstract
Background: Esophageal cancer is associated with a poor long-term prognosis. Only a 10% 5-year survival rate is reported. This article aims to evaluate the feasibility and efficacy of laparoscopic esophagectomy for the palliative treatment of advanced esophageal cancer (T3-T4 Nx-N1) after neoadjuvant therapy.
Methods: From March 1998 to July 2002, 35 patients (mean age, 64.6 years; range, 35–72 years) affected by advanced cancer of the middle lower third of the esophagus came to the authors' observation. All received neoadjuvant radiochemotherapy. Of the 35 patients, 22 (62.9%) showed a positive response to treatment (≥50% reduction of maximal cross-sectional area of the tumor), and surgical intervention was performed 4 weeks after the end of the therapy. The operations were accomplished through the laparoscopic approach and left lateral cervicotomy.
Results: The mean operative time was 160 min (range, 120–260 min). One patient (4.5%) experienced a cervical anastomotic leak. Three patients (13.6%) died in the postoperative period: one of myocardial infarction and two of acute respiratory failure. The mean postoperative hospital stay was 12.1 days (range, 9–23 days). After a mean follow-up period of 20.2 months (range, 10–40 months), 13 patients (68.4%) were alive.
Conclusions: The laparoscopic approach seems to be effective for the palliative treatment of advanced esophageal cancer. Further trials will be necessary to evaluate the advantages of this technique.

Key words: Esophageal cancer — Esophagectomy — Laparoscopy — Radiochemotherapy

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Despite aggressive surgical interventions, esophageal cancer still is associated with a poor long-term outcome. Only a 10% rate of 5-year survival is reported [26].

Conventional approaches involving thoracotomy, laparotomy, or both are associated with high morbidity and mortality rates and delay in return to normal activity [28, 36].

Advances in minimally invasive surgery with its known benefits in terms of operative morbidity, shorter hospital stay, and more rapid recovery, have led some surgeons to explore the possibility of performing total esophagectomy by the laparoscopic approach [10, 24, 39]. Their results seem to demonstrate that this technique was feasible and safe in centers with great laparoscopic experience [10, 24, 39].

On the basis of their reports, since November 1998, we have managed locally advanced (T3-T4/Nx-N1) squamous cell carcinomas of the middle lower third of the esophagus by the laparoscopic approach, after neoadjuvant chemoradiotherapy.

Materials and methods

From March 1998 to July 2002, 35 patients (20 men and 15 women; mean age, 64.6 years; range, 35–72 years) affected by a locally advanced squamous cell carcinoma (T3-T4/Nx-N1) of the middle lower third of the esophagus (6 pts T3N0, 18 T3N1, 11 T4N1) came to our observation. Complete pretreatment evaluation included barium esophagogram, esophagogastric endoscopic examination, esophageal endoscopic ultrasound, and computed tomography scan of the neck, chest, and abdomen. Bronchoscopy was performed if there was suspicion of tracheal carina infiltration. All the patients received a combined neoadjuvant chemoradiotherapy and completed the 4 weeks treatment. Chemotherapy consisted of 5-FU 1,000 mg/m^2 by 24-h infusion for 4 days and CDDP 100 mg/m^2 on day 1 in the first and the fourth weeks. Concurrent radiotherapy was delivered at a total dose of 40 Gy in daily fractions of 2 Gy five times a week. Four weeks after the end of the treatment, the patients were reevaluated by endoscopic ultrasound and computed tomography scan and underwent surgery depending on the response to the neoadjuvant therapy.

Operative technique

The patient is placed in a supine, reversed Trendelenburg position with the legs abducted and the surgeon standing between the patient's legs.

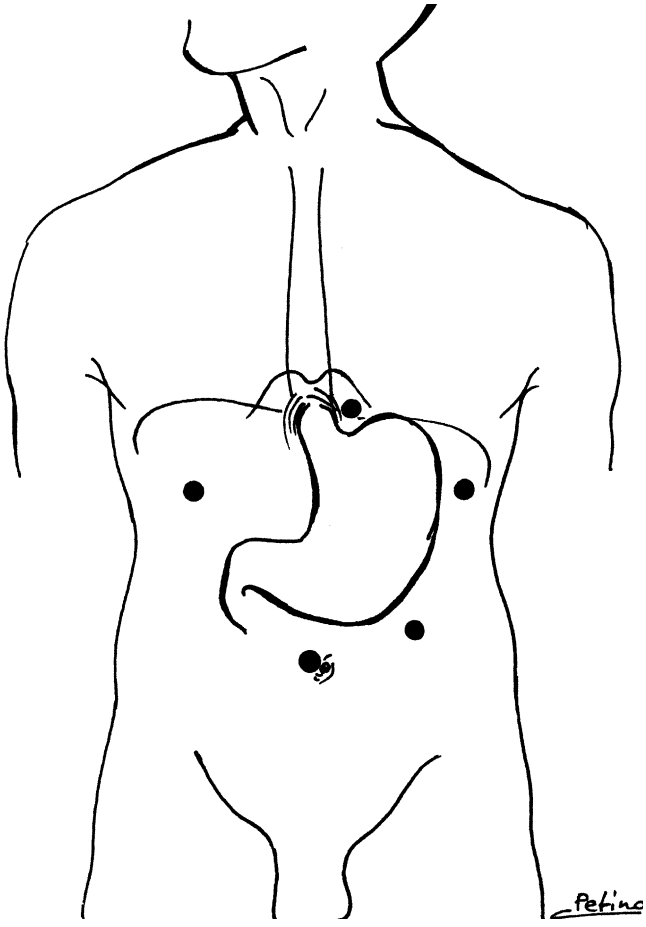

Fig. 1. Disposition of trocars.

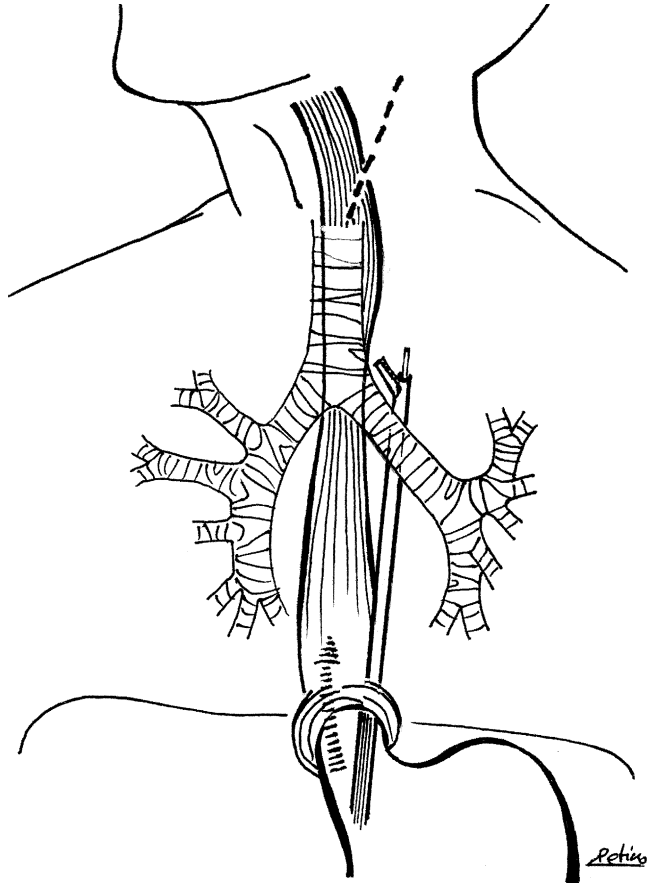

Fig. 2. Laparoscopic esophageal mobilization can reach tracheal bifurcation.

The first assistant is at the right of the surgeon, and the second is at the left with the camera on his right arm. After induction of a 12-mmHg pneumoperitoneum with a Veress needle introduced at the umbilicus, a first 10-mm trocar is inserted at the same site. The camera explores the abdominal cavity, verifying the absence of peritoneal spread or hepatic metastases. Then, under direct vision, a second 5-mm trocar is placed in the right subcostal space on the midclavear line, and a third 5-mm trocar in the epigastrium on the left of round ligament. A 10-mm trocar is inserted in the left subcostal space on the midclavear line, and the last 10-mm trocar is placed on the transverse umbilical line at the left of camera port (Fig. 1).

The stomach mobilization begins with dissection of gastrocolic omentum, preserving the right gastric epiploic vascular arcade. By ultrasonic coagulation (Ultracision, USSC, Norwalk, CT, USA), short gastric vessels are divided up to the left diaphragm. With a gentle retraction, the stomach is pulled up and the epiploic retrocavity is reached. Gastropancreatic adhesions are dissected up to the left gastric vessels and ligated by hemoclips. The gastrohepatic ligament is divided along the lesser curvature, always with preservation of the right vascular arcade. Then the mediastinal dissection is started.

The phrenoesophageal ligament is divided, and retroesophageal attachments are debrided. The abdominal esophagus is completely mobilized, and the anterior and posterior branches of the vagus nerve are sectioned. The mediastinal preparation is performed by ultrasonic scalpel under direct vision. All the mediastinal fat and lymphatic tissue are clearly dissected. The esophageal mobilization is continued up to the tracheal bifurcation (Fig. 2). The endoscope placed in the esophageal lumen is of great advantage for identifying the tumor margins and the level of superior dissection. A circular esophageal mobilization above the tumor level, as wide as possible, is achieved.

The neck dissection is performed through a left lateral incision with the head turned to the right. The cervical esophagus is identified, and then a blunt dissection is performed to mobilize the upper substernal portion, completing esophageal liberation. Under laparoscopic visualization, the stomach is transposed in the neck, with attention focussing on the vascular axis and without performing either pyloromyotomy or tubulization (Fig. 3). Then the esophagus is sectioned just below the cardia, and esophagectomy is performed.

Cervical anastomosis is realized in the following manner. In the first 11 cases of the current series, a mechanical end-to-end esophagogastric anastomosis was performed using a 25-mm EEA stapler (USSC, Norwalk, CT, USA).For the last 11 patients, we preferred to perform a side-to-side anastomosis using a 60–3.5-mm Endo-GIA II (USSC).

A linear TA stapler device is used to close the defect in the esophageal and gastric wall (Fig. 4). An endoscopic control of the anastomosis is performed. A nasogastric tube is routinely positioned in the distal stomach to prevent respiratory complications caused by gastric distension. A mediastinal suction drain is placed through the hiatus at the end of the procedure. If a pneumothorax occurs, a thoracic drain is placed under laparoscopic visualization.

During the postoperative hospital stay, total parenteral nutrition via a central venous catheter is realized. A gastrografin swallow is performed on postoperative day 7 to check cervical anastomosis and gastric emptying. The patient then is able to start a liquid diet and is discharged home 2 to 3 days later.

Results

The success of neoadjuvant treatment was evaluated by endoscopic ultrasound. The response to preoperative chemoradiation was defined as at least a 50% reduction in the maximal cross-sectional area of the tumor. Of the 35 patients observed, 22 (62.9%) showed a positive response and underwent surgery. Because 13 of patients (9

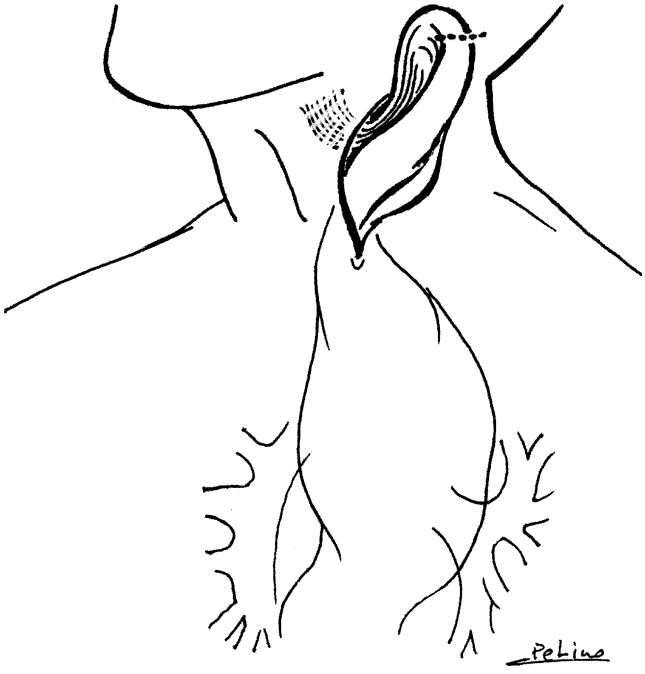

Fig. 3. Whole stomach transposition can be accomplished easily through combined cervical and laparoscopic access

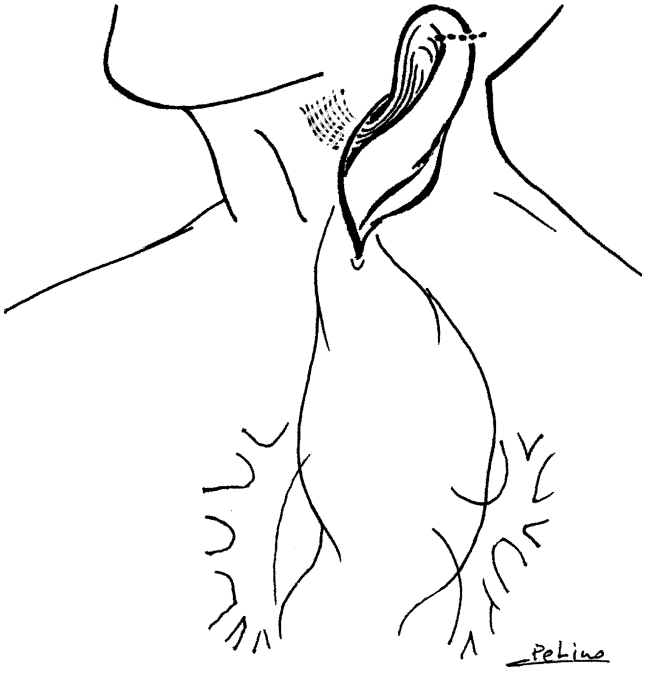

Fig. 4. Side-to-side anastomosis procedure.

T4N1 and T3N1) had no response to neoadjuvant treatment, they were submitted to palliative procedures.

All the interventions were completed using the laparoscopic approach. No intraoperative mortality was observed. Pleural perforations occurring in four patients (18.2%) were treated with a thoracic aspiration drainage at the end of the procedure. The mean duration of surgery was 160 min (range, 150–260 min), and the mean blood loss was 400 ml (range, 200–750 ml).

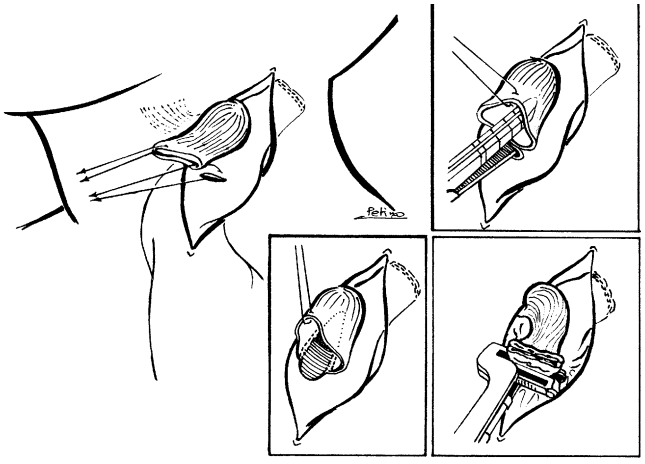

Fig. 5. Global survival curve (Kaplan–Meyer test).

Transfusions were required for only two patients. Three patients were admitted to intensive care unit for ventilatory support at the end of the surgical procedure (two patients for 24 h and one patient for 48 h).

Perioperative morbidity included one cervical anastomotic leak (4.5%) among the first patients, which was managed conservatively. No postoperative leak was evident when a side-to-side esophagogastric anastomosis was performed. Two patients (9.1%) experienced delayed gastric emptying, with spontaneous resolution after 1 to 2 weeks. One patient (4.5%) reported recurrent laryngeal nerve injury.

Three patients (13.6%) died, one suddenly of myocardial infarction on postoperative day 15, and two of acute respiratory failure (one pulmonary embolism on the postoperative day 12 and one on postoperative day 14 as well as one bacterial pneumonia on postoperative day 5. No aspiration pneumonia was observed.

The mean number of lymph nodes relieved in the specimen was 8 (range, 2–11). The final pathologic staging was as follows: four T2N0, four T2N1, three T3N0, and nine T3N1. In two cases, a complete disappearance of residual disease was observed in the specimen. The surgical margins were microscopically disease free in all cases. The mean postoperative hospital stay was 12.1 days (range, 9–23 days).

At a mean follow-up of 20.2 months (range, 10–40 months), 13 patients (68.4%) were still alive: 9 disease free and 4 with distant cancer recurrence. The remaining six patients died of metastatic cancer during the first two postoperative years.

The median disease-free survival time, according to Kaplan–Meyer testing, was 23.7 months. The global survival curve, including operative-related mortality, is shown in Fig. 5.

Discussion

Despite progress in anesthesia and postoperative care, open conventional esophagectomy using thoracotomy still is associated with high morbidity (60–84%) and

mortality (2–10%) rates [13, 25, 46], especially subsequent to pulmonary complications. Delay of diagnosis and rapid metastatic spread offer very low possibilities of determinative therapeutic interventions. The necessity of an aggressive therapy to achieve an improvement in the long-term survival rates has been supported by many authors. These authors have stressed the need for esophagectomy associated with two-field lymphadenectomy, defined as a radical resection of abdominal and thoracic lymph nodes. Furthermore, several esophageal centers, particularly in Japan, have used a more radical treatment, the threefield lymphadenectomy, including dissection of cervical nodes [2, 22, 27]. Isono et al. [22] reported a 56% 5-year survival rate for patients with a negative three-field lymph node dissection, and a 30% 5-year survival rate for patients with metastatic cervical lymph nodes. Nishihira et al. [27] observed an improvement in the long-term survival for patients who underwent an extended lymphadenectomy, as compared with conventional procedure (66.2% vs 48%), but the difference was not statistically significant ($p = 0.192$).

In clear contrast to this surgical trend, Orringer and Sloan [31] purposed a less invasive surgical procedure: the transhiatal esophagectomy without associated thoracotomy. In their opinion, a careful mediastinal and thoracic lymph node dissection can improve cancer staging but not survival. In effect, lymph nodal involvement represents a negative survival prognostic factor in all the series. The long-term survival results in the Orringer and Sloan [31] study (27% at a 5-year follow-up assessment) (30) are comparable with those reported after transthoracic esophagectomy. Other series seem to confirm these results, with no statistically significant differences in the long-term survival between transthoracic and transhiatal esophagectomy [14, 19, 32, 42]. Table 1 presents the 5-year survival rates for the surgical techniques in the various series.

Table 1. Five-year survival rates in the different series

	Stage I (%)	Stage II (%)	Stage III (%)	Stage IV (%)	Overall (%)
Ivor–Lewis					
Mathisen DJ [25]					31
Wu C [51]					48.4
Lozac'h P [23]	53.2	30.6	27.2		33.3
THE					
Gelfand GA [17]					21
Paç M [32]					13
Fok M [14]					30
Vigneswaran W [47]	47.5	37.7	5.8		20.8
Orringer M [20]	59	63 (IIA) 24 (IIB)	38	12	27
Dudhat SB [11]	100	80 (IIA) 58 (IIB)	15		37
Ikeguchi M [20]	58				
TTE					
Paricio PP [33]					20.8
Paç M [32]					10
Fok M [14]					33
Fok M [15]	66.1	28.1 (IIA) 49.6 (IIB)	13.9	6.6	
Altorki NK [1]		13	11		11.4
Nishihira T [27]					48
Woronoff AS [50]					23.5
Ando N [3]	88	44.2 (IIA) 42.8 (IIB)	17.1	13.2	37.6
Ikeguchi M [20]	62				
TTE Three-field lymphadenectomy					
Galandiuk S [16]			33.6		
Nishihira T [27]					66.2
Tachibana M [41]					45.8
Fang W [12]					55.4
Udagawa H [43]					53.8
Tabira Y [40]	55.7	49.4			43.8
Radical *en bloc* esophagectomy					
Skinner DB [38]		50 (IIA) 50 (IIB)			
Altorki NK [1]	75	32.9	34.5		41.5

THE, transhiatal esophagectomy; TTE, transthoracic esophagectomy

The development of mini-invasive surgery at the beginning of the 1990s gained a consensus for a mini-invasive approach to esophagectomy. Two different techniques have been used more frequently: thoracoscopic esophageal mobilization [7, 9, 37] and the laparoscopic approach [10, 24, 39]. No clear advantages have been demonstrated in terms of postoperative morbidity and mortality for the thoracoscopic approach, as compared with thoracotomy [18, 34], and in some cases, the mortality has been relevant [37]. In particular, pulmonary complications have not been significantly different. In effect, the anesthesiologic techniques, single-lung ventilation, and lateral decubitus are the same among the thoracotomic and thoracoscopic groups, and potential beneficial effects of smaller thoracic incisions are difficult to demonstrate.

In contrast, laparoscopic esophagectomy series reported in literature [10, 24, 39] have demonstrated that minimally invasive esophagectomy is technically feasible and safe in centers with advanced mini-invasive experience, resulting in low postoperative morbidity and mortality rates. The series concerned either benign (advanced achalasia, esophageal reflux stricture) or malignant conditions (adenocarcinoma and squamous cell carcinoma) and showed no difference in terms of postoperative outcome between the two groups.

The oncologic role of laparoscopy still raises major concerns, especially with regard to the possible influence on the development of port-site metastases. In the absence of conclusions for the argument, we preferred to include in our series only patients affected by a locally advanced esophageal squamous cell carcinoma (T3-T4 Nx-N1) with a poor long-term prognosis.

All the patients in our series received preoperative chemoradiotherapy (CT-RT). The addition of preoperative to radiation therapy may downstage disease and facilitate surgical resection, improving local control and reducing the rate of micrometastatic disease [48]. This approach has been shown to result in a pathologic complete response rate of 20% to 30%, a median survival of 16 to 24 months, and a therapy-related mortality of 10% to 12% [35].

Some randomized trials have compared preoperative chemoradiotherapy with surgery alone. Walsh et al. reported [49] a significantly better long-term survival for patients treated with multimodal therapy

(52%, 37%, and 32% alive at 1, 2, and 3, years vs 44%, 26%, and 6% in the surgical group). Bosset et al. [5] observed that neoadjuvant treatment did not improve overall survival, but did prolong disease-free survival. Instead, Urba et al. [45] did not demonstrate a statistically significant survival difference for preoperative chemoradiotherapy. Nevertheless, in a recent phase 2 trial (44) with the administration of a preoperative regimen of cisplatin, paclixatel, and radiotherapy, the same authors observed a complete histologic response in the resected specimen from 19% of patients, who demonstrated 1-, 2-, and 3-year survival probabilities of 75%, 50%, and 34%, respectively. In our series, endoscopic ultrasound showed a positive response to chemoradiotherapy in 22 of 35 patients (62.9%), with more than a 50% reduction on the maximal cross-sectional area of the tumor. We preferred this type of evaluation because endoscopic ultrasound has a low sensitivity for assessing TNM staging after neoadjuvant therapy [6, 21]. Nevertheless, we also achieved an effective histologic cancer downstaging in 15 of 22 patients (68.2%).

Our 2-year survival rates (68.4%) are comparable with those reported in other series, both laparoscopic and open. Furthermore, no port-site metastases were observed, and the reported recurrence rates are compatible with the advanced disease of these patients and not dependent, in our opinion, on the surgical approach. The operative time was not influenced by the laparoscopic approach, and we believe the duration of the surgical procedure was acceptable.

Blood loss was minimal, and only two patients were transfused. The direct visualization of the mediastinal space and the use of ultrasonic coagulating shears also allowed coagulation of minimal blood vessels to the superior margin of the tumor. Blunt dissection was limited to the mediastinal space immediately below the cervical incision, and was performed in a space free of tumoral infiltration.

Most authors strongly support the need for a piloromyotomy or a gastric tubularization, believing that they can improve the rate of gastric emptying /4, 13]. In our opinion this is not mandatory, and we agree with other authors [8] who relieved a normal motility of the transposed stomach. It is more physiologic for the preservation of gastric integrity, avoiding the section of blood vessels along the lesser curvature. Furthermore, piloromyotomy can increase bile reflux without improving the rate of gastric emptying. In our series, only two patients (9.1%) experienced delayed gastric emptying, with spontaneous resolution after 1 to 2 weeks, and no patient presented with digestive troubles at the long-term follow-up visit.

Changing the performance of esophagogastric anastomosis in the manner described by Orringer et al. [29] greatly contributed to a decreased incidence of anastomotic leak in our series. Whereas one patient among the first 11 (9.1%) experienced a cervical anastomotic leak, this complication was not observed among the last 11 patients. Our data seem to confirm the results described by Orringer et al. [29], who reported a 2.7% rate of anastomotic leak in his last 111 patients, as compared with a 10% to 15% rate for the manually sewn anastomosis in 1,000 patients.

Despite the encouraging data regarding long-term survival and functional results, our postoperative mortality rate (13.6%) is disappointing. This rate is largely attributable to respiratory troubles that arose in the first 2 postoperative weeks. The advanced disease stage can partially explain these events, but they probably are primarily the result of our learning curve. All 3 patients who died were among the first 10 patients, whereas no death was observed in the last 12 patients who underwent surgery.

Also, the hospital stay did not differ significantly from that experienced with the open approach (12.1 days). Respiratory troubles greatly prolonged the median length of the hospital stay. We hope that with more experience our results will ameliorate. However, most patients avoided time on a ventilator and a stay in the intensive care unit, and their recovery was very short. They resumed quotidian activities in 2 to 3 weeks.

Conclusions

Our early experience with laparoscopic esophagectomy demonstrates the feasibility of this approach in the palliative treatment of locally advanced esophageal cancer. Our mortality rate is dependent, on our opinion, on the advanced disease and the learning curve for this challenging procedure.

Oncologic safety of laparoscopy is far from being demonstrated, but laparoscopy could represent a viable alternative in the treatment of these patients with a poor prognosis. It has a clear advantage in terms of postoperative assistance and recovery. However, more extensive trials are necessary to confirm any advantages over the traditional approach, and to obtain standardization of the technique.

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