

# IMPACT OF MINIMALLY INVASIVE SURGERY IN THE TREATMENT OF ESOPHAGEAL CANCER

*Impacto da cirurgia minimamente invasiva no tratamento de câncer de esôfago*

Italo BRAGHETTO M; Gonzalo CARDEMIL H; Carlos MANDIOLA B; Gonzalo MASIA L; Francesca GATTINI S.

From the Department of Surgery, Faculty of Medicine, "Dr. José Joaquín Aguirre" Universidad de Chile Clinical Hospital, Universidad de Chile, Santiago, Chile

**ABSTRACT - Background:** Surgical treatment of esophageal cancer is associated to a high morbidity and mortality rate. The open transthoracic or transhiatal esophagectomy are considerably invasive procedures and have been associated to high rates of complications and operative mortality. In this way, minimally invasive esophageal surgery has been suggested as an alternative to the classic procedures because would produce improvement in clinical longterm postoperative outcomes. **Aim:** To assess survival, mortality and morbidity results of esophagectomy due to esophageal cancer submitted to minimally invasive techniques and compare them to results published in international literature. **Method:** An observational, prospective study. Between 2003 and 2012, 69 patients were submitted to a minimally invasive esophagectomy due to cancer. It was recorded postoperative morbidity and mortality according to the Clavien-Dindo classification. The survival rate was analyzed with the Kaplan-Meier method. The number of lymph nodes obtained during the lymph node dissection, as an index of the quality of the surgical technique, was analysed. **Results:** 63.7% of patients had minor complications (type I-II Clavien Dindo), while nine (13%) required surgical re-exploration. The most common postoperative complication corresponded to leak of the cervical anastomosis seen in 44 (63.7%) patients but without clinical repercussion, only two of them required reoperation. The mortality rate was 4.34%, and reoperation was necessary in nine (13%) cases. The average survival time was 22.59±25.38 months, with the probability of a 3-year survival rate estimated at 30%. The number of resected lymph nodes was 17.17±9.62. **Conclusion:** Minimally invasive techniques have lower morbidity and mortality rate, very satisfactory lymphnodes resection and similar long term outcomes in term of quality of life and survival compared to results observed after open surgery.

**DESCRITORES** - Neoplasia esofágica. Câncer. Esofagectomia. Videotoroscopia.

## Correspondence:

Italo Braghetto  
 E-mail: ibraghet@hcuch.cl

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**RESUMO - Racional:** O tratamento cirúrgico do câncer de esôfago está associado com alta morbidade e mortalidade. Os acessos transtorácicos abertos ou os transmediastinais são considerados procedimentos invasivos e têm sido associados a altas taxas de complicações e de mortalidade operatória. Desta forma, a operação do esôfago minimamente invasiva tem sido sugerida como alternativa aos procedimentos clássicos, porque iria produzir melhora no desempenho pós-operatório a longo prazo. **Objetivo:** Avaliar a sobrevida, mortalidade e morbidade da esofagectomia por câncer de esôfago submetidos às técnicas minimamente invasivas e compará-los com os resultados publicados na literatura internacional. **Método:** Estudo observacional, prospectivo. Entre 2003 e 2012, 69 pacientes foram submetidos à esofagectomia minimamente invasiva devido ao câncer. Foram analisadas morbidade e mortalidade pós-operatória de acordo com a classificação Clavien-Dindo. A taxa de sobrevivência foi analisada pelo método de Kaplan-Meier. O número de nódulos linfáticos obtidos durante a dissecação do nódulo linfático foi analisado como um índice da qualidade da técnica cirúrgica. **Resultados:** 63,7% dos pacientes tiveram complicações menores (tipo I-II Clavien Dindo), enquanto nove (13%) necessitaram de re-exploração cirúrgica. A complicação pós-operatória mais comum correspondeu a deiscência da anastomose cervical observada em 44 (63,7%) pacientes, mas sem suas repercussões clínicas, apenas dois deles necessitaram de reoperação. A taxa de mortalidade foi de 4,34%, e reoperação foi necessária em nove (13%) casos. O tempo médio de sobrevivência foi de 22,59±25,38 meses, com a probabilidade de uma taxa de sobrevida em três anos estimada em 30%. O número de linfonodos ressecados foi 17,17±9,62. **Conclusão:** As técnicas minimamente invasivas têm menor morbidade e mortalidade, satisfatório número de linfonodos ressecados e resultados a longo prazo semelhantes após operação aberta, em termos de qualidade de vida e sobrevida.

**HEADINGS** - Esophageal neoplasm. Cancer. Esophagectomy. Videotoroscopy.

## INTRODUCTION

Surgical treatment of esophageal cancer is associated to a high morbidity and mortality rate, even in specialized centers. An open transthoracic or transhiatal esophagectomy are the most common procedures performed in order to treat this disease<sup>1-3</sup>. Both procedures are considerably invasive and have been associated to high rates of complications and operative mortality<sup>1,3-5</sup>. Notwithstanding, although an open transhiatal esophagectomy with gastric mobilization and cervical anastomosis theoretically presents less surgical trauma, it has significant limitations with regards to the feasibility of resecting the middle third of the esophagus along

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with an inadequate dissection of lymph nodes on this level, in addition to an increased risk of lesions in the adjacent structures which can reach up to 50% in some cases, and a mortality rate of 8 to 23%<sup>6-8</sup>.

In this way, minimally invasive esophageal surgery has been suggested as an alternative to the classic procedures that are generally performed since it represents less surgical trauma, a lower risk of bleeding, and a lymphadenectomy performed more carefully, thus potentially implying an improvement in clinical outcomes and postoperative remote patient outcomes. In recent years, a progressive increase has been observed in the number of centers that use this procedure as their surgical approach of choice<sup>9,10</sup>. However, their results have not been well established with regards to the long term prognosis from an oncological point of view.

The objective of this study is to assess survival, mortality and morbidity results of an esophagectomy due to cancer during its different clinical stages through minimally invasive techniques, and compare them to results published in international literature.

## METHOD

An observational, prospective study in which the clinical results of 69 patients submitted to a minimally invasive esophagectomy due to cancer was recorded, between 2003 and 2012, at the Department of Surgery at the University of Chile Hospital.

All patients were subjected to a preoperative study protocol which included an upper GI endoscopy with biopsy, a barium x-ray study, CT scans of the chest, abdomen and pelvis, cardiopulmonary function tests, nutritional assessment and clinical staging of the esophageal cancer according to TNM classification.

Was employed a transthoracic esophagectomy, and the transit reconstruction techniques used consider gastric tubulization and mobilization by laparoscopic approach in the majority of patients or the ascendant colon interposition using open procedure in those patients when it was not possible to used stomach.

Perioperative morbidity was defined as the complications that arose up until the 30<sup>th</sup> postoperative day and were analyzed according to the Clavien-Dindo classification<sup>11</sup>. Late complications were defined as those which are unrelated at the time of the surgical procedure and that presented themselves as of the 31<sup>st</sup> postoperative day. In the same way, operative mortality was defined as an event occurring up to the 30<sup>th</sup> postoperative day. The survival rate was analyzed with the Kaplan-Meier calculator, determined in a general manner and by clinical-pathological stage based on the 2010 guide updated and reviewed by the American Joint Committee on Cancer<sup>12</sup>. Furthermore, an analysis was performed of the number of lymph nodes obtained during the lymph node dissection, as an index of the quality of the surgical technique.

The statistical analysis and record of the data was carried out using Excel Microsoft Office 2010 program, obtaining the Kaplan Meier curves with the MedCalc 12.3.0.0 program. The comparison between the survival curves was performed using the Log-Rank method, establishing statistical significance as  $p < 0.05$ .

## RESULTS

A total of 69 patients were subjected to a minimally invasive esophagectomy during a 10 year period. The mean age of the patients was  $63 \pm 10$  years (range 41–80 years)

(Table 1), with 26 (37.68%) women and 43 (62.31%) men. Of the 69 patients, two (2.89%) were in stage 0, seven (10.14%) were included in stage I (Ia=3, Ib=4), 23 (33.33%) in stage II (IIa=6, IIb=17), 34 (49.27%) in stage III (IIIa=17, IIIb=7, IIIc=10) and one (1.44%) patient in stage IV. With regards to the adjuvant oncology therapy, only two patients (2.89%) received neoadjuvant treatment. A stage II patient was treated with preoperative chemotherapy and radiotherapy, and a stage III patient just with chemotherapy prior to surgery. Adjuvant chemoradiotherapy after surgery was indicated in stages II and III depending on the clinical and pathological characteristics in seven patients (10.14%), of which five received adjuvant chemoradiotherapy and two postoperative chemotherapy (Table 1).

**TABLE 1** - Demographic characteristics of patients subjected to a minimally invasive esophagectomy due to esophageal cancer

	n patients (%)
Patients participating in the study	69 (100%)
Mean age (years)	63 ± 10 (range 41 – 80)
Sex	
Male	43 (62.31%)
Female	26 (37.68%)
Clinical stage	
0	2 (2.89%)
IA	3 (4.34%)
IB	4 (5.79%)
IIA	6 (8.69%)
IIB	17 (24.63%)
IIIA	17 (24.63%)
IIIB	7 (10.14%)
IIIC	10 (14.49%)
IV	1 (1.44%)
Neoadjuvant treatment (Qt and/or Rt)	2 (2.89%)
Postoperative adjuvant treatment (Qt and/or Rt)	7 (10.14%)

From a surgical point of view, the conversion rate to open surgery was one case (1.44%). This case corresponded to a secondary hemorrhage due to pulmonary vein and azygos vein. Regarding the transit reconstruction technique, the procedure of choice performed during the same surgical moment, after the esophagectomy, was the tubularized gastric pull-up with cervical esophago-gastric anastomosis, which was performed in 64 patients (92.75%), while the ascendant colon interposition was carried out in five cases (7.24%). Based on the pathology report, the majority of the surgical resections resulted to be R0 in a total of 52 patients, corresponding to 75.36% of all cases, while it was R1 in six (8.69%) and R2 in one patient (1.44%). In 10 (14.49%), it was not possible to determine the presence of any residual tumor. Of all the patients subjected to surgery, the pathological study demonstrated the presence of squamous carcinoma in 32 (46.37%) cases, demonstrating the presence of adenocarcinoma in 37 patients (53.62%). An average of  $17.17 \pm 9.62$  lymph nodes (range 2–46) were resected per patient (Table 2).

In an attempt to evaluate the morbidity in a standardized manner, an analysis was conducted of postoperative complications using the Clavien-Dindo classification, which stratifies the seriousness of the complication based on the required treatment. In this way, it was seen that in 11 patients (15.94%), the postoperative evolution was favorable and/or required basic pharmacological management, while 33 patients (47.82%) presented a spectrum of complications which required management through medication without the need for invasive procedures that can significantly affect their postoperative evolution (Table 3).

**TABLE 2** - Minimally invasive esophagectomy techniques used in the surgical treatment and anatomopathological results

	n patients, (%)
Esophagectomy technique	
Thoracoscopic	39 (56.52%)
Transhiatal	30 (43.47%)
Reconstitution of transit	
Tubularized gastric mobilization	64 (92.75%)
Ascendant colon interposition	5 (7.24%)
Conversion for open surgery	1 (1.44%)
Resection	
R0	52 (75.36%)
R1	6 (8.69%)
R2	1 (1.44%)
Rx	10 (14.49%)
Histological type	
Adenocarcinoma	37 (53.62%)
Squamous carcinoma	32 (46.37%)
Number of resected lymph nodes	17.17±9.62 (2 – 46)
Stage	
0	11.00 ± 7.07
IA	7.33 ± 5.03
IB	19.50 ± 4.16
IIA	6.66 ± 5.17
IIB	17.29 ± 10.36
IIIA	20.00 ± 11.27
IIIB	18.85 ± 5.26
IIIC	22.30 ± 7.28
IV	13.00

**TABLE 3** - Perioperative complications according to Clavien–Dindo standarized classification (the most serious complication for each patient is described)

Stage	n (%)
I	11 (15.94%)
II	33 (47.82%)
IIIA	4 (5.79%)
IIIB	6 (8.69%)
IVA	4 (5.79%)
IVB	8 (14.49%)
V	3 (4.34%)

Type I: Seroma, nausea and/or vomiting; Type II: Low flow leak, stenosis, pneumonia, atelectasis, pleural effusion, collections, vocal fold paralysis, deep vein thrombosis, atrial fibrillation, urinary infection, paralytic ileus, delirium, high blood pressure crisis, acute kidney failure; Type IIIA: Severe stenosis, gastric dilation, hydropneumothorax; Type IIIB: High flow leak, pleural empyema, paraesophageal abscess, evisceration, airway injury, azygos vein injury, chylothorax; Type IV: Septic shock, respiratory and/or urinary foci, multiple organ dysfunction syndrome, septic embolism, mediastinitis; Type V: Death

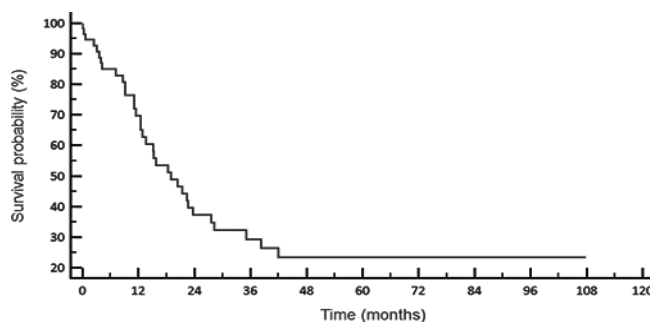
Notwithstanding, a group of patients required surgical, endoscopic and/or radiological procedures, with a total of nine patients of our series subjected to surgery for a second time. The most common cause of re-intervention corresponded to postoperative pleural empyema and/or complex pleural effusion (n=5 patients), a patient with a lesion in the left main bronchus and of thoracic duct with secondary chylothorax, hemothorax in a patient with innominate vein injury, an contained evisceration and a paraesophageal abscess. The most common postoperative complication corresponded to leak of the cervical anastomosis seen in 44 (63.7%) patients. However, only two of them corresponded to significant leaks which required surgical intervention once again. The rest of the patients presenting leaks (n=42), represented radiological findings of a leak of lesser importance without being clinically significant which was managed in a conservative manner. With regards to late complications, stenosis of the cervical anastomosis was one of the most common, with an incidence of 16 (23.18%) patients. Hospital stay of the analyzed patients was 26.78±19 days (Table 4).

**TABLE 4** - Postoperative specific complications.

	n patients, (%)
Medical complications	
Respiratory	16 (23.2%)
Cardiovascular	10 (14.5%)
Tromboembolism	6 (8.6%)
Surgical complications	
Anastomotic leakage	44 (63.7%)
High flow	2 (2.8%)
Low flow	42 (60.8%)
Hemorrhage	2 (2.8%)
Mediastinitis	2 (2.8%)
Reoperations	9 (13%)
Mortality	2 (2.8%)
Late complications	
Stenosis	16 (23.2%)

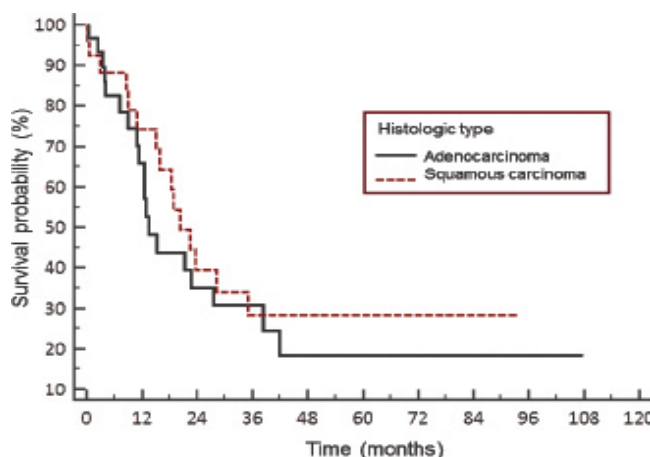
Perioperative mortality (Clavien Dindo Type V complication) occurred in two cases (2.8%) (Table 4). Among the causes of death within the context of surgical intervention, a patient died for acute mediastinitis secondary to perforation of the interposed colon and a second died for medical complications and injury to the left main bronchus during reoperation for chylothorax.

The global survival rate during the follow up period conducted on our series of patients subjected to an esophagectomy due to cancer using minimally invasive techniques is 22.59±25.38 months, with the probability of a three year survival rate estimated for approximately 30% (Figure 1).



**FIGURE 1** - General survival rate of minimally invasive esophagectomy due to esophageal cancer (n=69)

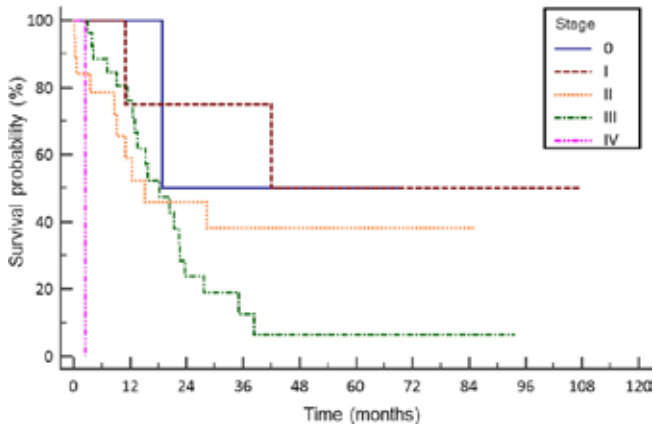
When analyzing the survival rate of patients based on histological type of cancer, it was observed that there are no significant differences between patients with adenocarcinoma and squamous carcinoma, with the postoperative follow up during the first years being very similar p=0,45; hazard ratio=0.7740; CI 95% (0.3952-1.5161) (Figure 2).



**FIGURE 2** - Survival rate of patients subjected to a minimally

invasive esophagectomy based on the histological type of cancer ( $p=0.45$ ; hazard ratio=0.7740; CI 95% (0.3952-1.5161)

Notwithstanding, such differences in survival rates can be appreciated with regards to clinical stages in which patients underwent surgery ( $p=0.0052$ ), with the probability of survival being greater in earlier stages (Figure 3). These survival rate curves are very similar to those obtained by our group during the open surgery era<sup>6</sup>.



**FIGURE 3** - Survival rate of patients subjected to a minimally invasive esophagectomy based on the clinical stage (n=69),  $p=0.0052$

## DISCUSSION

Recent literature has confirmed the high rate of complications and postoperative mortality depending of the annual volume of hospital operations<sup>7,8</sup>.

During the last two decades, minimally invasive approaches have become increasingly popular for performing several surgical procedures which treat benign as well as malignant diseases<sup>9,10</sup>.

The minimally invasive surgical techniques described for treatment of esophageal cancer corresponds to a video-assisted esophagectomy in addition to open or laparoscopic gastric tubulization which allows to obtain improved vision of the operating field in the mediastinum, avoiding blind dissection and reducing the risk of postoperative and intraoperative complications. In this way, allowing better visibility in the dissection of paraesophageal lymph nodes and improved postoperative staging. On the other hand, a transhiatal or transthoracic esophagectomy in addition to laparoscopic gastric tubulization has reported results comparable to the technique with the best postoperative evolution and lower rate of complications without increasing the immediate mortality and improving five year survival rate<sup>7,13-24</sup>.

When analyzing the results observed after introducing minimally invasive surgery for esophageal cancer, certain questions immediately arise: does it have an impact on complications and postoperative mortality? What is the proportion of R0 resections? Is the lymph node harvest the same? Does it have repercussions on the survival rate? These are some of the questions that shall be analyzed in this discussion in light of the results obtained by our group and the results published to date in the international literature. In recent years, many authors around the world have written reports analyzing these questions<sup>7-10,24-28</sup>.

When analyzing the results, our data shows a mortality rate inferior to the transhiatal as well as transthoracic open esophagectomy rate in comparison to the Hulscher et al meta-analysis (4.34% vs 5.7% y 9.2% respectively); and when compared to our historic results observed during the

transhiatal and transthoracic open surgery and in accordance with what has been demonstrated in other studies with a greater amount of patients such as Luketich et al's study with 222 patients, which demonstrated a mortality rate of 13%, far below the mortality rate for open esophagectomy<sup>3,24</sup>. Likewise, it is noteworthy to mention that the introduction of minimally invasive surgical techniques have allowed to significantly decrease the perioperative mortality of our own historic series of patients subjected to an open approach which corresponded to an 11.8% and 8.6% for the transthoracic approach and open transhiatal respectively. Furthermore, since its implementation in our first series of patients treated with minimally invasive surgery in an esophagectomy during the 1993-2003, we have managed to decrease the mortality rate from 6.4% in the previous experience<sup>6</sup> to a 2.8% in our current series. With regards to postoperative complications in our most recent series, the most important early complication continues to be dehiscence of the cervical anastomosis. Three percent of patients required surgical reintervention due to high flow leaks, a result that is comparable to other studies and meta-analysis that fluctuates between 4-11.7%, with an average of 7.7%<sup>24-34</sup>. On the other hand, the most common later complication was stenosis of the cervical anastomosis in 23.18% of patients, results comparable to those shown by Henriques et al.<sup>35</sup> in patients subjected to an esophagectomy due to cancer and advanced megaesophagus, with 24% incidence in 36 months of follow up. In our series, the conversion rate to open surgery was 1.44%, corresponding to a patient with vascular lesions of azygos and pulmonary veins, a rate that is comparatively less than other series such as the study by Luketich with a 7.2% of conversions<sup>22-24</sup>. When reviewing the literature, it can be seen that the complications observed by our group are quite similar to those published by different authors in Europe, the US and Asian countries<sup>7,26,27,35-38</sup>.

Warner<sup>27</sup>, in a recent study, reported 40% of minor complications and 30% of more serious complications, with 7% reoperations, 1.6% hemorrhage, leaks in 14%, respiratory complications in 3%, and stenosis in up to 20%. We have observed a higher percentage of leaks in comparison to other series, and we believe that this is due to the fact that in more than 90% of cases we performed cervical anastomosis which presents a higher percentage of leaks in comparison to intrathoracic anastomosis (pleural), but the current mortality rate is just as low as those reported by different groups which ranges between 2-5%<sup>37,38,39</sup>. In a systematic review which included more than 1,100 patients in which the open approach was compared with the minimally invasive technique, it was confirmed that in the latter, a lower morbimortality and a shorter hospital stay was associated even in patients who were previously subjected to chemoradiation for advanced tumors, without an increase in operative morbimortality, and the survival rate does not seem to have been compromised due to the minimally invasive approach<sup>26</sup>.

One might conceivably think that the minimally invasive approach techniques could eventually have deleterious results with regards to the survival rate of patients. Ever since the advent of minimally invasive surgery, the proper oncological resection in comparison to open surgery has been questioned with regards to the margins of resection, the complete lymphadenectomy, the correct postoperative staging and long term survival rate. However, the results obtained with regards to the percentage of patients with R0 section and the harvest of lymph nodes have demonstrated to be equal to or even better than surgery performed using the classic approach which obviously has a direct incidence on the survival rate of patients<sup>22-28</sup>. There have been excellent papers recently reporting on the results of the survival rate and the tendency to accept that minimally invasive surgery without compromising the oncological results<sup>39,40-43</sup>. All potentially curative oncological resections require a complete margin of



R0 primary tumor resection, with this being the greatest factor of importance in the survival rate of patients. Although it is true that a minimally invasive esophagectomy was initially reserved for early stages, its indication has currently been broadened for more advanced stages based on recent studies. Our group achieved an R0 resection level in 75.36% of all patients, and in 14.49%, it was possible to detect the presence of residual tumor, probably within the neoadjuvant treatment context. Near 10% of patients had positive margins, with these results being comparable to those obtained by Smithers et al. with an 18.9% of positive margins using the open approach technique<sup>29</sup>. In the same way, Thomson et al. was able to demonstrate that there was no significant difference in the levels of tumor recurrence based on the level of resection for both surgical approaches, open or minimally invasive, results comparable to those in our series<sup>30</sup>. On the other hand, the extent of the lymphadenectomy required for patients with esophageal cancer is still under analysis. It has been confirmed that a minimally invasive lymphadenectomy obtains results which are similar and comparable to those obtained through the open approach, with an average of  $17.17 \pm 9.62$  lymph nodes (range 2-46) compared to the open approach in different series, with an average of 16-18 lymph nodes (range 1-44), and literature by Smithers and others have validated the equivalence between both approaches with regards to lymph node resection<sup>28-30</sup>. In the study conducted by Luketich et al.<sup>24</sup>, the average number of lymph nodes removed was 21, which is comparable with the open series: similarly, the R0 resection rate with negative margins is comparable to the series of esophagectomies performed with the open approach<sup>3,8,24,38,39</sup>.

In this way, the results obtained in our series of patients subjected to an esophagectomy through minimally invasive techniques are similar to the literature showing a lower morbidity and mortality rate in comparison to an open approach, without representing an impairment of the quality of the tumor resection and in the lymphadenectomy. The results showed a survival rate similar to the open surgical technique for different clinical stages, and it can be performed in a safe manner, even in advanced stages. Therefore, it is oncologically equivalent to resections using the open approach, offering excellent quality of life while being cost effective.

Finally, it is noteworthy to mention that in order to maximise the benefits provided by minimally invasive surgical techniques in the neoplastic disease of the esophagus, it is necessary to properly select patients, being the most widely accepted indication an early stage cancers, even though it has also been indicated for more advanced stage cancers in recent years. However, in our practically unanimous opinion, studies are pending with regards to long term results with new modalities of combined oncology therapy in order to obtain definite results<sup>44,45</sup>.

## CONCLUSION

Minimally invasive techniques have lower morbidity and mortality rate, very satisfactory lymphnodes resection and similar long term outcomes in term of quality of life and survival compared to results observed after open surgery.

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