

Salvage esophagectomy after exclusive chemoradiotherapy: results at the Brazilian National Cancer Institute (INCA)

C. E. Pinto, D. de Souza Fernandes, E. A. Moura Sá, E. L. R. Mello

Department of Abdominopelvic Surgical Oncology, INCA, Rio de Janeiro, RJ, Brazil

SUMMARY. Surgical resection is considered the gold standard treatment for esophageal cancer, with global cure rates ranging from 15 to 40%. Exclusive chemoradiotherapy has been used for patients with locally advanced esophageal carcinoma or without clinical conditions for esophagectomy, reaching a 5-year survival rate of up to 30%. However, locoregional control is poor, with local recurrence of 40–60%, being reported in the literature. Maybe, these patients can benefit from salvage surgery. In this study, 15 patients with esophageal cancer submitted to salvage esophagectomy after exclusive chemoradiotherapy treatment were retrospectively analyzed. Salvage esophagectomy was demonstrated to be technically feasible. However, it presents with high surgical morbidity. Currently, salvage esophagectomy is considered the best available treatment to attempt cure in cases of tumor recurrence or persistence after exclusive chemoradiotherapy. All the other types of treatments are regarded as palliative with discouraging survival results.

KEY WORDS: esophagectomy, exclusive chemoradiotherapy, salvage esophagectomy, salvage surgery.

INTRODUCTION

Esophageal cancer represents 1–2% of all malignant tumors and is the seventh leading cause of cancer death in the USA. In Brazil, it is the ninth neoplasia in incidence, and the sixth leading cause of cancer death.^{1–3} Diagnosis is usually made in advanced stages, which hinders adequate treatment, thus, leading to unfavorable prognosis.⁴ Surgical resection has become the gold standard treatment for esophageal cancer, with cure rates ranging from 15 to 40% (less than 5% for the advanced stages),^{4–6} For decades, surgical mortality has been around 10%, being today less than 5% in reference centers.^{7,8} Because of low effectiveness achieved, in terms of cure, by using only esophagectomy, new therapeutic modalities have been searched, mainly the ones in combination with the surgical resection. Radiotherapy, chemotherapy, or chemoradiotherapy (adjuvant and/or neoadjuvant), or yet the exclusive radical chemoradiotherapy are part of the currently available armory.⁹

Exclusive chemoradiotherapy (maximum dose of chemoradiation) has been indicated for patients with locally advanced esophageal carcinomas (T3 or T4) or without physiological reserve for the esophagectomy, having the 5-year overall survival rate ranging from 10 to 30%. However, locoregional control is poor, with local recurrence of 40–60%, as mentioned in the literature. Salvage esophagectomy is the only possible cure for selected patients with tumoral recurrence or persistence of disease after exclusive chemoradiotherapy, with a 5-year overall survival rate of 25%.¹⁰

From a theoretical point of view, salvage surgery is accomplished with high degree of technical difficulty and surgical morbimortality because of the high dose of radiation applied in the tumoral field and also because of the long interval between the ending of chemoradiotherapy and the surgery (which determines a high degree of fibrosis in periesophageal structures). Such fact, associated with the skepticism in relation to the cure of esophageal cancer, accounts for the reluctance of many surgeons in performing such operation (salvage esophagectomy).

The main objective of the present study is to report the experience and the results of the study of the Brazilian National Cancer Institute (INCA) on

Address correspondence to: Dr Daniel de Souza Fernandes, PhD, FACS, Rua Caçapava, N 99 Building 8, Apartment 504, Rio de Janeiro 20541-350, Brazil. Email: danielsfernandes@gmail.com

salvage esophagectomy (esophagectomy after exclusive chemoradiotherapy). This surgical procedure has represented the latest therapeutic modality over the past few decades.

PATIENTS AND METHODS

We perform a retrospective analysis of 15 patients admitted to INCA with esophageal cancer submitted to salvage esophagectomy after exclusive chemoradiotherapy treatment, between March of 1999 and December of 2006. The study bases were the handbooks and the total quality program of INCA Abdominopelvic Surgery Department.

Eight patients were men and seven were women, with median age of 62 years (39–72 years). In relation to tumor topography in the esophagus, the lower third was involved in seven patients, middle third in other seven patients, and superior third in one patient. The predominant histological type was epidermoid carcinoma in 12 patients, with adenocarcinoma being observed in three patients (Table 1). The indication for primary treatment with exclusive chemoradiotherapy was esophageal cancer stage T3 or T4 in accordance with 6^a edition of TNM Classification of Malignant Tumors (TNM) classification International Union Against Cancer (UICC) or patients without clinical conditions for esophagectomy.

The standard radical combined treatment used in INCA corresponds to Radiation Therapy Oncology Group (RTOG) 85-01 protocol, namely: Chemotherapy with cisplatin (or CDDP), 75 mg/m² (first day of weeks 1, 5, 8, and 11), and 5-fluoracil, 1000 mg/m² (continuous infusion in the four first days of each cycle of cisplatin) and radiotherapy (30 Gy – 15 fractions in 3 weeks with reinforcement of 20 Gy – 10 fractions in 2 weeks). Two patients

received reinforcement in tumoral field with complementary brachytherapy (15 Gy).

All patients underwent surveillance endoscopy every 3 months or when any symptom was reported, after primary treatment with exclusive chemoradiotherapy. Tumor persistence was considered in patients who presented positive endoscopy biopsy for malignancy, with a period of time equal or less than 3 months after the end of exclusive chemoradiotherapy treatment, while recurrence was considered in patients with positive biopsy 3 months after the end of exclusive chemoradiotherapy treatment.

The diagnosis was confirmed with endoscopic biopsy, and preoperative evaluation was carried out with thoracic, abdominal, and pelvic computed tomography scan, evaluation of pulmonary (arterial gasometry and respiratory function test) and cardiac functions (electrocardiogram and echocardiogram). Only after this were patients considered for salvage esophagectomy.

The following variables were analyzed: demographic data, histological type of primary tumor, localization of primary tumor, illness-free interval, surgical access, number of resected lymph nodes, surgical time, hospital time, TNM stage before and after surgery, surgical morbidity, overall survival, and surgical mortality. Surgical morbidity was defined as any clinical or surgical complication related to esophagectomy, and surgical mortality was considered when death occurred within 30 days after the surgical procedure.

RESULTS

The relapse time interval after exclusive chemoradiotherapy varied from 2 to 35 months, with an average of 9.73 months. Esophagectomy with thoracotomy

Table 1 Patient characteristics

Patients	Age	Sex	Histological type	Tumor localization	PS	TNM/Clinical†	Stage	ECRSI (month)	TNM/Pathological	Stage
1	61	M	Adenocarcinoma	Inferior	2	T4 N0 M0	III	2	pT4 pN1 pM0	III
2	39	F	Epidermoid	Inferior	1	T4 N0 M0	III	2	pT3 pN1 pM0	III
3	43	M	Adenocarcinoma	Inferior	1	T4 N1 M0	III	2	pT4 pN2 pM0	III
4	58	F	Epidermoid	Middle	2	T3 N0 M0	IIA	2	pT2 pN0 pM0	IIA
5	54	F	Epidermoid	Middle	2	T3 N0 M0	IIA	7	pT3 pN0 pM0	IIA
6	71	F	Epidermoid	Inferior	2	T3 N0 M0	IIA	35	pT3 pN0 pM0	IIA
7	70	M	Adenocarcinoma	Inferior	1	T4 N0 M0	III	20	pT3 pN0 pM0	IIA
8	65	M	Epidermoid	Middle	2	T3 N0 M0	IIA	6	pT3 pN1 pM0	III
9	71	M	Epidermoid	Inferior	1	T4 N0 M0	III	6	pT3 pN1 pM0	III
10	72	F	Epidermoid	Middle	1	T3 N0 M0	IIA	12	pT1 pN1 pM1	IIA
11	56	M	Epidermoid	Middle	1	T4 N0 M0	III	20	pT3 pN0 pM0	IIA
12	66	F	Epidermoid	Middle	2	T3 N0 M0	IIA	9	pT3 pN0 pMx	IIA
13	58	M	Epidermoid	Inferior	2	T3 N0 M0	IIA	2	pT0 pN0 pM0	0
14	40	F	Epidermoid	Middle	2	T3 N0 M0	IIA	9	pT3 pN0 pM0	IIA
15	66	M	Epidermoid	Superior	1	T4 N0 M0	III	12	pT3 pN0 pM0	IIA

†TNM before exclusive chemoradiotherapy. ECRSI, exclusive chemoradiotherapy-surgery interval; PS, performance status before exclusive chemoradiotherapy; TNM, TNM Classification of Malignant Tumors.

was carried out in 13 patients and transhiatal esophagectomy without thoracotomy in the two other patients. The number of resected lymph nodes varied from zero to 42 lymph nodes (average of 12.8 lymph nodes), being positive for neoplasia in five patients (average of 1.3 metastatic lymph nodes). In one case, mediastinal metastatic lymph nodal mass was present, and was completely en bloc resected with esophagus.

In 14 patients, surgery was registered as R0 (without residual tumor) through congelation biopsy in all tumoral limits. In another case, a nodule was found in the apex of the right lung, whose congelation biopsy was negative for malignancy (later, the paraffin examination showed metastatic lesion).

The mean surgical time was 325 min (240–430 min), and only two patients were submitted to blood transfusion during surgery. Three patients needed prolonged mechanics ventilation (defined as more than 24 h), and 12 patients were extubated in the operation room. The mean time of intensive care unit was 5 days (2–37 days) and hospital mean time was 16.8 days (11–59 days).

Complications after salvage esophagectomy are shown in Table 2. Some of the technical complications reported were: two cases of cervical anastomotic leak with spontaneous resolution; one case of gastric tube dehiscence with mediastinitis that needed removal and drainage of mediastinal space; one case of gastric tube necrosis because of venous congestion (without anastomotic leak), which also needed removal; and one case of esophageal-tracheal fistula treated conservatively. Five cases of pneumonia, four cases of sepsis, one case of urinary tract infection, one case of surgical site infection, one case of paralytic ileus, one case of venous thrombosis, and one case of pulmonary tromboembolism had also occurred. Surgical morbidity was 71% and surgical mortality was zero.

The average follow-up was 18.4 months with three patient deaths. One patient died after 12 months of follow-up with locoregional recidive (mediastinal lymph nodes), another one died after 4 months, also due to cervical lymph nodes recidive and pulmonary

metastasis, and the third died after 16 months of follow-up due to pulmonary metastasis. Twelve patients are still alive without evidence of local disease. The median survival of the series was 16.4 months.

DISCUSSION

Over the past few decades, an epidemiological alteration in stomach and esophageal tumors has been observed, with gradual increase in the incidence of proximal gastric and distal esophageal cancer.^{4,11,12} Currently, distal esophageal adenocarcinoma represents the most common esophageal neoplasia in the western world, whereas in Asia, the epidermoid carcinoma of middle esophagus continues to be the most frequent.¹³ In our study, we observed high incidence of epidermoid esophageal cancer in the middle esophagus.

Low effectiveness of esophagectomy in terms of cure is accounted, in part, for early systemic dissemination of esophageal cancer due to its histological characteristic. In general, this happens because the patients already present occult metastasis at the moment of diagnosis. Another reason is the intrinsic anatomical relation between the esophagus and vital structures such as superior cava vein, aorta, and respiratory tract (structures that cannot be sectioned to obtain an R0 surgery).^{14,15}

Because of the low effectiveness of surgical treatment alone, other therapeutic modalities have been developed, generally associated with surgery. These associations involve radiotherapy, chemotherapy, or chemoradiotherapy, which can be neoadjuvant and/or adjuvant. Also, there is the combined treatment with exclusive radical chemoradiotherapy (without surgery).^{16,17} The combination of radiotherapy (maximum dose) with chemotherapy (exclusive chemoradiotherapy) is accepted today as the primary treatment for local advanced esophageal injuries (T3 and T4) and for patients with low performance status or clinical contraindications to surgery. The benefits of exclusive chemoradiotherapy in relation to isolated radiotherapy are registered in randomized and controlled clinical studies.^{18,19} A survival average of 12–18 months and 15% in 5 years has been reported in the literature.²⁰ Nonrandomized comparative series suggest that exclusive chemoradiotherapy is equivalent, if not superior, to isolated surgical resection when compared with long-term survival for advanced tumors.^{21,22} There are no randomized clinical trials comparing exclusive chemoradiotherapy with isolated surgery in these cases.

Salvage esophagectomy appeared with the advent of exclusive chemoradiotherapy and its inherent locoregional failure (up to 60% in some series). The high rate of this procedure morbimortality is

Table 2 Complications after salvage esophagectomy

Complication	Incidence
Pneumonia	33.3% (5/15)
Sepsis	26.7% (4/15)
Cervical anastomotic leak	13.3% (2/15)
Mediastinitis	6.7% (1/15)
Gastric tube necrosis	6.7% (1/15)
Esophageal-tracheal fistula	6.7% (1/15)
Urinary tract infection	6.7% (1/15)
Surgical site infection	6.7% (1/15)
Paralytic ileus	6.7% (1/15)
Venous thrombosis	6.7% (1/15)
Pulmonary tromboembolism	6.7% (1/15)

Table 3 Comparison of INCA results with Japanese and American schools

	MDACC (2002)	TWMC (2004)	INCA/Brazil (2006)
No. of cases	13	27	15
Surgical time (medium)	542 min	312 min	325 min (240–430)
ICU time (medium)	12.2 days	5.9 days	5 days (2–37 days)
Fistula rate (n/%)	05/38%	06/22%	02/13, 3%
Hospital internment (medium)	29.4 days	39.9 days	16.8 days (11–59 days)
Global morbidity	77%	NR	71%
Surgical mortality	02 (15%)	01 (3.7%)	0
R0 surgical resection (n/%)	NR	18/67%	14/93.3%
Follow-up (medium)	27 months	NR	18.4 months
Survival (medium)	NR	NR	16.4 months

ICU, intensive care unit; INCA, Brazilian National Cancer Institute; MDACC, MD-Anderson Cancer Center²³; NR, not reported; TWMC, Tokyo Women's Medical University.²⁴

recognized mainly when compared with the esophagectomy after neoadjuvant therapy, which requires a lesser dose of radiotherapy application and a lesser time interval between combined treatment ending and surgery (4–6 weeks). In salvage surgery, radiotherapy dose applied is higher and interval between radiotherapy and surgery is unknown. This causes higher degree of fibrosis and adherences between the periesophageal structures with a consequent increased difficulty in esophageal dissection technique, highest index of iatrogenic injuries and surgical morbimortality. Because of this, majority of our cases were submitted to esophagectomy with thoracotomy (13 patients), instead of transhiatal esophagectomy (two patients), to have a better exposition of esophagus and adjacent structures.

In 2002, MD-Anderson Cancer Center (MDACC) published an important study that constituted in a series of 13 patients submitted to salvage esophagectomy after exclusive chemoradiotherapy. Using a heterogeneous control group of 99 patients submitted to neoadjuvant bimodal therapy, high surgical morbimortality of salvage surgery was found when compared with surgery after neoadjuvant therapy and the 5-year overall survival rate was 25%.²³

Nakamuras *et al.* published in 2004 a series of 27 patients submitted to salvage surgery of esophageal epidermoid carcinoma after exclusive chemoradiotherapy and they were also compared with a control group of 28 patients undergoing neoadjuvant therapy (28 cases). In nine cases, surgical resection was incomplete with residual disease (R1 or R2). In contrast with the study of MDACC, this publication did not find differences in terms of surgical morbimortality and survival between the two groups.²⁴

In January of 2005, a nonrandomized prospective study was published evaluating the necessity of 53 patients being submitted to esophagectomy after exclusive radical chemoradiotherapy. In this series, using the combined treatment, esophagectomy did benefit the patients. However, for nonrespondents patient, surgery increased 5-year overall survival.²⁵

In fact, it is recognized that esophagectomy after chemoradiotherapy (neoadjuvant or exclusive) has higher morbimortality when compared with patients with no previous treatment. Fistulas and anastomotic dehiscence, adult respiratory distress syndrome, and complications related to respiratory tract airways are more common in patients submitted to chemoradiotherapy before surgery. Specialized reference centers report mortality of approximately 10% (doubled when compared with patients treated with surgery alone).^{2,26}

The two major salvage esophagectomy complications are related with anastomosis and pulmonary function, which was confirmed in this study. Other complications specifically related to salvage surgery are: respiratory tract airways necrosis and fistulas, recurrent laryngeal nerve injury, chylothorax and pericardial effusions. All of these complications are related to the higher radiation dose applied on the mediastinum.

We had one case of dehiscence, one case of esophageal-gastric anastomotic fistula, a case of cervical esophageal-traqueal fistula, and five cases of pneumonia, which confirms the data cited above. In Table 3, the results were compared with two major and updated works published by the time, being one of the American school (MDACC) and another Japanese (Tokyo Medical Women's University).

It was shown that the series sample is still restricted even in specialized reference centers for esophageal cancer treatment. Since 1999, salvage esophagectomy has been performed in INCA, being most of then carried out recently (2004–2006); therefore, our short follow-up average presented 18.4 months.

Exclusive chemoradiotherapy for esophageal cancer has gained sufficient popularity in recent years, mainly in the locoregional advanced cases (T3 or T4) and in those patients without physiological reserve for esophagectomy (Performance status 3 or 4 or incapacity comorbidity). In fact, many patients had recovered from the clinical condition and performance

status (PS) after combined treatment ending, which makes them eligible to surgical procedure.

Thus, salvage esophagectomy proved to be technically feasible. Despite its high morbidity, it revealed the only cure possible in cases of recidive or disease persistence after exclusive chemoradiotherapy. Therefore, it represents the second best line treatment for locoregional failure after exclusive chemoradiotherapy. So, more studies for its complete validation are required. In INCA, protocols for a prospective study are being drawn up to enable, in the future, a more accurate result of salvage esophagectomy.

References

- 1 Brasil. Ministério da Saúde. Instituto Nacional de Câncer. Estimativas de incidência e mortalidade, 2003. Rio de Janeiro: INCA, 2003.
- 2 Brown L M, Devesa S S. Epidemiologic trends in esophageal and gastric cancer in the United States. *Surg Oncol Clin N Am* 2002; 11: 235–56.
- 3 Crew K D, Neugut A I. Epidemiology of upper gastrointestinal malignancies. *Semin Oncol* 2004; 31: 450–64.
- 4 Stein H J, Brucher B L, Sendler A *et al.* Esophageal cancer: patient evaluation and pre-treatment staging. *Surg Oncol* 2001; 10: 103–11.
- 5 Gamliel Z, Krasna M J. Multimodality treatment of esophageal cancer. *Surg Clin N Am* 2005; 85: 621–30.
- 6 Penman I D, Henry E. Advanced esophageal cancer. *Gastrointest Endosc Clin N Am* 2005; 15: 101–16.
- 7 Swisher S G, Deford L, Merriman K W *et al.* Effect of operative volume on morbidity, mortality, and hospital use after esophagectomy for cancer. *J Thorac Cardiovasc Surg* 2000; 119: 1126–35.
- 8 Lerut T. The surgeon as a prognostic factor. *Ann Surg* 2000; 232: 729–32.
- 9 Urba S. Combined modality therapy of esophageal cancer – standard of care? *Surg Oncol Clin N Am* 2002; 11: 377–86.
- 10 Urschel J D, Ashiku S, Thurer R *et al.* Salvage or planned esophagectomy after chemoradiation therapy for locally advanced esophageal cancer – a review. *Dis Esophagus* 2003; 16: 60–5.
- 11 Gee D W, Rattner D W. Management of gastroesophageal tumors. *Oncologist* 2007; 12: 175–85.
- 12 Keeney S, Bauer T L. Epidemiology of adenocarcinoma of the esophagogastric junction. *Surg Oncol Clin N Am* 2006; 15: 687–96.
- 13 Devesa S S, Blot W J, Fraumeni J F. Changing patterns in the incidence of esophageal and gastric carcinoma in the United States. *Cancer* 1998; 83: 2049–53.
- 14 Patel A M, Buenaventura P O. Current staging of esophageal carcinoma. *Surg Clin N Am* 2005; 85: 555–67.
- 15 Nishimaki T, Shimoji H, Sunagawa H. Recent changes and the future roles of esophageal cancer surgery. *Ann Thorac Cardiovasc Surg* 2004; 10: 324–32.
- 16 Das P, Fukami N, Ajani J A. Combined modality therapy of localized gastric and esophageal cancers. *J Natl Compr Canc Netw* 2006; 4: 375–82.
- 17 Mooney M M. Neoadjuvant and adjuvant chemotherapy for esophageal adenocarcinoma. *J Surg Oncol* 2005; 92: 230–8.
- 18 Herskovic A, Martz K, al-Sarraf M *et al.* Combined chemotherapy and radiotherapy compared with radiotherapy alone in patients with cancer of the esophagus. *N Engl J Med* 1992; 326: 1593–8.
- 19 Wong R, Malthaner R. Combined chemotherapy and radiotherapy (without surgery) compared with radiotherapy alone in localized carcinoma of the esophagus. *Cochrane Database Syst Rev* 2006; 1: CD002092.
- 20 Minsky B D. Carcinoma of the esophagus. Part 1: Primary therapy. *Oncology* 1999; 13: 1223–36.
- 21 Chan A, Wong A. Is combined chemotherapy and radiation therapy equally effective as surgical resection in localized esophageal carcinoma. *Int J Radiat Oncol Biol Phys* 1999; 45: 265–70.
- 22 Murakami M, Kuroda Y, Nakajima T *et al.* Comparison between chemoradiation protocol intended for organ preservation and conventional surgery for clinical T1-T2 esophageal carcinoma. *Int J Radiat Oncol Biol Phys* 1999; 45: 277–84.
- 23 Swisher S G, Wyn P *et al.* Salvage esophagectomy for recurrent tumors after definitive chemotherapy and radiotherapy. *J Thorac Cardiovasc Surg* 2002; 123: 175–83.
- 24 Nakamura T, Hayashi K, Ota M *et al.* Salvage esophagectomy after definitive chemotherapy and radiotherapy for advanced esophageal cancer. *Am J Surg* 2004; 188: 261–6.
- 25 Fujita H, Sueyoshi S *et al.* Esophagectomy: is it necessary after chemoradiotherapy for locally advanced T4 esophageal cancer? Prospective nonrandomized trial comparing chemoradiotherapy with surgery versus without surgery. *World Surg* 2005; 29: 25–31.
- 26 Urschel J D, Sellke F W. Complications of salvage esophagectomy. *Med Sci Monit* 2003; 9: RA173–80.