

Multimodal treatment for oesophageal primary cancer. A preliminary study



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OBJECTIVE: *This study examines the role of chemoradiotherapy, surgical reconstructive techniques of the esophagus and lymphadenectomy in relation to morbidity and mortality.*

METHODS. *From January 2005 to January 2008 we observed 18 patients with esophagus cancer. Eleven patients manifested a lesion of the middle third, 4 patients had a lesion of the upper third and 3 patients had a lesion of the lower third. Preoperative histological evaluation revealed 3 adenocarcinomas and 15 squamous carcinomas. Four patients with a lesion of the upper third received neoadjuvant chemotherapy.*

RESULTS: *In 13 patients reconstruction used stomach and 5 patients underwent reconstruction with the colon. Complications ensued in 3 of the latter: dehiscence of the anastomosis, anastomotic stenosis and chylothorax. Three patients highlighted a moderate malabsorption syndrome. A T₃N₁M₀ patient received postoperative cisplatin/5-fluorouracil and radiation therapy.*

CONCLUSIONS: *The use of the stomach represents the therapeutic gold standard for minimized incidence of complications. Lymphadenectomy allows to establish a precise stage of cancer. Chemoradiotherapy is recommended in case of risk of relapse.*

KEY WORDS: Esophagus Primary Cancer, Complications; Chemotherapy, Lymphadenectomy, Radiotherapy, Surgical treatment.

Introduction

Total esophagectomy with cervical anastomosis continues to be the elected technique in primary cancer of the esophagus, despite a low percentage of recovery. The use of the stomach with gastroesophageal anastomosis¹ or colon with jejunoesophagostomy² has yet to be debated. Anastomotic fistula, bile reflux or dumping syndrome are the most frequent complications accounting for up to 60%³. The incidence of anastomotic stenosis was

dramatically reduced with the use of circular stapler device in respect to manual suture. The survival of patients depends on stage of cancer and on complete surgical removal⁴. Excision of abdominal and subcarinal lymph nodes has been associated to bilateral resection of superior and middle mediastinum lymph nodes⁵. Neoadjuvant and adjuvant chemoradiation therapy display doubts and perplexity concerning the contrast results. The study aims to evaluate trimodality treatment based on morbidity and mortality.

Methods

From January 2005 to January 2008 we observed 18 patients with primary cancer of the esophagus; 10 males (55.5%) and 8 females (44.5%), with a medium age of 52 ± 1 (extremes: 45-69 years). All patients complained

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of progressive dysphagia associated to retrosternal pain; 4 patients (22.3%) had heartburn and hoarseness. Vitamin B₁₂, antiendomysium antibodies (EMA) which are the autoantibodies against the enterocytes, and antigliadin antibodies which are the autoantibodies against gliadin protein, were in the norm. Preoperative tests consisted in Rx esophagogram, total body computed tomography (CT), esophagogastroduodenoscopy (EGDS) with multiple biopsies and fiberoptic bronchoscopy. In 11 patients (61.1%) carcinoma was localized in the middle third, in the 4 patients (22.3%) in the superior third and in the remaining 3 patients (16.6%) in the inferior third; in two cases the lesion pathology developed on Barret's esophagus. Preoperative histologic diagnosis obtained by EGDS showed 15 squamous carcinomas and 3 adenocarcinomas. Four patients with a squamous carcinoma of the superior third underwent neoadjuvant chemotherapy (Table 1). In 13 patients (72.2%) the stomach was used in reconstruction of the digestive path with an extended lymphadenectomy, in 5 patients (27.8%) the colon was used of which two with Barret's esophagus.

SURGICAL TECHNIQUES

Anaesthesia included 2 mg/kg of Propofol, 0.15-0.20 mg/kg of Cisatracurium besilate and 1 fl of 0.1 mg/kg of Fentanyl Citrate in bolus. Maintenance was carried out with 0.25 Å/kg/min of Remifentanyl intravenous (i.v.), 0.50 mg/Kg/min of Propofol and 2 fl (40 mg) of Cisatracurium besilate at 5 ml/hour. There was a selective tracheobronchial intubation with a left Mallinckrodt tube. The patient was positioned on his back. Respiratory and cardiac systems were monitored. Intervention is in three stages: abdominal, thorax and cervical.

Abdominal stage: laparotomic xifombelical incision; following exploration of the peritoneal cavity, if the stomach is used there is a mobilization of the organ associ-

ated to dissection and section of left gastric artery, left gastroepiploic artery and hepatogastric, splenogastric and phrenogastric ligaments. We prepared the esophagus in craniocaudal sense with a section of vagi nerves and the stomach along the small bending with a linear stapler device. The cardial fornix bending and abdominal esophagus were eliminated. We used layer suture of the laparotomic incision.

Thoracic stage: the patient was placed on his left side. Right thoracotomy was effected to the V costal space. We sectioned the mediastinal pleural, with total dissection of the esophagus and esophageal arteries with their mobilization and section. The thoracic duct was isolated near the intermediate bronchus. This manoeuvre is more easily effected following the assumption of a meal rich in fats. Verification of hemostasis. We positioned two aspirative drainage tubes n° 28 Ch and n° 36 Ch and we used layer suture for the thoracotomy.

Cervical stage: the patient was positioned on his back. Oblique cervicotomy along medial margin of sternocleidomastoid muscle. Section of lower thyroid artery and medial of larynx, trachea and cervical esophagus. Creation of retrosternal tunnel, with transjugular and transphrenic access. Attraction in the cervical region of the stomach with strip; esophagogastrostomy with separated stitches in vicryl 3 zero in the posterior wall. If we used right colon, thoracic and cervical times were the same. In the abdominal phase we resected the ileus to 10 cm of ileocecal valve, the transverse colon in the middle third and we preserved right colic artery. We used 1/2 fl of Buprenorfine, 1/2 fl of Ketorolac, 1 fl of Metoclopramide hydrochloride, 1 fl of Ranitidine i.v. for pain killer therapy, 1/2 h before the end of intervention. Maintenance therapy consisted in 1+1/2 fl of Buprenorfine, 2 fl of Ketorolac, 2 fl of Ranitidine, 2 fl of Metoclopramide hydrochloride i.v. at the rate of 2 ml/h in 24 hours total parenteral nutrition was reinstated 5 ± 2 days after intervention with food of 1 g of

TABLE I – Neoadjuvant treatment in 4 squamous carcinoma patients

Sex	Age	Stage	Chemotherapy	Dosage	Administration	Frequency
M	47 years	III T ₃ N ₁ M ₀	Platin Fluoro	80-100 mg/m ²	i.v. in 3 hours	Every 21 days
M	61years	II A T ₃ N ₀ M ₀	Platin Fluoro	80-100 mg/m ² 1000 mg/m ²	i.v. in 3 hours i.v.	Every 21 days
F	50 years	II B T ₁ N ₁ M ₀	Platin Fluoro	80-100 mg/m ² 1000 mg/m ²	i.v. in 3 hours i.v.	Every 21 days
M	53 years	II B T ₁ N ₁ M ₀	Epirubicin Cisplatin 5-Fluorouracil	50 mg/m ² 60 mg/m ² 200 mg/m ²	i.v. i.v. i.v.	1° day 1° day 1°-21° day

protein pro/kg with 20 Kcal/prokg with increase of 5 Kcal/prokg daily. Enteral nutrition consisted in:

- 50 ml in bolus every 6 h first day;
- Continuous infusion at 20 ml/h second day;
- Increase of 20 ml/h to 80 ml/h starting third day;
- Reduction of 5 ml/die of parenteral nutrition until suspension;
- Patients underwent the following exams:
- Chest X-ray in the first three months;
- EGDS during first and third months;
- CT of the thorax during the sixth month;
- 18f-fluorodeoxyglucose positron emission tomography (FDG-PET) total body during the second year. FDG-PET total body if there was a diagnostic doubt at CT.

STATISTICAL ANALYSIS

Clinical and laboratory parameters were analyzed in multivariate analysis that was performed using SPSS 10.0; data were entered into a data base using SPSS Data Entry II (SPSS Inc., Chicago, IL, USA). Data were expressed as mean $\pm$ and standard deviation (range 95%). All P values less than 0.05 were considered to indicate significance and CI at 95%. The log-rank test was used for the P value.

Results

Esophagogastroduodenoscopy for preoperative histologic examination showed diagnostic accuracy of 100%. Postoperative stage and the histologic evaluation were as follows: stage I ($T_1N_0M_0$) in 10 patients (55.5%), 1 adenocarcinoma and 9 squamous carcinomas; stage II A ($1 T_2N_0M_0 - 3 T_3N_0M_0$) in 4 patients (22.3%), 1 adenocarcinoma and 3 squamous carcinomas; stage IIB ($T_1N_1M_0$) in 3 patient (16.6%), 1 adenocarcinoma and 2 squamous carcinomas; stage III ($T_3N_1M_0$) in 1 patient

(5.6%), a squamous carcinoma. We observed 3 (16.6%) complications following reconstruction with colon (Table II):

- dehiscence of the anastomosis, manifesting itself on the fourth postoperative day with elimination of food materials to the pleural drainage tubes;
- an anastomotic stenosis on seventh day, upon assumption of food, manifesting itself with vomit and evidenced at esophagogastroduodenoscopy;
- a chylothorax due to a lesion of the thoracic duct appeared on second day.

The dehiscence of the anastomosis needed suture reinforcement with separate stitches. The anastomotic stenosis was resolved positively by means of rigid esophagoscopy, while the chylothorax required the closure of the duct by thoracotomy. The Stage III patient underwent adjuvant chemoradiotherapy consisting in:

- a) 75 mg/m² of Cisplatin in first day i.v. in 2 hours;
- b) 1000 mg/m² of % 5-Fluorouracil (5-FU) on the first and the fourth day in continuous infusion;
- c) 50 Gy in 25 fraction every 5 weeks of radiotherapy after 3 cycles of chemotherapy.

The use of stomach had no complications, there was no FEV₁ reduction and Tiffenau index (FEV₁/FVC) with lymphadenectomy. Three patients (16.6%) had moderate degree malabsorption syndrome, with presence of antiendomysium and antigliadin antibodies; 9 (50%) patients had a slight degree of malabsorption syndrome, with a decrease of vitamin B₁₂. The presence of this autoantibodies could be responsible for the low degree of malabsorption. Eighteen patients are still living with a follow-up at 36 months; recurrent and repetitive lesions have not been revealed (Tables III and IV).

STATISTICAL ANALYSIS

The analysis of the data reported in Table 3 and confirmed in Table 4 shows a highly significant relationship

TABLE II – Clinical status in anatomical complications patients with reconstruction by colon

Sex	Age	Neoadjuvant Chemotherapy	Adjuvant Chemotherapy	Histologic Diagnosis	Stage	Complication
M	47 years	Platin: 80-100 mg/m ² Fluoro: 1000 mg/m ²	Cisplatin: 75 mg/m ² 5-Fluorouracil: 1000 mg/m ²	Squamous Carcinoma	III ($T_3N_1M_0$)	Dehiscence of the anastomosis
M	53 years	Epirubicin: 50 mg/m ² Cisplatin: 60 mg/m ² 5-Fluorouracil: 200 mg/m ²	\	Squamous Carcinoma	II B ($T_1N_1M_0$)	Stenosis of the anastomosis
F	51 years	/	/	Adenocarcinoma	I ($T_1N_0M_0$)	Lesion the thoracic duct

TABLE III- Actual clinical patterns concerning all operated patients

Sex	Age	Reconstruction	Stage	Chemoradiotherapy	Complications	Histologic Diagnosis
M	47years	Colon	III T ₃ N ₁ M ₀	Neoadjuvant + adjuvant+radio	Dehiscence of the anastomosis	Squamous Carcinoma
M	53years	Colon	IIB T ₁ N ₁ M ₀	Neoadjuvant	Stenosis of the anastomosis	Squamous Carcinoma
M	55years	Colon	I T ₁ N ₀ M ₀			Squamous Carcinoma
M	60years	Stomach	IIA T ₂ N ₀ M ₀			Adenocarcinoma
M	56 years	Stomach	I T ₁ N ₀ M ₀			Squamous Carcinoma
M	45 years	Stomach	I T ₁ N ₀ M ₀			Squamous Carcinoma
M	61 years	Stomach	IIA T ₃ N ₀ M ₀	Neoadjuvant		Squamous Carcinoma
M	53 years	Stomach	IIB T ₁ N ₁ M ₀			Adenocarcinoma
M	58 years	Stomach	I T ₁ N ₀ M ₀			Squamous Carcinoma
M	63 years	Stomach	I T ₁ N ₀ M ₀			Squamous Carcinoma
F	50 years	Colon	IIB T ₁ N ₁ M ₀	Neoadjuvant		Squamous Carcinoma
F	51 years	Colon	I T ₁ N ₀ M ₀		Lesion of the thoracic duct	Adenocarcinoma
F	64 years	Stomach	IIA T ₃ N ₀ M ₀			Squamous Carcinoma
F	53 years	Stomach	I T ₁ N ₀ M ₀			Squamous Carcinoma
F	68 years	Stomach	I T ₁ N ₀ M ₀			Squamous Carcinoma
F	59 years	Stomach	I T ₁ N ₀ M ₀			Squamous Carcinoma
F	69 years	Stomach	IIA T ₃ N ₀ M ₀			Squamous Carcinoma
F	66 years	Stomach	I T ₁ N ₀ M ₀			Squamous Carcinoma

to reconstruction vs complication ($p=0.002$) and antibody antigen (Ab-Ag) ($p=0.0007$). A relative relationship shows the reconstruction of esophagus with colon vs chemoradiotherapy ($p=0.01$). A less significant degree of reconstruction indicates that age and sex have no impact on the risk of death (Table V).

Discussion

Our preliminary study showed that the use of stomach had a low morbidity in respect to the use of colon, though we prefer colon if there is a cancer in the Barrett's esophagus with elimination of distal segment and metaplastic epithelium. Our complications had a ratio of frequency of 5.5%. Allium et al ⁶ showed that the incidence of anastomotic dehiscence could not be superior to 5%; this complication is linked to the worst postoperative mortality due to ischemia of the neoesophagus. Junemann-Ramirez et al ⁷ showed a postoperative mortality of 35.7% and 4.2% respectively if there was dehiscence or not. We use manual cervical anastomosis because it respects the anatomic planes, an evaluation of pressure on the suture and a correct stratification of mucosae. In literature many authors prefer the stapler for minor incidence of complications in respect to manual suture. Singh et al ⁸ had a percentage of anastomotic stenosis of 17% vs 58%, Orringer et al ⁹ had a percentage of 35% vs 48%. Chunwei et al ¹⁰ in a study of cervical esophagogastric anastomosis with circular stapler, shows stenosis rate to 10.9%, positively treated in 91.7% of cases through dilatations (range of 1-5). The minor complications were represented by the chylothorax and the acid or bile reflux. Shibuya et al ¹¹ had a gastroesophageal reflux in 56.4% of patients with a cer-

vical anastomosis and in 88.6% patients with intrathoracic anastomosis. The chylothorax for mediastinic lymphadenectomy with high infection and postoperative cachexia was treated with a reintervention to tie a thoracic duct. Alexiou et al ¹² highlight chylothorax in 4.8% of cases; reintervention was needed in 3 patients (37.5%) and medical treatment in 5 (62.5%). Vagotomy reduces intraluminal acidity ¹³; bile reflux after pyloroplasty in the stomach was positively treated with gastric drainage ¹⁴. In our study the use of the stomach in respect to the colon displayed a high nutritional value. Resection of vagus nerve seems to be the main cause of clinical malabsorption syndrome ^{15, 16}. An extended lymphadenectomy was recommended in all cancers, especially if they were upper-carina, for minor incidence of local relapse. At the moment of intervention the lymph node invasion was of 30-80%. In the extended lymphadenectomy we removed lymph nodes of the splenic artery, superior right and left mediastinum, subcardinal, paracardiac, celiac and lymph nodes of the left gastric artery. In a study by D'Journo et al ¹⁷ the rate of survival was 49% in extended lymphadenectomy and 21% in standard lymphadenectomy. The presence of 4 metastatic lymph nodes increase the risk of local and distance relapse, above all in lung and liver. D'Journo et al ¹⁸, carried out a standard lymphadenectomy in 35 patients with esophagus neoplasia, and extended lymphadenectomy in 67 patients. The rate of metastatic lymph nodes was 8% vs 15% in mediastinic lymph nodes, 14% vs 24% in abdominal lymph nodes, 5% vs 10% in celiac lymph nodes. Survival at 5 years was superior in extended lymphadenectomy (41% vs 10%), relapse was minor (24% vs 38%). The lymph node ratio (LNR) was an important prognostic factor for survival. The LNR > 0.1 identified N+ patients with a risk of

TABLE IV – Malabsorption syndrome after surgical treatment

Sex	Age	Reconstruction	Vitamin B12	EMA	Antigliadin Antibodies
M	47 years	Colon	500 ng/ml	++	+
M	53 years	Colon	650 ng/ml	+	++
M	55 years	Colon	800 ng/ml		
M	60 years	Stomach	160 ng/ml		
M	56 years	Stomach	190 ng/ml		
M	45 years	Stomach	130 ng/ml		
M	61 years	Stomach	710 ng/ml		
M	53 years	Stomach	280 ng/ml		
M	58 years	Stomach	680 ng/ml		
M	63 years	Stomach	120 ng/ml		
F	50 years	Colon	760 ng/ml	+	++
F	51 years	Colon	540 ng/ml		
F	64 years	Stomach	150 ng/ml		
F	53 years	Stomach	530 ng/ml		
F	68 years	Stomach	220 ng/ml		
F	59 years	Stomach	280 ng/ml		
F	69 years	Stomach	350 ng/ml		
F	66 years	Stomach	270 ng/ml		

TABLE V – Multivariate analysis; Pareto chart of *t*-values for coefficients; *df*=16

Parameters	P values
Age vs Reconstruction	0.01
TNM vs Reconstruction	0.02
Complication vs Reconstruction	0.002
EMA vs Reconstruction	0.0007
Chemoradiotherapy vs Reconstruction	0.01
Ab-Ag vs Reconstruction	0.0007
Sex vs Reconstruction	0.01

general or local relapse. For this reason these patients underwent adjuvant chemotherapy. A high percentage of irradical resections was reported in literature using surgery, with or without neoadjuvant chemotherapy¹⁹. In our experience 3 stage II and 1 stage III patients underwent neoadjuvant chemotherapy and a complete R0-resection. The stage III patient was also treated with adjuvant chemoradiotherapy and do not displays recurrence of pathology after 26 months from intervention. Marano S et al²⁰, in 4 patients with adenocarcinoma of the proximal esophagus and overall cytoreductive response, show a median survival rate of 54 months. The Academic Medical Center of Amsterdam²¹ started a new CROSS phase III trial comparing neoadjuvant chemoradiation followed by surgery vs surgery alone. One hundred-seventy-five patients per arm was included; Paclitaxel (50 mg/m²), Carboplatin (Area-Under-Curve=2) and a total dose radiation of 41.4 Gy were administered. The median survival of the surgery alone arm was 16 months vs 22 months of multimodal treatment arm, associated with chemoradiation toxicity. Donahue et al²² in 162 esophageal cancer patients show

a 5-year survival rate of 55%, 27% and 27% in case of pathologic response of neoadjuvant chemoradiotherapy was complete, near complete and partial respectively. Chao et al²³, in 70 squamous cell carcinoma patients with pathologic complete response of preoperative chemoradiotherapy, highlighted mortality and recurrence rate of 25.7% and 31.4%. The 5-year disease-free survival was 45% for T₃-T₄ patients and 85% for T₁-T₂ patients.

In conclusion, in our experience the use of stomach was a therapeutic gold standard because the absence of anatomical and clinical complications in patients with an esophagus cancer. The extended lymphadenectomy allows a precise stage and minor relapse. Neoadjuvant and adjuvant chemoradiotherapy was futile for prognosis because of its goal is linked to the cancer size; this method is advised in case of risk of recurrence. Our preliminary study can be a start to other studies of the best reconstructive techniques of the esophagus towards an elimination of malabsorption syndrome.

Riassunto

OBIETTIVO: Il nostro studio esamina il ruolo della chemioradioterapia, delle tecniche ricostruttive dell'esofago e della linfadenectomia in relazione alla morbidità e mortalità.

METODI: Da gennaio 2005 a gennaio 2008 sono giunti alla nostra osservazione 18 pazienti affetti da un cancro dell'esofago. Undici pazienti manifestavano una lesione del 1/3 medio, 4 del 1/3 superiore e 3 del 1/3 inferiore. La valutazione istologica preoperatoria ha rilevato 3 adenocarcinomi e 15 carcinomi squamosi. I 4 pazienti con neoplasia del 1/3 superiore sono stati sottoposti ad una chemioterapia neoadiuvante.

RISULTATI: In 13 pazienti si è proceduto ad una ricostruzione con stomaco e in 5 pazienti con colon. Abbiamo registrato 3 complicanze: una deiscenza dell'anastomosi, una stenosi dell'anastomosi e un chilotorace. Tre pazienti hanno manifestato una moderata sindrome da malassorbimento. Un paziente T₃N₁M₀ è stato sottoposto ad un trattamento chemioradioterapico postoperatorio.

CONCLUSIONI: L'uso dello stomaco rappresenta il "gold standard" terapeutico in quanto minimizza l'incidenza di complicanze. Un'estesa linfadenectomia consente l'esatta stadiazione della neoplasia. La chemioradioterapia è giustificata in caso di elevato rischio di fenomeni ripetitivi.

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