

## Distant Oncologic Outcome of Patients with Locally Advanced Unresectable and Metastatic Esophageal Cancer after Multimodality Treatment

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### Rezumat

*Evoluția pe termen lung a pacienților cu cancer esofagian local avansat și metastatic după tratamentul multimodal*

**Introducere:** Terapia multidimodală este utilizată ca tratament de referință în cazul cancerului esofagian și al cancerului de joncțiune eso-gastrică, la nivel mondial, dar nu există un consens unanim.

**Metode:** Au fost revizuite retrospectiv dosarele medicale a 132 de pacienți diagnosticați cu cancer esofagian local avansat, neoperabil și metastatic, internați în centrul nostru în perioada 2010-2015. Tratamentul multimodal a constat în chimioterapie, radioterapie sau chimio-radioterapie și chirurgie și a fost planificat în funcție de extinderea tumorii și statusul de performanță a pacientului.

**Rezultate:** În urma examenului histopatologic, 77% dintre pacienți au fost diagnosticați cu carcinom scuamos și 23% au fost diagnosticați cu adenocarcinom. Dintre aceștia, 16,6 % (22 de pacienți) au fost diagnosticați în stadiul IV, 19,7 % (26 de pacienți) au efectuat chimio-radioterapie concomitentă, iar 68,9% (91 de pacienți) au urmat chimioterapie în timp ce 62,9% (83 pacienți) au urmat radioterapie. După tratamentul combinat, intervenția chirurgicală cu intenție radicală a fost posibilă la 15,9 % (21 pacienți). După o urmărire de 17,3 luni, mediana supraviețuirii globale (OS) a populației a fost de 12 luni, cu o rată de supraviețuire la un an și la 2 ani de 49,2% și 17,4%. La pacienții metastazați, supraviețuirea mediană globală a fost de 10 luni. Pacienții care au fost convertiți la operabilitate au avut o mediană a supraviețuirii OS de 20 de luni, comparativ cu 10 luni, la pacienții care nu au urmat intervenții chirurgicale

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( $p = 0,002$ ). Chimio-radioterapia a fost superioară în ceea ce privește supraviețuirea globală în comparație cu chimioterapia sau radioterapia administrată secvențial (17 luni vs. 10 luni,  $p = 0,013$ ). **Concluzii:** Tratamentul multimodal în cancerul esofagian avansat la nivel local (radio-chimioterapie concomitentă, urmată de chirurgie) poate fi considerat superior fiecărei metode administrate ca mono-terapie, iar radioterapia și chimioterapia pot determina ca anumite tumori esofagiene avansate la nivel local să fie rezecabile.

**Cuvinte cheie:** cancerul esofagian, radioterapia, chimioterapia, chirurgia, tratamentul multimodal

## Abstract

**Background:** Combined modality therapy has been employed for the treatment of choice for locally advanced esophageal and esogastric junction cancers all around the globe but a unanimous consensus is missing.

**Methods:** Medical files of 132 patients with confirmed locally advanced unresectable, and metastatic esophageal cancer who presented to our center between 2010-2015 were retrospectively reviewed. Multimodality treatment consisting of chemo-radiotherapy or chemotherapy or radiotherapy alone and surgery in patients who convert to operability was planned according to tumor extent and performance status of the patient.

**Results:** Seventy seven percent of the patient presented with squamous carcinoma and 23 % were adenocarcinoma. At the diagnosis 22 patients (16.6%) were stage IV. Concurrent chemo-radiotherapy was administered in 26 patients (19.7%), chemotherapy in 91 patients (68.9%), radiotherapy in 83 patients (62.9%). After combined treatment, surgery with radical intent was possible in 21 patients (15.9%). After a follow up of 17.3 months, overall survival (OS) was 12 months, with one and two-year survival rate of 49.2% and 17.4%. In metastatic patients OS was 10 months. Patients who were converted to operability had a OS of 20 months vs. 10 months in patients who doesn't undergo surgery ( $p=0.002$ ). Chemo-radiotherapy was superior in terms of OS compared with chemotherapy or radiotherapy administered sequential (17 vs. 10 months,  $p=0.013$ ).

**Conclusions:** Multimodality treatment in locally advanced esophageal cancers (concurrent radio-chemotherapy followed by surgery) can be considered superior to each method as single therapy and radiotherapy and chemotherapy can make certain locally advanced esophageal tumors resectable.

**Key words:** esophageal cancer, radiotherapy, chemotherapy, surgery, multimodal treatment

## Introduction

Esophageal cancer is the eight most common cancer worldwide and the sixth most cause of death from cancer (1). Most cases occur in less developed countries and in Europe is the 19<sup>th</sup> most common cancer. Differences in the incidence of the esophageal cancer around the globe can be linked to the differences in exposure to risk factors (2). The most common histopathological type is squamous cell carcinoma, but the mortality rates in adenocarcinomas

are higher in some regions in Europe. The early diagnosis with a good management of the disease is of utmost importance in order to ensure treatment effectiveness (3). Despite the advancements in treatment and diagnostics, the 5-year survival remains very poor (15-20%) (4). Esophageal cancer is recognized to be aggressive and has complex lymphogenic-hematologic pathways, resulting into distant metastases that cause the cancer-related deaths (5). Combined modality therapy has been employed for the treatment of choice for

locally advanced esophageal and esophageal gastric junction (EGJ) cancers all around the globe but a unanimous consensus is missing. The aim of the study was to evaluate the results of multimodality treatment and the distant outcome of patients with locally advanced unresectable and metastatic esophageal cancer.

## Patients and Methods

Medical files of 132 consecutive patients with confirmed locally advanced unresectable, unoperable and metastatic esophageal cancer who presented to our centre between 2010-2015 were retrospectively reviewed.

Inclusion criteria consisted all histopathological confirmed squamous or adenocarcinoma of the oesophagus with locally advanced or metastatic unresectable disease, (stage III and IV) ECOG 0-2, with normal hematologic, liver and renal function, fit and willing to undergo multimodality treatment.

Demographic data of the patients such as age, gender, performance status was obtained. The analysed variables were oncologic stage, histopathological type, grade of cellular differentiation, the therapeutic sequences, survival time, progression free survival time.

Multimodality treatment consisting of chemo-radiotherapy or chemotherapy or radiotherapy alone was planned according to tumour extent and performance status of the patient. Radiotherapy was administered in a 3D conformal external beam manner to a total dose of 45-50.4 Gy. Chemoradiotherapy consisted in administration of radiotherapy concurrent with Cisplatin 75 mg/m<sup>2</sup> Day 1 + 5-fluorouracil (5-FU) 750-1000 mg/m<sup>2</sup> Days 1-4 q4w or Paclitaxel 50 mg/m<sup>2</sup> IV + Carboplatin AUC 2 IV Day 1 q1w or Cisplatin 40 mg/m<sup>2</sup> q1w. Chemotherapy used consisted in Cisplatin 75 mg/m<sup>2</sup> Day 1 + 5-FU 750-1000 mg/m<sup>2</sup> Days 1-4 q4w or Paclitaxel 175 mg/m<sup>2</sup> + Cisplatin 75 mg/m<sup>2</sup> or Carboplatin AUC 5 q3w, or for adenocarcinoma Docetaxel 75 mg/m<sup>2</sup> IV Day 1 + Cisplatin 75 mg/m<sup>2</sup> IV Day 1 + 5-FU 750 mg/m<sup>2</sup> IV Day 1-5 q4w or Epirubicin 50 mg/m<sup>2</sup> IV day 1 + Oxaliplatin 130 mg/m<sup>2</sup> IV day 1 + Capecitabine 625 mg/m<sup>2</sup> BID Day 1-21.

All eligible patients were included in the statistical calculations. The statistical analysis was performed using SPSS 17.0 for Windows. The following endpoints were analysed: progression free survival PFS, defined as the interval between the date of diagnosis and first progression of the disease or death by any cause; and overall survival OS, defined as the interval from date of diagnosis until the date of death by any cause. Survival data were calculated using the Kaplan-Meier method.

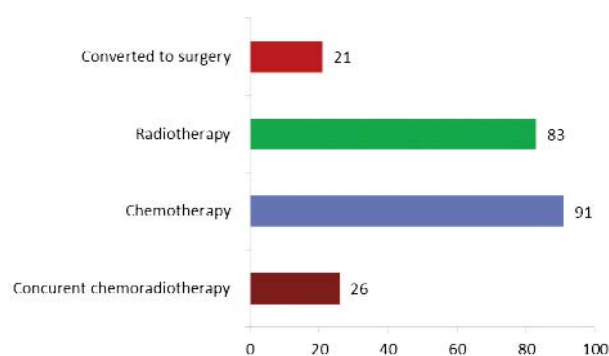
## Results

Demographic characteristics showed a higher incidence in men (78%) and median age at diagnosis was 61.5 (range 49-82). In our lot of patients, the big majority presented with squamous carcinoma (78%) and 23 % were adenocarcinoma according to biopsy. At the diagnosis 22 patients (16.6%) were stage IV and 50 (37.9%) presented with good performance status ECOG 0, 63 (47.7%) with ECOG 1 and 19 (14.4%) with ECOG 2. Patients characteristics are summarised in *Table 1*.

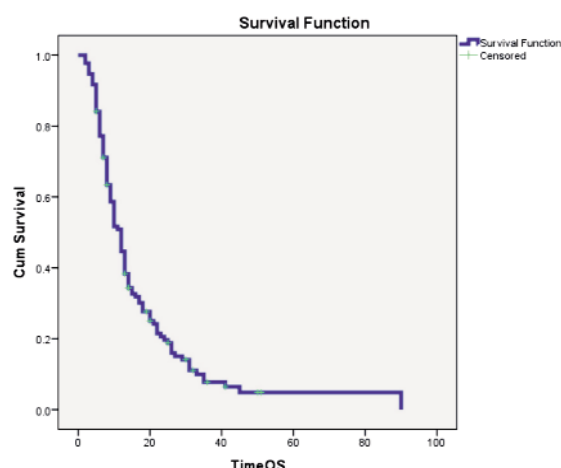
Regarding treatment modality, radiotherapy was administered in 83 (62.9%) of patients. After conversion to surgery radiotherapy was administered as adjuvant treatment in 8%. Mean dose of radiotherapy administered was 48.6Gy. Median duration of radiotherapy was

**Table 1.**

Characteristics	Number of patients (%)
Number of patients	132 (100%)
Median age (years)	60.6 (range 33-82)
Gender	
Feminin	29 (22%)
Masculin	103 (78%)
Stage	
Stage III	110 (83.3.3%)
Stage IV	22 (16.6%)
Histological type	
Squamous	53 (77.7%)
Adenocarcinoma	13 (22.3%)
ECOG	
ECOG 0	50 (37.9%)
ECOG 1	63 (47.7%)
ECOG 2	19 (14.4%)



**Figure 1.** Treatment modality



**Figure 2.** Overall survival in all patients

41 days. Concurrent chemo-radiotherapy was administered in 26 (19.7%). Chemotherapy was administered in 91 patients (68.9%). The most used regimen was 5-FU and Cisplatin in 68.1% of the patients who underwent chemotherapy. (Fig. 1). After multimodality treatment 21 (15.9%) inoperable at diagnostic patients were converted to surgery. Surgery consisted in subtotal or total esophagectomy or gastrostomy.

Eighty four percent of patients in metastatic setting received second line chemotherapy.

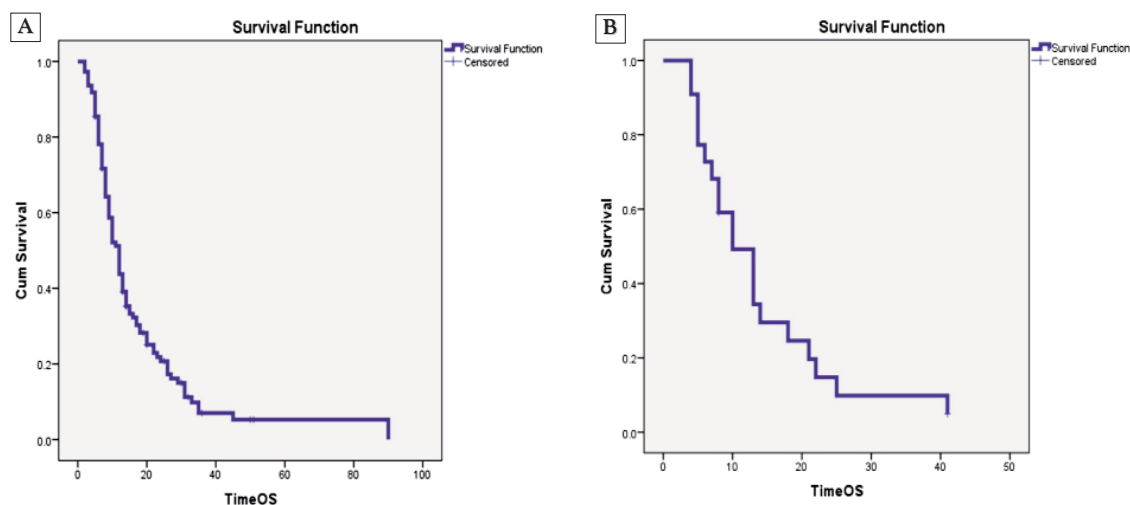
After a median follow up of 17.3 months median overall survival (OS) for the population was 12 months, with one-year survival rate of 49.2% and 2-year survival rates of 17.4%. (Fig. 2)

In metastatic patients median overall

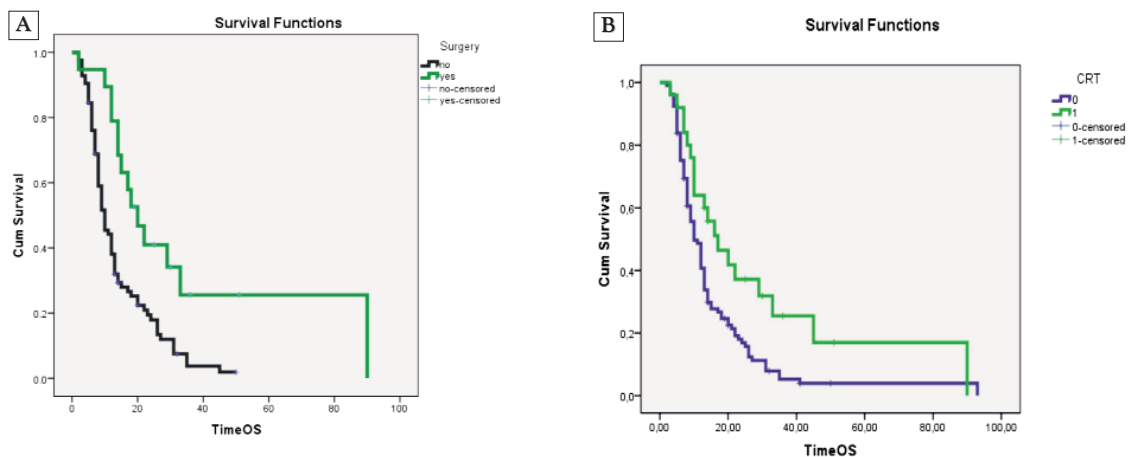
survival was 10 months and one year survival rate of 45.45% and 2 year survival rate of 13.63%. For stage III median overall survival rate was 12 months and one year survival rate of 50% and 2 year survival rate of 18.2%. (Fig. 3)

In locally advanced patients there was a clear advantage for three modality treatments. Patients who were converted to operability had a median estimated OS of 20 months compare to 10 months in patients who did not undergo surgery ( $p=0.002$ ) (Log Rank) (Fig. 4 A).

Chemo-radiotherapy was superior in terms of overall survival compare with chemotherapy



**Figure 3.** Median overall survival in stage IV (A) and III (B)



**Figure 4.** Median overall survival according to treatment (A) Benefit for adding surgery; (B) Benefit of chemoradiotherapy compare to radiotherapy alone

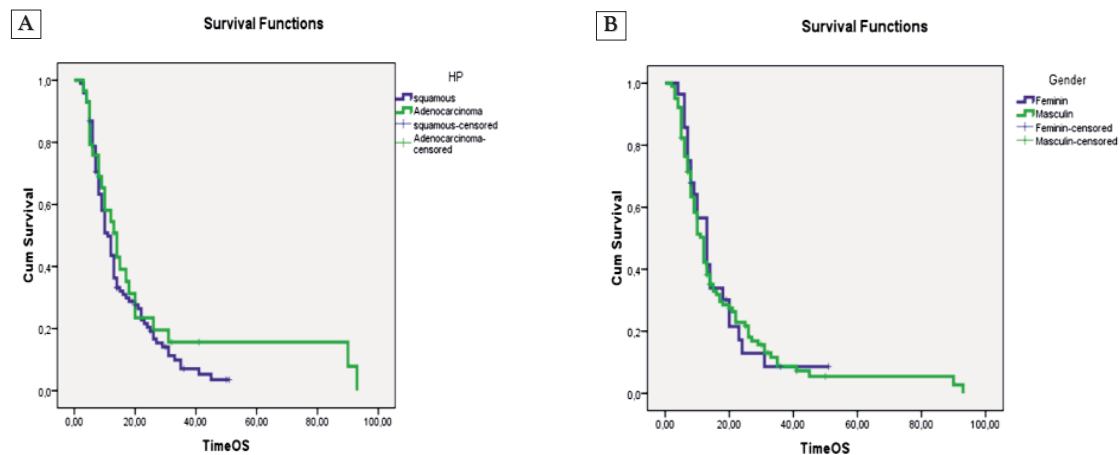
or radiotherapy administered sequential (17 months vs. 10 months),  $p=0.013$  (Log Rank). The rate of haematological toxicity (all grades according to CTCAE4) during chemo-radiotherapy was 38.4% but only 3 (11.5%) were severe (grade 3 and 4) (Fig. 4 B).

In our group of patients there was no significant difference regarding OS between genders, histological type, chemotherapy vs. radiotherapy as the first treatment choice. (Fig. 5).

## Discussions

There is no consensus regarding the treatment of patients with locally advanced and metastatic esophageal cancer and the best modality is that the treatment strategy has to be individualised and the case discussed in a tumour-board including a surgent, radiotherapist and oncologist.

In an attempt to improve the outcome of patients, considering that the relapse is



**Figure 5.** No significant difference between gender, histological type



frequently locally and distant, chemo-radiotherapy was tested in patients with locally advanced oesophageal cancer. RTOG 85-01 study (6) Herskovic included patients with squamous cell carcinoma and esophageal adenocarcinoma who were expected to receive 4 cycles of chemotherapy consisting of 5-Fluorouracil and cisplatin, concurrently with external beam radiotherapy to a total dose of 50 Gy. The control arm of the study consisted only in radiotherapy at a higher dose than in concomitant chemoradiotherapy (64 Gy). Patients who were randomized to concomitant chemoradiotherapy had an improvement in median survival (14 months vs. 9 months) and survival at 5 years (27% vs. 0%). Also, the incidence of local relapses (defined as lesion persistence or recurrence) was lower in the arm of patients receiving chemoradiotherapy (47% vs. 65%). However, chemoradiotherapy was associated with a higher rate of toxicity (Grade 3: 44% vs. 25%, Grade 4: 20% vs. 3%, Grade 5: 2% vs. 0%). (7) Escalation of the radiotherapy dose received concurrently with chemotherapy from 50.4 Gy to 64.8 Gy was tested in INT 0123 study but unfortunately there was no statistically significant differences in median survival (13 vs. 18.1 months) or 2 years (31% vs. 40%) between higher radiation doses and those who received the dose standard (8). In our lot, the patients receiving concurrent chemoradiotherapy had a significantly better overall survival compared to radiotherapy and compared to chemotherapy alone, emphasising the importance of multidisciplinary team in fit patients suitable for aggressive treatment. Unfortunately, radio-chemotherapy could be administered only in 26 patients (19.7%).

Nowadays it was attempted to incorporate in the chemoradiotherapy regimes the new compounds that proved to be effective. Thus, chemoradiotherapy with docetaxel (60 mg/m<sup>2</sup>) and cisplatin (80 mg/m<sup>2</sup>) administered at 3 weeks in combination with external radiotherapy was tested in 59 patients with esophageal squamous cell carcinoma and associated with a response rate of 98% and a 71% complete response rate, which resulted in a median survival of 23 months (9). Li

Paclitaxel and carboplatin administered in a weekly manner is another option with a better toxicity profile. In our lot of patients this treatment proved to be efficacious and well tolerated.

The best treatment strategy for the non-metastatic disease patients was to be converted to surgery. In our study 21 of 110 (19,1%) non-metastatic patients converted to surgery. In this subset of patients, median overall survival was 39 months vs. 15 month with chemo and radiotherapy. The decision and the difficulty of surgery after chemoradiotherapy is well known but the benefit of trimodally treatment is clear (10). Several meta-analyses have attempted to determine the exact benefit of radio-chemotherapy followed by surgical intervention as opposed to surgery alone. Most of the studies tested the combination of cisplatin 75 mg/m<sup>2</sup> and 5-Fluorouracil 1000 mg/m<sup>2</sup> day 1-4 or 1-5 associated with external radiotherapy (30-60 Gy) and followed 4-8 weeks after surgery. The complete pathologic response rate was between 15 and 25%, (OR = 0.53) for the combination of chemoradiotherapy and surgery, higher for patients with squamous cell carcinoma and for those receiving higher doses of radiotherapy; the rate of local and distant recurrence was lower for triple therapy (OR = 0.66 for local relapses and OR = 0.44 for distant metastases) Postoperative mortality rate was less than 10% higher for combination therapy (OR = 1.63) (11). Survival data show a benefit of approximately 10% in favor of concomitant chemoradiotherapy followed by surgical intervention as a single therapeutic approach (the 3-year mortality rate favoured triple treatment OR = 0.53 p = 0.03) (12). Also, a meta-analysis involving 1209 resected patients with esophageal adenocarcinoma and squamous cell carcinoma treated with chemoradiotherapy and 1724 surgical patients showed statistically significant survival benefit (OR = 0.81, p = 0.002), which corresponds to an absolute survival difference of 13% at 2 years (13). In 2009, Stahl publish a study that tested neoadjuvant chemotherapy followed by surgery vs. neoadjuvant chemotherapy followed by radio-chemotherapy,

followed by surgery and showed a statistically significant increase in overall survival at 3 years (27.7% vs. 47.7%,  $p=0.07$ ) (14).

A more recently analysis showed that in a group of 85 patients treated with concurrent chemo-radiotherapy, 32 were pathologically responders and 48 underwent resection. The conclusion of the study was that chemo-radiotherapy increase resectability, improves survival and does not affect postoperative complications and postoperative mortality, (15). Much effort should be made in order to identify the patients who will benefit the most from neoadjuvant chemotherapy (16).

The possibility to incorporate all this trials into clinical practice is limited by the fact that our patients especially those with squamous histology presented in very advanced stage and had a lot of comorbidities which reflects the big number of patients with ECOG 1 and 2 and the possibility to administered toxic concurrent treatment to a small amount of patients.

## Conclusion

In conclusion, concurrent radio-chemotherapy followed by surgery can be considered superior to each method as single therapy and radiotherapy and chemotherapy can make certain locally advanced esophageal tumors resectable. Multimodality treatment gives the best chance of overall survival. For metastatic patients, multiples lines of chemotherapy are feasible and provides the best outcome.

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