

# Results of transthoracic esophagectomy following chemoradiation in locally advanced esophageal cancer

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## ABSTRACT

We investigated patients treated with chemoradiation and subsequent esophagectomy. 10 patients were treated between 2004-2007. The chemoradiation regimen was concurrent 46-50 Gy radiation with cisplatin and 5-fluorouracil. Average age was 58 (31-74, 5 females). Clinical stages were T3-4N0-1M0. 9 patients completed the curative or neoadjuvant chemoradiation regimen. Pathologies were squamous cell (n=9) and adenocarcinoma (n=1). All patients underwent esophagectomy via a right thoracic approach, followed by laparotomy and cervical incision. There was no postoperative mortality. 7 patients had complications, 4 of them were major. Postoperative stages were T2N0 (n=3), T3N0 (n=3), T2N1 (n=1) and T3N1 (n=3). One patient died due to local and distant recurrence. Two patients (>70 years) died of non-cancer related causes at 2 and 8 months. Seven patients are alive without disease, 3 of them at 36, 19 and 18 months. Esophageal resection following concurrent chemoradiation is a high risk procedure that can be applied in well selected patients. [Turk J Cancer 2008;38(1):20-25]

## KEY WORDS:

Esophageal cancer, squamous cell carcinoma, transthoracic esophagectomy, concurrent chemoradiation

## INTRODUCTION

Surgical resection is the primary treatment for early stage esophageal cancer. In locally advanced stages, multimodality treatment regimens are preferred. Definitive chemoradiotherapy in locally advanced esophageal carcinoma has curative potential but, there is high local and distant failure rates following this treatment (1). Although randomized studies comparing definitive chemoradiotherapy with neoadjuvant chemoradiation followed by surgical resection, failed to show any survival benefit in the first 3 years, local recurrence and disease-free survival rates favor surgical option (2-4). Walsh and colleagues (5) published strikingly favorable survival (32% at 3 years) a decade ago in patients who underwent surgical resection following neoadjuvant chemoradiotherapy. However this study was severely criticized due to the very low survival rate in the surgery alone arm and thus could not establish standard approach. In recent years, definitive chemoradiotherapy has gained ground in the primary treatment of esophageal cancer supported by studies from continental Europe (2,3). However, several retrospective studies reveal a 5-year survival rate of 30-60% in locally advanced esophageal cancer with surgical resection following neoadjuvant chemoradiotherapy, especially in downstaged tumors (6,7).

The type of esophagectomy following chemoradiotherapy is decided according to the location and local extension of the tumor in the esophagus, postoperative reflux, extent of lymphadenectomy and surgeon's preference. In our clinic, esophagectomy routinely starts with a right thoracic approach, and is completed by a median laparotomy and cervical esophagogastrostomy via a left neck incision in the same session (8). In this study, we represent our experience with transthoracic esophagectomy and cervical esophagogastrostomy following neoadjuvant/curative chemoradiation.

## PATIENTS AND METHODS

Thirteen patients were evaluated for surgical resection following neoadjuvant or curative chemoradiation between June 2004 - July 2007. 10 patients underwent resection. Clinical staging was performed with upper gastrointestinal (GI) endoscopy, chest and upper abdominal computed tomography (CT) scans. Positron emission tomography (PET) scan was also performed when available. All patients had clinical T3-4 and N0-1 tumors. Feeding jejunostomy was placed prior to neoadjuvant treatment in some patients according to their nutritional status.

One patient underwent cervical mediastinoscopy due to a pathologic size left lower paratracheal lymph node. The pathology was benign and patient was assigned for neoadjuvant treatment due to T stage of the tumor (Figure 1).

### Technique of neoadjuvant and curative concurrent chemoradiotherapy

Radiotherapy was administered with 6 or 15 MV photons, in supine position with parallel opposed, anterior and posterior fields. Patients received 46 Gy of radiation with 2 Gy daily fractions, 5 times a week. For simulation process, pretreatment tomographic scans, endoscopic findings and barium swallow graphs were used. Treatment fields were planned to include at least 5 cm of distal and proximal ends of the tumor with 2 cm radial margins. For lymph node coverage, radiation fields also included one level above and one level below situated lymphatic regions, beside the coverage of the lymphatic region where the tumor is situated.

Concurrent with radiotherapy, cisplatin (40 mg/m<sup>2</sup> per week) was administered weekly starting with the first day of radiation and continued throughout the whole radiation treatment duration. UFT 300 mg/m<sup>2</sup> was administered orally, divided in two daily doses, for five days from Monday to Friday, starting on the first day, and ending on the last day of radiation. All patients were planned to undergo surgical resection 4-8 weeks after the completion of concurrent chemoradiotherapy.

Some patients received curative radiation dose of 50 Gy and cisplatin due to their rejection of surgery as the primary treatment.

### Preoperative evaluation

All patients underwent clinical re-staging with upper GI endoscopy, thoracic and upper abdominal CT scans

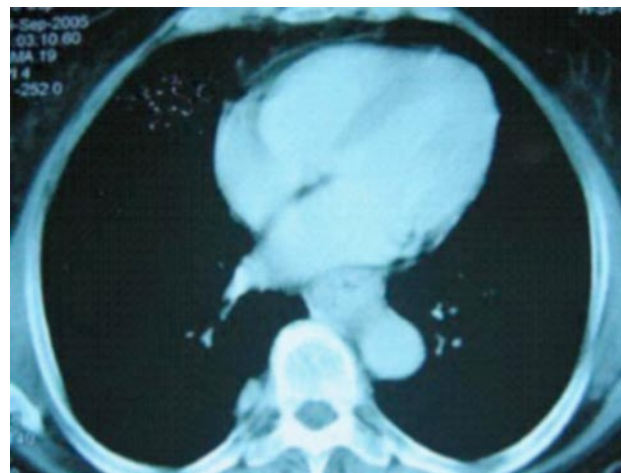


Fig 1. The tumor in the esophagus was completely invading the esophageal wall in the initial evaluation

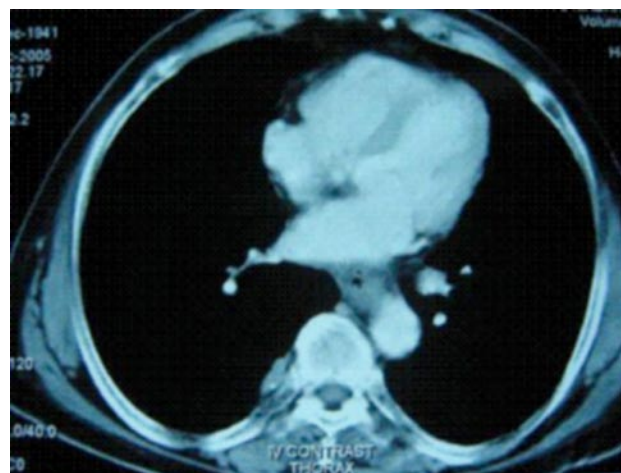


Fig 2. Following neoadjuvant treatment there was significant radiologic and clinical response. The histology of the tumor was squamous cell carcinoma and pathologic stage was T3N0

**Table 1**  
**Patient characteristics and results of surgical resection**

Age	Gender	Histology	Tumor sizes (cm)	Radiation dose (cGy)	Chemo-therapy cycles	Pathologic stage	Complications	ICU stay	HS	Status	Survival (mo)
57	Female	SCC	29	4600	2	T3N1M0	Intraoperative left bronchus injury, left pleural effusion	3	10	DOD	12
32	Female	SCC	35	4600	2	T3N0M0	None	2	8	AWOD	36
74	Female	SCC	33	4600	2	T2N0M0	Left pleural effusion	2	10	DOC	2
73	Male	SCC	31	2200	1	T3N1M0	Atrial flutter, delirium	3	11	DOC	8
65	Female	SCC	27	4600	2	T3N0M0	None	3	10	AWOD	19
65	Male	Adeno	35	4400	2	T3N1M0	Re-exploration for bleeding	2	10	AWOD	18
58	Male	SCC	35	4600	2	T2N0M0	Anastomotic leak, pneumonia	2	20	AWOD	6
49	Male	SCC	38	5000	6	T2N0M0	Chylothorax, RLNI	5	15	AWOD	4
53	Female	SCC	29	5000	6	T2N1M0	Pulmonary emboli, respiratory failure	19	36	AWOD	2
54	Male	SCC	38	5000	6	T3N0M0	None	2	13	AWOD	1

SCC: Squamous cell carcinoma; Adeno: Adenocarcinoma; RLNI: Recurrent laryngeal nerve injury; ICU: Intensive care unit; HS: Hospital stay; DOD: Dead of disease; DOC: Dead of other cause; AWOD: Alive without disease

after neoadjuvant treatment. Additionally, 5 patients had upper abdominal ultrasonography, 4 had bone scans and 1 had an upper GI endoscopic ultrasonography. 4 patients who had PET scan did not undergo bone scans and upper abdominal ultrasonography. Patients who had stable or regressed tumor that were amenable for surgical resection and patients who gave consent for surgery underwent resection.

Other than routine radiologic and biochemical investigations, all patients underwent pulmonary function tests, electrocardiography and echocardiography to assess ventricular ejection fractions.

#### **Technique of surgical resection (8)**

Right thoracic exploration was performed in left lat-

eral decubitus position in all patients. Thoracic esophagus was mobilized from diaphragmatic hiatus to sternoclavicular junction en bloc with neighboring lymph nodes in 8 patients via right thoracoscopy. Thoracoscopic mobilization of the esophagus was attempted in 2 patients, but a thoracotomy was performed in one of them due to dense fibrotic adhesions between esophagus and posterior pericardium. All patients then underwent a median laparotomy and left cervical incision. A 4-5 cm wide great curvature tube supplied by right gastroepiploic artery was prepared from the stomach. Following transection of the esophagus in the cervical area the esophagectomy and proximal gastrectomy specimen was delivered from the abdomen and great curvature tube was anastomosed to the remaining esophagus in the left cervical area. Gastro-

esophageal anastomosis was performed on the posterior wall of the conduit with full thickness separate 3/0 silk sutures. Heineke-Mikulicz pyloroplasty was performed in the first 3 patients and no pyloric drainage procedure was performed in the last 7 patients. Feeding jejunostomy was placed in 7 patients at the same session.

Oral intake was started on postoperative day 7 following a control barium swallow study. Patients were scheduled for follow-up every 3 months in the first 2 years and every 6 months afterwards.

## RESULTS

Patient characteristics and tumor stages are presented in table 1. Average age was 58 (32–74). 9 patients completed the curative (n=3)/neoadjuvant (n=6) chemoradiation. The treatment was halted due to treatment toxicity in one patient. The average time period between completion of neoadjuvant treatment and surgical resection was  $7.6 \pm 1.7$  weeks. In 3 patients, salvage esophagectomy was performed following 12, 33 and 110 weeks after curative chemoradiation.

Four patients had comorbidities prior to surgery. Two patients over the age of 70 had prior cerebrovascular accident. One of them had diabetes and the other hypertension. Two patients had diffuse pleural adhesions and plaques due to previous tuberculosis infection. Median preoperative weight of the patients was 53 kg (40–63). Patients were ex-smokers (n=7), never-smokers (n=2) and active smokers (n=1). Average FEV1 was  $83 \pm 22\%$ .

In 5 patients, radiologic response was observed following neoadjuvant treatment (Figure 1), in the other 2 patients, there was no response to preoperative treatment. Patients who had curative chemoradiation had recurrent tumor on CT and PET scans.

There was no in-hospital or 30-day mortality. Early complications are listed in table 1. Three patients developed anastomotic stricture and 2 patients required bougie dilatation twice and 1 patient was dilated once. Dysphagia symptoms were relieved following dilatation. One patient developed a tracheoesophageal fistula 10 days after bougie dilatation and was successfully managed with esophageal stent placement.

Pathologic stages of the patients are shown in table 1. In 2 of the patients extracapsular lymph node invasion was noted. In 3 patients, only 1 lymph node and in one patient, 3 lymph node metastasis were found.

The patient who eventually died of disease recurrence developed a bone metastasis 4 months postoperatively. 2 elderly patients died of non-cancer related causes, one due to major depression and cerebrovascular accident at second month and the other due to dementia, cerebrovascular accident and pulmonary complications at 8th month postoperatively.

## DISCUSSION

Different approaches exist for the treatment of locally advanced esophageal cancer. While North American centers prefer surgical resection following neoadjuvant chemoradiation, European centers prefer definitive chemoradiation.

Although, recent studies showed no superiority of these treatments to each other, fewer local recurrences and longer disease-free survival are observed in patients undergoing surgical resection (3,5,9). Several factors are shown to influence survival following resection of esophageal tumors. Among the most important ones are: involvement of lymph nodes, more than 4 lymph nodes involved, involvement of lymph nodes distant from the primary tumor and extracapsular nodal invasion (10-12). Lerut and his colleagues (12) in their 195 esophageal cancer patients showed that even after complete resection of esophageal tumors with extracapsular lymph node invasion 5-year survival rate was only 18%, while the 5-year survival rate was 57% in patients with no lymph node involvement.

Neoadjuvant treatment is the preferred treatment modality of clinical T3-T4 tumors with or without locoregional lymph node involvement. This treatment modality can cause regression or even tumor sterilization, and thus can increase the rate of complete surgical resection. A recent randomized study from Australia showed that while complete resection rate following neoadjuvant treatment was 80%, it was only 59% in patients who directly underwent surgery ( $p=0.0002$ ) (4). The number of involved

lymph nodes was found to be less in the neoadjuvant treatment group (43 vs. 67%,  $p=0.003$ ).

Complete pathologic response rate that can be achieved in esophageal cancer treated with neoadjuvant concurrent chemoradiation is nearly 25 to 30% (7-9, 13). In 5 of our 7 patients (neoadjuvant chemoradiation), a clinical response (Figure 2) was observed. 3 additional patients who completed the neoadjuvant treatment did not undergo surgical resection; due to development of lymphatic metastasis in posterior cervical chain ( $n=1$ ), patient denial following a complete clinical response ( $n=1$ ) and social security problems ( $n=1$ ).

Re-staging following neoadjuvant treatment is also controversial. Although invasive staging with endoscopic ultrasound biopsies, videothoracoscopy and laparoscopy provide useful information, clinical applicability of these methods for the patient, surgeon and clinician is cumbersome (14). We re-stage our patients with radiologic methods. PET and PET-CT provide useful information about the T, N and M status of the patient, however their sensitivity is lower if the size of the lymph nodes are less than 1 cm in diameter (15).

There are several factors that influence the technique of esophageal resection following neoadjuvant chemoradiotherapy. The tumors in our patients were located at the mid-lower 1/3<sup>rd</sup> of the esophagus, thus we preferred a right thoracic approach and finalized the operation with laparotomy and left cervical anastomosis. Our choice was due to the considerations like, performing the anastomosis in a non-radiated field, performing a less morbid cervical rather than thoracic anastomosis, minimizing postoperative reflux with a high anastomosis, achieving lengthy proximal-distal margins to increase chances of complete resection and finally sampling and dissecting intrathoracic

lymph nodes. We were able to achieve complete resection in all of our patients. The surgical resection following neoadjuvant treatment is usually proposed 4-8 weeks following completion of the treatment. Our data was concordant with this with an average of  $7.6\pm 1.7$  weeks.

Preoperative chemoradiotherapy is believed to increase postoperative morbidity and mortality. However, in experienced centers with large patient series, morbidity and mortality rates are acceptable. Esophagectomy mortality rate following neoadjuvant treatment was 9-10% in randomized studies from France and Germany (2,3). In series from Australia and USA, mortality rates are usually below 5% (4,6,9,16). The high mortality rates following neoadjuvant chemoradiotherapy in the European randomized studies could well be the reason for lack of any survival advantage. Treatment related complications and postoperative mortality are adversely affected in patients with poor nutritional status prior to treatment, thus instituting an enteral route (preferably a feeding jejunostomy) prior to treatment is strongly advocated (17). In a study from Turkey, 13 patients with esophageal cancer received neoadjuvant chemotherapy. There was one treatment related mortality and 2 postoperative mortality in 8 of the patients who underwent resection. They concluded that the use of neoadjuvant chemotherapy in esophageal cancer may be harmful (18).

The use of preoperative chemoradiation in esophageal cancer is still under debate (1,19). Long-term survival (>50% 5 year survival) can be achieved with good patient selection and appropriate surgical treatment in patients without lymph node involvement (20).

In conclusion, our limited experience shows that esophagectomy following chemoradiation can be performed in a well-selected patient group and lead to long-term survival.

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