

## Non-surgical Treatments of Esophageal Cancer

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### ABSTRACT

Esophageal cancer is one of the most common malignancies with a growing occurrence. It presently ranks ninth among the most frequent cancers in the world and the sixth leading cause of death from cancer. For a variety of reasons, the mainstream of patients with esophageal cancer is actually not suitable for Esophagectomy. More than 50% have locally advanced unresectable or metastatic tumors at diagnosis. Other reasons which exclude Esophagectomy include old age, comorbidity or refusal by the patient. For more advanced stages of esophageal cancers, the basis of non-surgical treatment is chemotherapy (CT) or radiotherapy (RT), either alone or in combination as chemoradiotherapy (CRT). The purpose of this study is to summaries and judgmentally analyzes current non-surgical treatments. Although the best treatment for locally advanced esophageal cancer is still being debated, the use of neoadjuvant chemoradiotherapy has gained acceptance.

**Keywords:** Esophageal cancer; Radiation therapy; Neoadjuvant chemoradiation; Definitive chemoradiotherapy

### INTRODUCTION

Esophageal cancer (EC) has been informed as the eighth most common cancer and the sixth most lethal cancer worldwide [1]. In 2012, 400,000 patients died from esophageal cancer globally [2]. In the United States, EC is in charge for more than 4% of annual cancer-related deaths and an estimated 16,980 cases of esophageal cancer were diagnosed in 2014, with 15,590 deaths per year expected from the disease [3]. Institute of Public Health Research of Tehran University (IPHR) and the International Agency for Research on Cancer (IARC) have publicized that North-eastern Iran is a very high occurrence region for esophageal cancer [4-7]. There are two histological types of esophageal cancer with different pathologic features: esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC). Squamous-cell carcinoma ascends from the epithelial cells that line the esophagus. Adenocarcinoma arises from glandular cells

existing in the lower third of the esophagus, often where they have already converted to intestinal cell type (a condition known as Barrett's esophagus) [8]. Squamous-cell carcinoma is linked to lifestyle factors such as smoking and alcohol while the occurrence of AC has been expanding due to a dramatic rise in the percentage of overweight and obese people leading to increases in gastro esophageal reflux disease [9] and this histological type has greatly increased in the last decade in several European countries and in the United States [10]; Tobacco is a risk factor for both types [11].

Selection of treatment scheme depends mainly on the patient's performance status, stage or extent of the disease, histology, and position of the primary tumor. The main curative treatment modalities are surgery and concurrent radiotherapy and chemotherapy [12].

Managing of locally advanced esophageal tumors has moved from surgery alone to multimodality approaches [13]. Over the last 20

years, there has been a development in using combined chemotherapy with radiation therapy. For most of the patients suffering advanced illness, curative treatment left overs to be a challenge. To improve the deprived outcomes of locally advanced esophageal cancer, many treatment modalities have been attempted such as addition of adjuvant radiotherapy and/or chemotherapy, neoadjuvant radiotherapy and/or chemotherapy, and definitive chemoradiotherapy (CRT) with various radiation doses and techniques. Consequently multimodal therapies, including chemotherapy and radiotherapy were presented. This review summaries and judgmentally analyzes current non-surgical treatments.

### ***Treatment of locally advanced esophageal cancer***

#### ***Radiation Alone***

Currently, radiotherapy is one of the chief, effective and relatively inoffensive curative modalities for esophageal carcinoma. It could be used for early stage and advanced diseases, and as a locally palliative treatment for metastatic disease. Radiotherapy is one of the main palliative approaches in patients with dysphagia [14]. It has been used definitively, both preoperatively and postoperatively. Definitive radiation results in poor local control and poor survival. Numerous studies looking at external-beam radiotherapy treatment alone found significantly low 5-year survival rates ranging from 0 % to 21 % [15-18]. Earlam and Cunha-Melo reviewed 49 series with 8,489 patients treated with radiation alone and found the survival rates to be 18% at 1 year, 8% at 2 years, and 6% at 5 years [19]. Recent clinical trials have shown radiotherapy as a singular modality to be lower advantageous than chemoradiation. In conclusion, radiation alone should only be considered for palliative treatment and should not be considered for curative intent [20]. But, patients who are unfortunate surgical risks and are incapable to bear chemotherapy, occasionally will need to be managed with radiation therapy alone with a small but real chance of survival.

### ***Principles of Radiation Therapy Planning***

Although radiotherapy has a clear role in the management of esophageal carcinoma, the challenge is in delivering the radiation dose precisely to minimize normal tissue toxicity. Radiotherapy for carcinoma of the esophagus presents a particularly difficult treatment planning problem. The planning target volume (PTV) is central, close to the spinal cord, and is almost completely surrounded by lung, a radiosensitive organ with a relatively low radiation tolerance [21] and definitions of the primary site of esophageal cancer and metastatic lymph nodes are essential [22]. Patient positioning in the lying position is preferable in thoracic lesions and is likely to move the esophagus further from the spinal cord. If the tumor is in the distal third or the celiac nodes are histologically or clinically positive, the target volume is enlarged to include this nodal volume. Doses to the spinal cord, heart, lungs, liver, and kidneys must be kept within the tolerance limits to reduce morbidity [15]. Three-dimensional conformal radiotherapy (3DCRT) improves the dose distribution in lesions and thereby allows significant increase of target dose and decrease of organ at risk (OAR) doses. A wide range of doses has been used with radiotherapy alone and will be a function of the tumor location and the normal tissue tolerance.

### ***Chemotherapy***

The disappointment of surgery to medications in localized esophageal cancer is as a consequence of the great number of lymph node involvement and distant metastases before symptoms happen. Preoperative (neoadjuvant or induction) chemotherapy has been used in an attempt to decline tumor activity, increase resectability and improve disease-free and overall survival. Chemotherapy drugs come into bloodstream and spread in the body, so it is valuable for extended cancers. Depending on the type and stage of esophageal cancer, Fluorouracil, also called 5FU, Capecitabine, also called Xeloda (X), Cisplatin, or sometimes carboplatin is used. Polee et al [23] have evaluated a biweekly combination of cisplatin

and paclitaxel in a phase II study, with hopeful results. Objective responses occurred in 59% of patients (total no. of 49), with median survival of 20 months and 32 months in patients who had disease responsive to chemotherapy; the 3-year survival rate was 32%.

The two almost the same trials were done; Allum WH [24] used 2 cycles of cisplatin and 5FU, and the Kelsen DP [25] used similar drugs but with 3 cycles. Allum WH experimental stated a positive outcome from pre-chemotherapy, but Kelsen DP reported that preoperative chemotherapy with a mixture of Cisplatin and fluorouracil did not improve overall survival between patients. However, in spite of the differing outcomes in those two trials, the most current pre-chemotherapy trials announce positive results [26, 27]. Data suggest that managing systemic chemotherapy prior to surgery for esophageal cancer increases survival compared to surgery alone [28, 29] and that the addition of simultaneous radiotherapy improves therapeutic yield, increases rates of pathologic complete response, decreases rates of local tumor recurrence and improves survival rate [30-32].

#### ***Definite Chemoradiotherapy***

The combined use of radiation therapy and chemotherapy in cancer treatment is a rational and functional approach that has already established favorable for several malignancies. Local control of the primary tumor mass (which can often be achieved by high-dose radiation), combined with systemic chemotherapy to control metastatic disease, should provide effective means to contest such a highly complex disease [33]. Many chemotherapy drugs which enhance effects of radiation provide even more impetus to integrate both modalities. The Radiation Therapy Oncology Group (RTOG) 85-01 trial was a randomized controlled comparison of definitive radiotherapy alone (64 Gy), and definitive concurrent chemoradiation (50 Gy delivered concurrently with 5-fluorouracil [5-FU] and Cisplatin). A statistically significant benefit was noted for overall survival among patients receiving concurrent chemoradiation [34, 35]. This study, however, was done in the 1980s when staging did not require CT scanning, which might have led to difference between study

groups. A follow-up trial (RTOG 94-05) compared chemoradiotherapy regimens with radiation doses of 64.8 Gy or 50.4 Gy. The addition of chemotherapy increased the median survival from 8.9 to 12.5 months. The 2-, 5- and 8-year overall survival was 38%, 27% and 22%, respectively in the combined therapy group; while the 2-year overall survival was only 10% in the patients given radiotherapy alone, and none survived 5 years [35]. On the basis of these results, 50.4 Gy is the standard dose used in the USA [1, 36]. It has confirmed that chemoradiotherapy is superior to radiotherapy in localized carcinoma of the esophagus [37]. All of these studies report a greater average existence in the chemoradiation arm vs. radiation alone. Thus, definitive chemoradiation vs. radiation alone seems to offer better therapeutic result. Moreover, proofs have confirmed that long-term outcomes after definitive chemoradiotherapy for stage I-III esophageal cancer is comparable to that following Esophagectomy [38, 39].

Chan, et al [40] indicated that in 82 patients undergoing definitive CRT, 5-year overall and disease-free survival was 25% and 23% versus 23% and 21% in 81 patients receiving surgery alone; no statistical difference was originate between the two groups. To put it briefly, definitive chemoradiotherapy is an upright substitute plan for patients with esophageal cancer who are not appropriate for surgical resection.

#### ***Adjuvant Chemoradiotherapy***

Adjuvant chemoradiotherapy is part of a multimodality treatment method so as to develop existence results after surgery in esophageal cancer. From the INT 0116 study [41], adjuvant chemoradiotherapy was established as the standard treatment in patients with node-positive AC of the gastroesophageal junction(GEJ ). This trial casually allocated 556 patients resected GEJ or stomach AC following surgery to either observation or adjuvant therapy with 4 monthly cycles of bolus 5-fluorouracil (5-FU) and leucovorin combined with radiation to 45 Gy in 25 fractions. With a median follow-up period of 5 years, the 3-year survival rate was 50% in the CRT group vs. 41% in the surgery alone group

( $P=0.005$ ). A Chinese study of stage II and III SCC of the esophagus was piloted where patients were randomly divided into three groups; surgery alone, preoperative chemoradiation and postoperative chemoradiation and OS was significantly better in patients treated with postoperative and preoperative chemoradiation compared to surgery alone [42]. However, a randomized trial of Tachibana et al failed to show a continued existence advantage of adjuvant chemoradiotherapy compared to adjuvant chemotherapy [43]. Based on the beyond trials, the patients probably benefit from postoperative chemoradiation will have either positive lymph nodes or positive margins.

#### **Neoadjuvant Chemoradiation**

Neoadjuvant methodologies purpose to enhance existence level by downstaging the tumor and annihilate micro metastatic disease at prompt stage. A neoadjuvant CRT method to the administration of esophageal cancer has several benefits over postoperative treatment. Patients will endure treatment better preoperatively, as they are not subject to the extended physiological recovery post-Esophagectomy. Several randomized trials determine the benefits of neoadjuvant chemoradiotherapy [31, 42, 44, 45]. The earliest trials of preoperative chemoradiation were based on the success of treating anal carcinoma. Franklin et al [46] treated 30 patients with 30 Gy/3 weeks concurrent with 5-FU (days 1-4 and 29-32) and Mitomycin C (day 1) followed by surgery (day 49-64). Postoperatively, 20 Gy was delivered to patients with residual disease. Follow-up revealed that four of the six histologically negative disease-free patients were alive for 95 to 190 weeks. One of the patients who refused surgery after radiation and chemotherapy was alive at 4 years. In Walsh TN et al study [47], patients received either surgery alone or two courses of neoadjuvant chemotherapy (Cisplatin/5-FU) with concurrent RT 40 Gy, 2.67 Gy per fraction. A statistically significant survival benefit was noted for the chemoradiation group with a median survival of 16 months vs. 11 months based on the intent to

treat analysis and 32 months vs. 11 months based on an analysis of actual treatment received. Three-year survival was also statistically significant favoring the chemoradiation arm (32% vs 6%,  $p=0.01$ ). In Dutch CROSS trial [48], 366 patients were randomized to neoadjuvant CRT with 5 weekly cycles of paclitaxel (50 mg/m<sup>2</sup>) and carboplatin (AUC 2) combined with concurrent radiotherapy (41.4 Gy in 23 fractions) or surgery alone. Both the median survival and overall survival was higher in the CRT group (49.4 versus 24.0 months,  $P=0.003$ ).

Meta-analyses also propose the valuable effects of neoadjuvant chemoradiotherapy. Urschel [49] and Fiorica [50] distinctly analyzed 6 identical randomized controlled trials comparing preoperative radiochemotherapy plus surgery with surgery alone for esophageal cancer. They found that a complete pathological response to chemoradiotherapy occurred in 21% of patients. Compared with surgery alone, neoadjuvant chemoradiotherapy significantly improved 3-year survival and reduced locoregional cancer recurrence ( $p = 0.016$ ).

## **RESULTS**

Numerous tactics have been attempted over the last couple of decades to treat patients with carcinoma of the esophagus in order to decrease the local tumor burden and treatment of micrometastatic disease. In table 1 several meta-analyses have been showed to determine the survival benefit of these treatments for esophageal cancer. These contain several combinations of radiation therapy, surgery, and chemotherapy. Chemoradiation has shown expectant results and seems to be superior to radiation therapy as the sole modality. Radiation therapy offers important palliation in patients with inoperable disease and is particularly beneficial in such a setting. There is a requirement for registering patients in sufficient numbers in prospective clinical trials that will allow clinicians to be able to describe the ideal sequencing and actual necessity of each individual module of mutual-modality therapy.

**Table 1.** Randomized trials on esophageal cancer therapy

Study	Treatment Modality	Chemotherapy Regimen	Radiotherapy Regimen	No. of Patients	Median Survival (months)	3-yr Overall Survival (%)	5-yr Overall Survival (%)	Definitive/Palliative treatment
Schlag [51]	Chemotherapy + Surgery	3 x Cis/5FU	-	46	10	n/s	n/s	Definitive
Boonstra et al [52]	Chemotherapy + Surgery	2 x Cis/etoposide	-	169	16	17	n/s	Definitive
Allum et al [53]	Chemotherapy + Surgery	2 x Cis/5FU	-	802	17	n/s	23	Definitive
Maipang et al [54]	Chemotherapy + Surgery	2 x Cis/vinblastine bleomycin	-	46	17	36	n/s	Definitive
RTOG 8501[35]	Radiotherapy alone	-	64 Gy/6.4 wks	60	9.3	n/s	0	Palliative
Jun et al [55]	Radiotherapy alone	-	70 Gy/35 fractions	110	n/s	24	17	Definitive
Walsh [47]	Neoadjuvant Chemoradiation	Cisplatin/5-FU	40 Gy/3 wks	58	16	32	n/s	Definitive
vanHagen [48]	Neoadjuvant Chemoradiation	Carboplatin/paclitaxel	41.4 Gy/4.5 wks	175	49.4	n/s	47	Definitive
Mariette[56]	Neoadjuvant Chemoradiation	Cisplatin/5-FU	45 Gy/5 wks	97	32	n/s	48.6	Definitive

Abbreviations: 5FU=5 fluorouracil, Cis=Cisplatin, n/s=not significant, wks=weeks

## CONCLUSION

In conclusion, patients with esophageal cancer who do not experience Esophagectomy will generally benefit from CRT.

The data that support the use of radiation alone for curative intent are limited and definitive chemoradiation is a respectable strategy for the treatment of locally advanced unresectable

esophageal cancer, but local control leftovers a problem, and it is necessary to explore potential ways of improving local control.

Neoadjuvant chemoradiation provides a significant benefit over surgery alone for esophageal cancer and it remains the standard non-surgical treatment for more advanced stages of esophageal cancers.

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