

Treatment Results and Prognostic Factors for Advanced Squamous Cell Carcinoma of the Larynx and Hypopharynx Treated with Concurrent Chemoradiotherapy after Induction Chemotherapy

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Abstract: Objective: This phase II prospective study was performed to assess the treatment outcomes and safety of induction chemotherapy (IC) by docetaxel, cisplatin and 5-fluorouracil (5-FU) followed by concurrent chemoradiotherapy in locally advanced laryngeal and hypopharyngeal squamous cell carcinoma (SCC) in our department. **Methods:** Patients diagnosed with locally advanced SCC of the larynx and hypopharynx who were attended from February 2010 to April 2014 underwent 3 cycles of IC at a dose of 75mg/m² docetaxel D1, 100mg/m² cisplatin D1, 1000mg/m² 5-FU D 1-4 every 3 weeks for 3 cycles followed by concurrent radiotherapy and weekly cisplatin 30mg/m². **Results:** Thirty patients were evaluated in the study. The median duration of follow-up was 18 months. The median age at diagnosis was 51 years and stage IV was 73%. After sequential therapy, a complete response and partial response was seen in 9 (30%) and 12 (40%) patients respectively. The overall response rate was 70%. Median survival and median progression-free survival (PFS) were 17 & 8 months respectively. Grade 3-4 neutropenia and anemia occurred in 40% and 10% respectively. Prognostic factors for PFS were T3 & N0-1 stage and laryngeal site. **Conclusion:** TPF induction chemotherapy followed by concurrent chemoradiotherapy showed a high response rate and Progression-free survival in Egyptian patients with locally advanced laryngeal and hypopharyngeal cancer. A significant longer PFS was achieved in patients with stage III laryngeal cancer.

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1. Introduction

Patients with laryngeal and hypopharyngeal cancer (LHC) represent an important subgroup of head and neck cancers sharing similar treatment concerns and overlapping clinical management strategies¹. More than 50% of patients with newly diagnosed LHC have locally advanced stage III or IV disease and are at high risk for laryngectomy and mortality. Clinical trials aimed at modifying these two outcomes by finding that alternatives to surgery have only been modestly successful. Advances in chemotherapy and radiotherapy have improved locoregional control and reduced the rate of laryngectomy, while maintaining but not improving survival in operable LHC². Other trials established cisplatin and fluorouracil (PF) induction chemotherapy and cisplatin based chemoradiotherapy as acceptable treatments for avoiding laryngectomy in operable LHC³. Although PF improves survival compared with surgery and / or radiotherapy in locally advanced head and neck cancer and is considered the standard of care for induction chemotherapy, the addition of docetaxel to cisplatin and fluorouracil (TPF) has further improved outcomes⁴. TPF induction chemotherapy significantly

improves survival and also significantly improves functional laryngeal preservation (FLP) defined as being alive without laryngectomy, gastric tube or tracheotomy⁵. Also TPF induction chemotherapy followed by chemoradiotherapy reduces the risk of death and risk of disease progression compared with PF followed by chemoradiotherapy in patients with operable tumors, operable with a low likelihood of cure, or inoperable tumors rather than radiotherapy alone⁶. The aim of the study was to assess the response rate, survival and toxicities of induction chemotherapy with docetaxel, cisplatin and 5-fluorouracil followed by concurrent chemoradiotherapy in Egyptian patients with locally advanced laryngeal and hypopharyngeal squamous cell carcinoma. Secondary objective was to define prognostic factors affecting survival in patients treated with concurrent chemoradiation after induction chemotherapy.

2. Materials and methods

2.1. Design and setting

This phase II prospective study was conducted in clinical oncology department, Assiut University

Hospital between February 2010 and April 2014 on previously untreated patients with locally advanced squamous cell carcinoma of the larynx and hypopharynx. The study was designed to have a minimal evaluable sample size of 30 patients according to the incidence of locally advanced laryngeal and hypopharyngeal cancer in our department. The protocol of the study was approved by the Ethics Committee of Faculty of Medicine, Assiut University, Assiut, Egypt before patients inclusion. The study was conducted in accordance with the Declaration of Helsinki. A written informed consent was obtained from all patients.

2.1. Inclusion criteria

The followings were set as the eligibility criteria: All patients had a Biopsy proven squamous cell carcinoma stage III or IVA according to the American Joint Committee of Cancer (AJCC) staging system 2010⁷ of the larynx and hypopharynx. Patients were eligible if the tumor was unresectable or the patients was a candidate for organ preservation, Patients had to be with an Eastern Cooperative Oncology Group performance status of 0 to 2, adequate bone marrow, kidney and liver function profile and had no prior surgery, chemotherapy or radiotherapy.

2.2. Exclusion criteria

The exclusion criteria were:

- 1) Evidence of distant metastasis.
- 2) Previous irradiation for head and neck tumors or previous chemotherapy.
- 3) Patients with other malignancy.
- 4) Major medical illness, hepatic or renal disease which would interfere with either completion of therapy or follow up.
- 5) Pregnant or lactating woman.

2.3. Pretreatment evaluation

The followings considered the pretreatment evaluation:

- 1) Complete medical history including onset, course and duration of the present symptoms, history of smoking or alcohol intake.
- 2) Clinical examination and scoring of performance status.
- 3) Ear, nose and throat (ENT) examination including examination and evaluation of masses in the neck. Fibroptic laryngopharyngoscopy and biopsy.
- 4) Dental consultation was done to all patients before treatment.
- 5) Complete blood picture (CBC), liver function tests and kidney function tests.
- 6) Radiological studies: chest x-ray and CT scan of the primary site and neck.
- 7) Nutritional care, the patients were advised to avoid spicy foods, very hot and cold drinks as well as solid and sour nutrients. Adequate nutrition by

frequent meals, diet supplement and high-calorie intake was supplied to all patients.

2.4. Treatment Design

A) Induction chemotherapy:

1) Docetaxel 75 mg/m² was administered as a 1 hr. I.V. infusion, followed by Cisplatin 100 mg/m² I.V. infusion administered during a period of 0.5-3 hours. After completion of cisplatin infusion, fluorouracil 1000 mg/m²/day was administered as a continuous 24 hour infusion for 4 days.

2) Dexamethasone 16 mg I.V bolus was given before docetaxel to prevent hypersensitivity reactions.

3) Routine hydration and diuresis were given before cisplatin administration and I.V. hydration 24 hours after the drug was given.

4) Antiemetic prophylaxis consisted of 8mg ondansetron given I.V bolus as a premedication measure 30 minutes before chemotherapy.

5) Complete blood picture and serum urea and creatinine were done every 3 weeks before each chemotherapy cycle.

6) Induction chemotherapy was given every 3 weeks for 3 cycles, unless there was disease progression or unacceptable toxic effects.

B) Chemoradiotherapy:

All patients were assigned to receive chemoradiotherapy beginning 3 to 8 weeks after the third cycle of induction chemotherapy. Weekly cisplatin at a dose of 30 mg/m² was administered as an I.V infusion during a 1 hour period for a maximum of seven weekly doses during the course of radiotherapy.

2.5. Radiotherapy

Treatment was delivered with linear accelerator machine 6 MV. Conventional two-dimensional radiotherapy was planned for all patients using simulator and appropriate immobilization using the thermoplastic mask and treated with shrinking field technique. All patients were treated with bilateral opposing portals to the primary sites and regional lymphatic area. For patients who had lymph node metastases, the lower neck region and supraclavicular fossae were irradiated with a total dose of 40Gy using an anterior single port. Patients who responded to induction chemotherapy, tumor volume should be based on the initial pattern of the disease. Lymph node metastases at presentation should be considered even if they are not enlarged after induction chemotherapy. Electron beams were used to boost the dose delivered to the posterior cervical lymph nodes. Spinal cord shielding was applied after 40Gy. The prescribed dose to the primary lesion and the involved nodal disease was 70Gy in 35 fractions. Uninvolved areas were electively treated with a total dose of 50Gy. All fractions were given as 5 fractions per weeks, 2Gy per fraction, one fraction per day.

2.6. Evaluation of response and toxicity

1) Tumor responses were assessed by ENT examination and CT scan of the primary tumor and neck 3 weeks after the end of induction chemotherapy and 4-6 weeks from the completion of radiotherapy.

2) Fiber optic endoscopy and biopsy from the primary site was taken for cytological examination 4-6 weeks after radiotherapy.

3) Assessment of response was characterized according to the Response Evaluation Criteria in Solid Tumors (RECIST)⁸: Complete response, partial response, stable disease and progressive disease.

4) Evaluation of the disease was done monthly by physical examination, monitoring of toxicity and CT scan every 3 months until disease progression, death or lost follow-up.

5) Toxic effects were assessed weekly during chemotherapy and radiotherapy and after completion of chemoradiotherapy by using common toxicity criteria of the National Cancer Institute version 4.0⁹.

6) Dose modifications were determined by hematological or non-hematological toxicities. The dose of docetaxel was reduced after grade 4 neutropenia lasting more than 5 days or grade 4 thrombocytopenia. The cisplatin dose was reduced 75% of the original dose in subsequent cycles if grade 2 nephrotoxicity occurred. If grade 3 diarrhea or mucositis occurred, a 25% reduction in the daily dose of 5-FU was required.

2.7. Statistical analysis

The outcome measurement of this treatment included response rate, progression-free survival and overall survival.

Progression-free survival (PFS) was calculated from the date of induction chemotherapy to the documented date of progression or date of death from any cause. Overall survival (OS) is defined as the time from the start of induction chemotherapy to death from any cause. Survival analysis was estimated with the use of Kaplan-Meier method. The log-rank test was used to compare between PFS of different subgroups of patients. A P value < 0.05 was considered statistically significant. All statistical analysis was performed using SPSS 21.0 (SPSS, Inc. Chicago, IL).

3. Results

Thirty-three patients were enrolled in the study. Thirty patients received induction chemotherapy and completed the sequential chemoradiotherapy regimen. Three patients died during induction chemotherapy and they are non-assessable. The cause of death was bleeding in one patient and anorexia with rapid deterioration of health in two patients. Table 1 shows patient and tumor characteristic in the studied thirty patients. Table 2 represents the treatment outcomes which include response, PFS and OS. Table 3 shows

adverse events (NCI) of TPF and chemoradiotherapy. Table 4 shows prognostic factors for progression-free survival after TPF induction chemotherapy and chemoradiotherapy. Significance difference was reported in T stage, N stage and primary site.

Figure 1 shows the PFS of the study patients, the median PFS was 8 months. Figure 2 shows the OS of patients with laryngeal and hypopharyngeal cancer treated with IC followed by CRT. Median OS was 17 months. Figure 3 shows the PFS of laryngeal vs. hypopharyngeal cancer after treatment with TPF/concurrent chemoradiation, P<0.03 which is the only significant value. Nine patients (30%) had treatment delay and dose modifications during TPF induction chemotherapy mainly due to adverse events. The percentage of planned chemotherapy treatment that patients received was 86.6% and chemoradiation was completed in 60% of patients.

Table 1. Patient and tumor characteristics

Characteristics	Number= 30 (%)
Age “years”	
Median	51.00
Range	23.0 – 80.0
Sex:	
• Male	16(53.3)
• Female	14(46.7)
Performance status “ECOG”:	
• 0	3(10.00)
• 1	21(70.0)
• 2	6(20.0)
Smoking:	
• Never	14(46.7)
• Cigarette smoking	16(53.3)
Cell differentiation	
• Well	12(40.0)
• Moderate	10(33.3)
• Poorly differentiated	8(26.7)
T stage	
• T3	8(26.7)
• T4	22(73.3)
N stage	
• N0	12(40.0)
• N1	1(3.3)
• N2	17(56.7)
Overall Stage:	
• III	8(26.7)
• IV	22(73.3)
Primary Site:	
• Larynx	15(50.0)
• Hypopharynx	15(50.0)

ECOG denotes Eastern Cooperative Oncology Group performance status.

Table 2. Treatment outcomes to TPF induction chemotherapy followed by chemoradiation

Outcome	Number= 30 (%)
Response after induction chemotherapy	
• CR	6 (20)
• PR	10 (33.3)
• PD	5 (16.7)
• SD	9 (30)
Overall response (CR+ PR)	16 (53.3)
Response rate after induction and CRT	
• CR	9 (30)
• PR	12 (40)
• PD	2 (6.7)
• SD	7 (23.3)
• Over all response (CR+ PR)	21 (70)
Overall survival	
Mean \pm SD	18.31 \pm 7.27
Median	17
Progression-free survival	
Mean \pm SE	11.70 \pm 3.41
Median	8

TPF= docetaxel, cisplatin and 5-fluorouracil, CR= complete response, PR= partial response, SD= stable disease, PD= progressive disease, CRT= chemoradiotherapy, \pm SD= standard deviation

Table 3. Adverse events (NCI) of TPF/chemoradiotherapy (total number= 30)

Event	Grade "1&2" n(%)	Grade"3&4" n (%)
Adverse events during induction chemotherapy:		
<i>Hematological:</i>		
Anemia	9 (30)	3 (10)
Neutropenia	8 (26.6)	12 (40)
Thrombocytopenia	1 (3.3)	1 (3.3)
<i>Non hematological:</i>		
Nausea & Vomiting	6 (20)	3 (10)
Diarrhea	5 (16.6)	3 (10)
Mucositis	6 (20)	3 (10)
Anorexia	12 (40)	3 (10)
Adverse events during chemoradiotherapy:		
Mucositis	12 (40)	8 (26.6)
Dysphagia	8 (26.6)	8 (26.6)
Nausea & vomiting	3 (10)	3 (10)
Diarrhea	5 (16.6)	0.0
Anorexia	4 (13)	3 (10)

TPF= docetaxel+ cisplatin+ fluorouracil induction chemotherapy, NCI= National Cancer Institute. Common Terminology Criteria for adverse events, v. 4.0

Table 4. Prognostic factors for Progression-free survival after TPF induction chemotherapy and chemoradiotherapy

Factor	Mean± SD	p-value
Age “years”		
• <50ys.	14.1±3.70	0.267
• ≥50ys.	9.30±1.79	
Sex:		
• Female	14.67±2.09	0.195
• Male	9.18±1.62	
Smoking:		
• Never	14.30±3.75	0.286
• Cigarette smoking	9.10±1.79	
Cell differentiation		
• Well	8.75±2.25	0.196
• Moderate	18.33±5.67	
• Poorly differentiated	7.80±1.15	
T stage:		
• T3	22.33±4.70	<0.001*
• T4	7.14±2.17	
N stage		
• N0-N1	24.52±2.74	<0.015*
• N2-N3	9.46±2.2	

TPF= docetaxel, cisplatin and 5-fluorouracil, ±SD= standard deviation. *= significant value

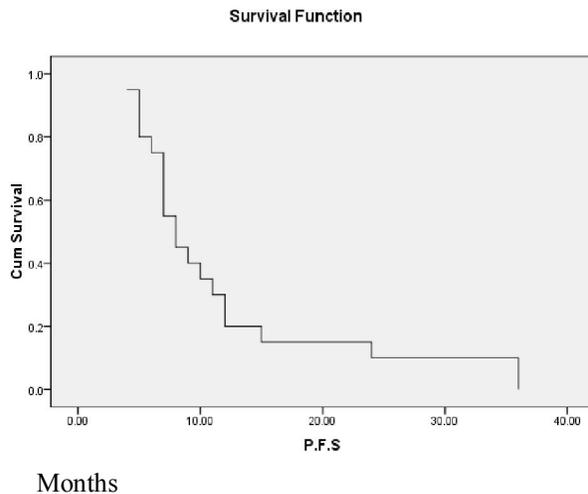


Figure 1: Progression-free survival (PFS) of 30 patients with locally advanced laryngeal and hypopharyngeal cancer treated by induction chemotherapy TPF (docetaxel+ cisplatin+ fluorouracil) followed by chemoradiotherapy, median PFS= 8 months

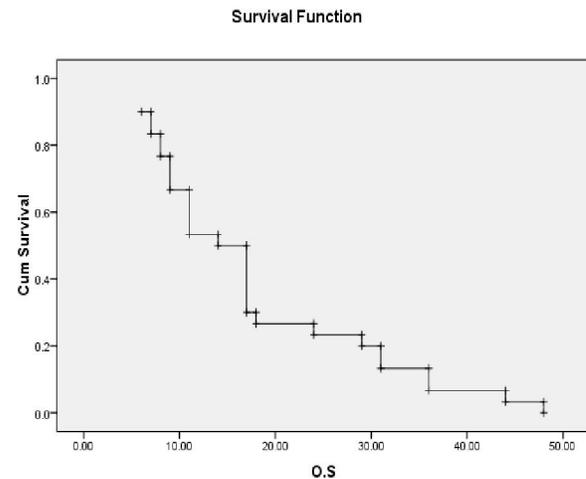


Figure 2: Overall survival (OS) of 30 patients with locally advanced laryngeal and hypopharyngeal cancer treated by induction chemotherapy TPF (docetaxel+ cisplatin+ te fluorouracil) followed by chemoradiotherapy, median OS= 17 months. += censoring at last visit date

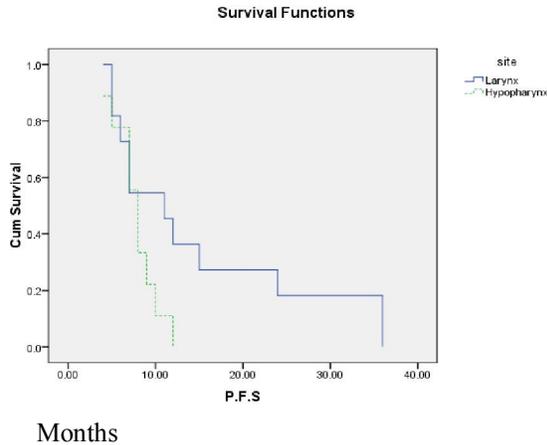


Figure 3: Primary site (larynx vs. hypopharynx) as a prognostic factor for progression-free survival (PFS) of 30 patients with locally advanced laryngeal and hypopharyngeal cancer treated by induction chemotherapy TPF (docetaxel+ cisplatin+ fluorouracil) followed by chemoradiotherapy $p < 0.03$

4. Discussion

Treatment strategies for patients with locoregionally advanced SCCHN have moved away from poorly effective single modality therapy and now encompass a multimodality approach (surgery, chemotherapy, radiation [RT], and targeted molecular therapeutics). In 2009, a large meta-analysis of the use of chemotherapy in head and neck cancer was updated, incorporating data from 87 trials and 17,346 patients, confirming the benefit of chemotherapy (given as concurrent chemoradiotherapy [CRT], induction chemotherapy [IC], or adjuvant treatment) in patients with locoregionally advanced SCCHN at all tumor sites¹⁰. Historically, the rationale behind the concept of induction based therapies relates to a number of advantages: tumor shrinkage, reducing metastatic disease, assessment of tumor responsiveness, and organ preservation in patients with laryngeal cancer¹¹. Following initial studies with earlier regimens in the 1980s, cisplatin plus 5-FU (PF) became the standard regimen for IC for many years based on the observation of high response rates and the elimination of the need for surgery in some patients⁶. One of the main questions debated was whether or not the advantages of induction treatment by achieving tumor control locally and at distant sites could overcome the potential harm resulting from the delay of definitive treatment—surgery or RT with or without chemotherapy in patients with locoregionally advanced curable stage III and stage IV¹². With TPF established as a standard for IC, a number of randomized trials have attempted to define the role of IC (as part of sequential treatment) versus the current standard of care, concurrent CRT. A European phase

II randomized trial investigated the efficacy of adding a TPF-based IC regimen to traditional concurrent CRT (CCRT) versus the current standard of care CCRT. Complete response rate was significantly higher in the TPF IC arm followed by CCRT than in the CCRT only arm (50% vs. 21.2%). Remarkably, the median PFS and overall survival (OS) times were longer in the TPF IC treatment. Hematologic and non-hematologic toxic effects during CCRT were similar in the two study arms¹³. The results of an international multicenter, phase III clinical trial comparing TPF IC followed by CCRT (sequential treatment) and cisplatin-based concurrent CRT in 145 patients with stage III or IV locally advanced SCCHN were reported. The 3-year survival rates were remarkably similar 73% in the sequential arm and 78% in the concurrent CRT arm and as expected the sequential treatment had a greater number of patients with grade 3 or 4 febrile neutropenia¹⁴. In present study the response after treatment with IC and CCRT were (30.0%) complete response, (40%) were partial response, (6.7%) were progress diseases and (23.3%) were stable diseases. This agree with the results of Avitia et al¹⁵ who reported CR in 13 patients (37%), partial response rate in 16 patients (46%) and progression rate in 6 patients (17%). Also Ahn et al¹⁶ found that after induction chemotherapy, 14 (28.6 %) and 29 (59.2%) patients achieved CR and PR respectively. The overall response of induction chemotherapy was 87.7%. After induction+ CRT, CR and PR were achieved in 65.2% and 30.2% respectively and an overall response rate of 95.4% which is higher than the overall response in our study. The overall response after IC was 53.3% and after IC+ CRT, the overall response was 70%. The reason of this difference may be the inclusion of different head and neck primary sites in his study including oropharynx and 26.5% of patients had stage III at presentation. In present study there were adverse events (NCI) of TPF and chemoradiotherapy. Adverse events during induction chemotherapy were as follow: grade 3-4 anemia, neutropenia thrombocytopenia and mucositis were 10%, 40%, 3.3% and 10% respectively. This is in agreement with the results of Ahn et al 2007¹⁶ who reported a grade 3-4 toxicity of neutropenia, anorexia and asthenia in 42%, 9.6% and 8.9% respectively. The trial conducted by Haddad et al¹⁷ reported that patients undergoing TPF/CRT had a higher risk of developing grade 3-4 hematologic adverse events compared with those undergoing CRT alone. In the current study, the median survival was 17 months and the median PFS was 8 months. This is agreeing with the results of Avitia et al 2013¹⁵ who reported a median survival and progression of 15 months and 11 months respectively. In a retrospective study done by Calderone et al¹⁸ on patients with

locally advanced HNSCC treated with TPF/CRT reported that 2-year overall survival and disease-free survival were 81% and 64% respectively. Results of the docetaxel-based chemotherapy plus or minus IC in head and neck cancer (DeCIDE) a trial done by Cohen et al 2012¹⁹ reported a high survival rates in both arms and no difference in the overall survival time. Interestingly, there were a lower number of distant failures with IC. In a recent study done by Ock et al 2016²⁰ showed that the 3-year OS rate was significantly higher in the TPF/CRT group compared to the CRT group (74.0% vs. 62.7%; $p = .045$). The 3-year PFS rate was 64.6% in the TPF/CRT group and 54.1% in the CRT group ($p = .060$). Subgroup analysis showed patients with high N classification (N2 or N3) oropharyngeal cancer had greater benefits when treated with TPF/CRT. Conversely, the meta-analysis of randomized trials concluded that additional induction chemotherapy with TPF before CRT did neither result in a significant improvement of OS nor in a statistically significant benefit of PFS in locally advanced HNSCC compared to definite CRT²¹. In our study, good prognostic factors for PFS were T3 and N0-1 stage and laryngeal primary site. This is agree with the results of Rades et al 2011²² who concluded that improved treatment outcomes were significantly associated with positive human papilloma virus status, better performance status, lower tumor stage and pretreatment hemoglobin level $> 12\text{g/dl}$. Females in the current study had a better response may be due to they are the non-smokers group. Another study done by Taquchi et al²³ reported that on multivariate analysis, T stage, N stage, and the contents of chemotherapy were significant prognostic factors for larynx preservation.

Conclusions

TPF chemotherapy followed by chemoradiotherapy is a highly effective treatment in terms of response and PFS. It could be recommended as a laryngeal preservation strategy in Egyptian patients with stage III laryngeal cancer. This regimen is more suitable in limited recourses settings.

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