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# Neoadjuvant or Definitive Chemoradiation for Locoregional Esophageal Cancer and its Outcome at South Egypt Cancer Institute (Retrospective Study)

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## Abstract

*Background:* It is well known about esophageal carcinoma, the aggressive and invasive nature, in addition to the poor outcome. The experience of south Egypt cancer institute was to review the locally advanced esophageal carcinoma, treated by chemo radiation either followed by surgery or not, and their outcome.

*Aim of Study:* In this study, we evaluate the efficacy of chemoradiation as a definitive or preoperative treatment.

*Patients and Methods:* During the period June 2008, till June 2014, 55 patients with locally advanced esophageal cancer were reviewed for treatment with preoperative or definitive concurrent chemo radiation, at Radiation Oncology Department, South Egypt Cancer Institute, Assiut University. Statistical analysis of data was done by the statistical package for the social science (SPSS) version 20.

*Results:* Out of 55 patients, 26 patients were included for definitive chemo radiation (dCRT). And 29 patients were included for neoadjuvant chemo radiation (nCRT). Squamous cell carcinoma (SqCC) represented in 72.7% of patients. Patients had disease stage II and III (32.7% and 67.3%) respectively. Median total radiation dose was 50.4 Gy over 28 fractions. Cisplatin+Fluorouracil regimen was received by 30 (54.5%) patients, while Paclitaxel+Carboplatin regimen was received by 25 (45.5%) patients. Overall response (CR+PR) was observed in 34 (72.3%) patients, while disease progression occurred in 5 (10.6%) patients and 17% (8 patients) had stable disease. The disease stage at diagnosis was a significant factor affecting clinical response. Out of 29 patients at neoadjuvant group, 18 patients (62%) underwent surgery, without major postoperative complications. Complete pathological response (no residual cancer cells) was observed in 6 (33%) patients. Median OS for dCRT and nCRT was 21 and 39 months respectively, it was in favor for nCRT group with no statistical significance ($p$-value=0.20). Median PFS for dCRT and nCRT was 16 and 18 months respectively, with no statistical significance ($p$-value=0.363). Disease stage at diagnosis and clinical response after radiotherapy were very highly significant factors affecting patients' overall survival and disease progression survival ($p$-value=0.014). Overall grade $\geq 3$ toxicity 26 events was observed in 16 (29.0%) of the patients.

*Conclusion:* Neoadjuvant chemo radiation followed by surgery is considered as a standard care management for patients with resectable locally advanced esophageal carcinoma and fit for surgery. For patients with inoperable disease or unfit for surgery, definitive chemo radiation is accepted treatment option. The used chemotherapy regimens, Cisplatin/Fluorouracil and Paclitaxel/Carboplatin, are tolerable in most patients with acceptable toxicity profile; and with no differences between two regimens.

***Key Words:*** *Esophageal carcinoma – Definitive concurrent chemo radiation – Neoadjuvant chemotherapy.*

## Introduction

**ESOPHAGEAL** cancer is considered the eighth most common cancer worldwide and the sixth most common cause of death from cancer **[1,2]**. At 2013 more than 1100 cases were diagnosed in Egypt, that according to the latest publication of national cancer registry program **[1]**. Esophageal cancer is aggressive and invasive in nature, more than 50% of patients have unresectable disease at time of diagnosis **[3]**. Preoperative chemo radiotherapy followed by surgery, was introduced to downstage the primary tumor, thus increasing the chance of resectability and eliminating micro metastases **[4, 5]**. In 1992 Nygaard et al., were the first group reported that preoperative chemotherapy and radiotherapy prolonged patient survival **[6]**. After that several studies showing survival advantages for preoperative chemo radiation followed by surgery over surgery alone **[7,9]**. A meta-analysis was conducted and reported a significant survival benefit for preoperative chemoradiotherapy followed by surgery in patients with esophageal squamous cell carcinoma **[10,11]**. The potential curative surgery is valid only for approximately 25% of patients

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[12]. In the rest of the patients with no metastatic disease, definitive concurrent chemo radiotherapy (CRT) is considered the standard treatment. Definitive CRT for esophageal cancer has not changed much in the past 23 years since the landmark RTOG 8501 trial [13]. Herskovic et al reported in 1992 that cisplatin and 5-fluorouracil (5FU) added concurrently to radiation (RT) improved local control, decreased metastases, and prolonged survival [13]. The updated outcome publication from RTOG 8501 trial reported a median survival of 14.1 months for the CRT-treated patients. This regimen was the standard of care [14]. Another chemotherapy regimen (weekly paclitaxel and carboplatin concurrently with RT) has been established as the preferred neoadjuvant treatment option for both squamous and adenocarcinoma of the esophagus after the long term results of CROSS trial have been published [15], and several studies have explored the use of this regimen in the definitive setting as well [16-20].

In our study; we reviewed the experience of South Egypt Cancer Institute in patients with locally advanced esophageal carcinoma treated by chemoradiation either followed by surgery or not; the efficacy and tolerability of different chemotherapy regimens used; and their outcome.

## Patients and Methods

We retrospectively studied 55 patients with locally advanced esophageal carcinoma who presented to south Egypt Cancer Institute at Assiut university since June 2008 to June 2014; they were treated either with preoperative chemoradiation followed by surgery or definitive concurrent chemo radiation.

For all patients, the medical records had reviewed for patients' characteristics: Age and sex of the patient, patient's performance status (PS) according to the eastern cooperative oncology group (ECOG) scale, the presenting symptoms; regarding dysphagia, weight loss, vomiting, chest pain and cough. Dysphagia was recorded according to dysphagia grading scale in European organization for research and treatment of cancer quality of Life questionnaire (EORTC QLQ-C30).

*Disease characteristics:* Tumor site, histopathological diagnosis, type and grade, as reported in the endoscopic biopsy, disease staging, according to the 7th edition of the tumor, node, metastasis [TNM] staging system of the American joint committee on cancer (AJCC).

*Treatment data:* Patients were categorized according to intention of treatment into: Definitive chemo radiation group (dCRT), including patients received definitive concurrent chemo radiation. This group includes patients with unresectable disease (based on CT imaging), and patients unfit for surgery, and neoadjuvant chemo radiation group (nCRT), including patients with resectable disease and fit for surgery. These patients received neoadjuvant concurrent chemo radiation, and then planned for surgery.

*Treatment plan:* All patients received chemo radiation, and after 4-6 weeks they were evaluated for response using response evaluation criteria in solid tumors (RECIST; version 1.1) for response definitions.

*Radiation therapy:* Was delivered using linear accelerator with photon energy of 6-15 MV, conventional fractionation (1.8-2GY) five fractions per week, for (5.6-6 weeks), aimed (50.4 Gy-60GY). The target volumes; for conventional 2D planning (16 patients, 29%) ; 5cm in cranial and caudal directions to the visualized lesion; to cover sub-mucosal spread, 1.5-2.5cm in lateral directions. Customized blocks were used to shape the treatment fields and to spare normal lung tissues. For conformal 3D planning (39 patients, 71%); GTV: gross tumor+involved lymph nodes, CTV: Tumor+3-5cm longitudinal+0.5-1cm circumferential, Involved nodes+0.5-1cm in all directions, PTV: CTV+0.5-1cm. Elective nodal coverage; upper tumors (above the carina); periesophageal, mediastinal and supraclavicular, lower tumors (below the carina); periesophageal, mediastinal, perigastric and celiac lympnodes. The field arrangement; for conventional 2D planning; anterior-posterior (AP/PA) fields were used up to 40-45 Gy, to minimize dose to the lungs then three fields (anterior open field and 2 anterior oblique wedged fields) were used; to spare the spinal cord. For conformal 3D planning; 3-5 beams were used; provided by DVH for GTV, PTV and normal organs at risk.

*Chemotherapy:* Two regimens were used and recorded (Cisplatin+Fluorouracil) Cisplatin:100 mg/m$^2$ IV on day 1, Fluorouracil: 1000mg/m$^2$ IV infusion over 1-2 hours on days 1-4. Cycle every 28 days; two cycles with radiation followed by two cycles of consolidation without radiation (weeks 1, 5, 8, 11). The second regimen (Paclitaxel +Carboplatin); Paclitaxel: 50mg/m$^2$ IV on Day 1,Carboplatin: AUC 2 IV on Day 1.The regimen was repeated weekly for 5 weeks, with radiation.

*Toxicity:* Acute toxicity; treatment related toxicities within the first 6 months after finishing the treatment were recorded according to common

terminology criteria for adverse events (CTCAE; version 3.0). Late toxicity; treatment related late toxicities after 6 months of starting the treatment were recorded according to CTCAE (version 3.0). Any palliative procedure against dysphagia was reported.

*Follow-up:* All patients were followed-up by CT scans and endoscopy every 3-6 months in first year, then 6 months in second year, and annually after then. Follow-up period calculated from first day of diagnosis till last follow-up visit or death.

Overall survival (OS) was measured from the first day of diagnosis to the time of death or the date of last follow-up. Progression free survival (PFS) was calculated from the first day of diagnosis to the time of first disease progression.

*Statistical analysis:* Statistical analysis of data was done by the statistical package for the social science (SPSS) version 20. Descriptive statistics was used as median, mean, number and percentage. Kaplan-Meier test used for survival analysis, and Log rank test was used to evaluate the significant differences between variables. Chi-square test was used to evaluate the relation between variables and treatment response. $p$-value was double sided and considered significant if was $\leq 0.05$.

## Results

55 patients with esophageal cancer were retrospectively reviewed. 26 patients were planned for definitive chemo radiation group, out of them; 11 patients with unresectable disease and 15 patients were medically unfit for major surgery. And 29 patients were included for neoadjuvant chemo radiation group, out of them 18 patients underwent surgery, 5 patients showed progressive disease after chemo radiation, 4 patients were medically unfit after chemo radiation and 2 patients refused surgery.

*Patient's characteristics:*The median age at time of diagnosis was 61 years. Males presented 63.6% of the patients' population while females presented 36.4%. According to ECOG scale; all our patients in the study between grade 1 and 2. The most common presenting complaint was dysphagia (94.5%), followed by significant weight loss (85.4%) (Table 1).

*Disease characteristics:*Regarding site; the tumor was found most frequently in lower esophagus in 52.7% of patients. Squamous cell carcinoma (SqCC) was the most common pathology (72.7%). Most of the lesions were moderately differentiated carcinomas (60%). All patients were with disease stage II and III (32.7% and 67.3% respectively). Node positive disease (N1-3) was diagnosed in 63.6% of patients (Table 2).

Table (1): Patient characteristics in neoadjuvant (nCRT) and definitive chemoradiation (dCRT) treatment groups at time of presentation.

| | Patient Characteristics | | |
|---|---|---|---|
| | dCRT Group (n=26) | nCRT Group (n=29) | All Groups (n=55) |
| *Age:* | | | |
| Median | 67 years | 57 years | 61 years |
| Range | 43-71 years | 38-70 years | 38-71 years |
| *Sex:* | | | |
| Male | 16 (61.5%) | 19 (65.5%) | 35 (63.6%) |
| Female | 10 (38.5%) | 10 (34.5%) | 20 (36.4%) |
| *ECOG performance status:* | | | |
| I | 5 (19.2%) | 16 (55.2%) | 21 (38.2%) |
| II | 21 (80.8%) | 13 (44.8%) | 34 (61.8%) |
| *Dysphagia grading scale:* | | | |
| Grade 1 | 1 (3.8%) | 11 (37.9%) | 12 (21.8%) |
| Grade 2 | 10 (38.5%) | 15 (51.7%) | 25 (45.5%) |
| Grade 3 | 11 (42.3%) | 3 (10.3%) | 14 (25.5%) |
| Grade 4 | 4 (15.4%) | 0 (0.0%) | 4 (7.3%) |
| Significant weight loss | 19 (73.1%) | 11 (37.9%) | 30 (54.5%) |

Table (2): Disease characteristics in neoadjuvant (nCRT) and definitive chemoradiation treatment (dCRT) groups at time of presentation.

| | Disease Characteristics | | |
|---|---|---|---|
| | dCRT Group (n=26) | nCRT Group (n=29) | All Groups (n=55) |
| *Tumor site:* | | | |
| Upper | 5 (19.2%) | 1 (3.4%) | 6 (10.9%) |
| Middle | 9 (34.6%) | 11 (37.9%) | 20 (36.4%) |
| Lower | 12 (46.2%) | 17 (58.6%) | 29 (52.7%) |
| *Histopat hology:* | | | |
| SqCC | 21 (80.8%) | 19 (65.5%) | 40 (72.7%) |
| AC | 5 (19.2%) | 10 (34.5%) | 15 (27.3%) |
| *Pathological grade:* | | | |
| Well Diff. | 3 (11.5%) | 3 (10.3%) | 6 (10.9%) |
| Mod. Diff. | 13 (50.0%) | 20 (69.0%) | 33 (60.0%) |
| Poorly Diff. | 10 (38.5%) | 6 (20.7%) | 16 (29.1%) |
| *T Stage:* | | | |
| T2 | 4 (15.4%) | 15 (51.7%) | 19 (34.5%) |
| T3 | 13 (50.0%) | 14 (48.3%) | 27 (49.1%) |
| T4a | 6 (23.1%) | 0 (0.0%) | 6 (10.9%) |
| T4b | 3 (11.5%) | 0 (0.0%) | 3 (5.5%) |
| *N Stage:* | | | |
| N0 | 12 (46.2%) | 8 (27.6%) | 20 (36.4%) |
| N1 | 5 (19.2%) | 8 (27.6%) | 13 (23.6%) |
| N2 | 7 (26.9%) | 11 (37.9%) | 18 (32.7%) |
| N3 | 2 (7.7%) | 2 (6.9%) | 4 (7.3%) |
| *Stage group:* | | | |
| IIA | 3 (11.5%) | 4 (13.8%) | 7 (12.7%) |
| IIB | 3 (11.5%) | 8 (27.6%) | 11 (20.0%) |
| IIIA | 7 (26.9%) | 9 (31.0%) | 16 (29.1%) |
| IIIB | 5 (19.2%) | 6 (20.7%) | 11 (20.0%) |
| IIIC | 8 (30.8%) | 2 (6.9%) | 10 (18.2%) |

Clinical response after chemo radiation and factors affecting the response: After chemoradiation therapy 18 patients in definitive dCRT groups and 29 patients in nCRT group was available for endoscopic evaluation and histopathological examination done revealed dCRT group and complete response in 7 patients (38.9%) and 16 patients (55. 2%) and partial response in with overall response 5 patients (27.8%) and 6 patients (20.7%) respectively. The overall response rate was 72.3% and progressive disease was on 17.2% of the patients all of them in the nCRT arm (Fig. 1) (Table 3).

Table (3): Treatment clinical response evaluation after chemoradiation therapy in neoadjuvant (nCRT) and definitive chemoradiation treatment (dCRT) groups.

| | dCRT Group (n=18) | nCRT Group (n=29) | All Groups (n=47) |
|---|---|---|---|
| Overall Response | 12 (66.7%) | 22 (75.9%) | 34 (72.3%) |
| Complete Response (CR) | 7 (38.9%) | 16 (55.2%) | 23 (48.9%) |
| Partial Response (PR) | 5 (27.8%) | 6 (20.7%) | 11 (23 .4%) |
| Stable Disease (SD) | 6 (33.3%) | 2 (6.9%) | 8 (17.0%) |
| Progressive Disease (PD) | 0 (0.0%) | 5 (17.2%) | 5 (10.6%) |

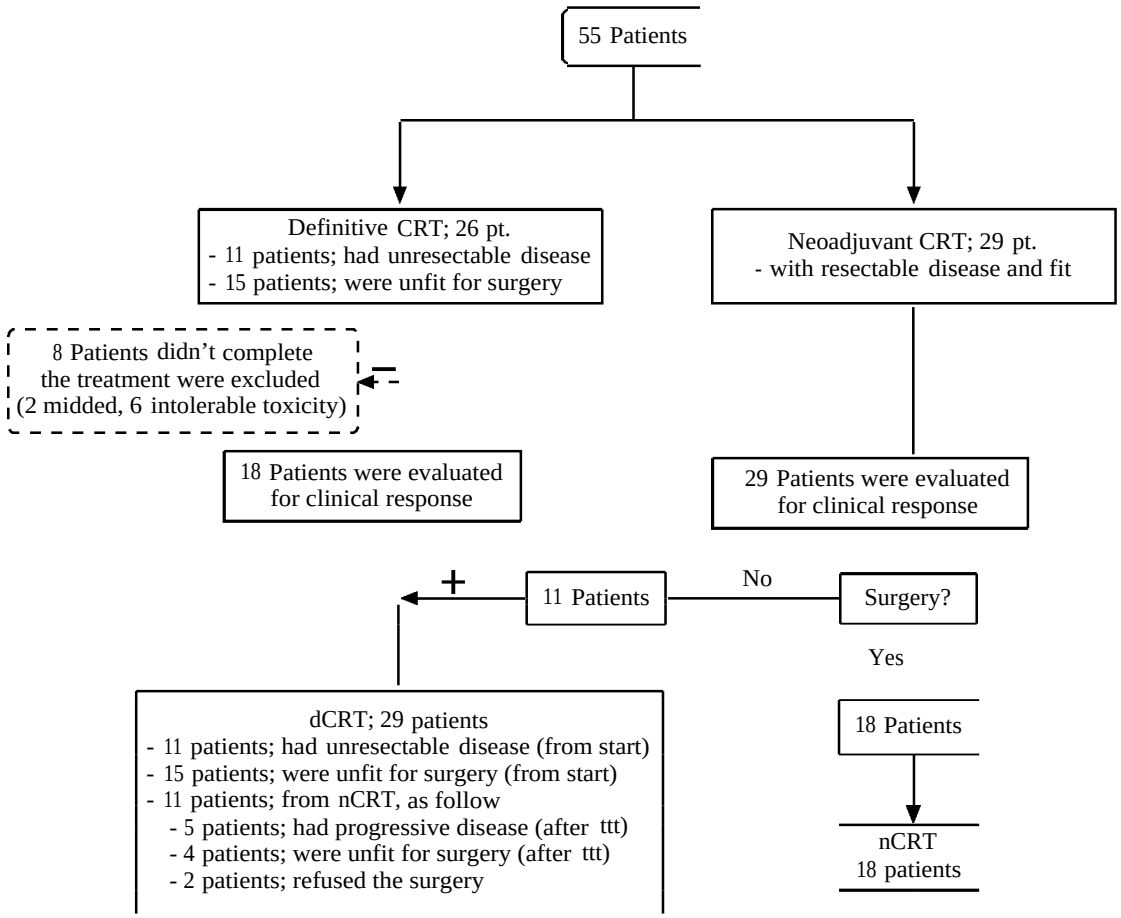


Fig. (1): Algorithm representing the patient's treatment groups neoadjuvant (nCRT) group 29 patients and definitive chemoradiation treatment (dCRT) group 26 patients.

Out of all the studied factors, only the disease stage group at diagnosis was a significant factor affecting clinical response (Table 4).

*Toxicity:*

*Acute toxicity:* Radiation therapy was tolerable for the majority of patients with mild to moderate complaints; this improved with supportive medical treatment, and did not require treatment interruption. Overall grade ≥3 toxicity 26 events was observed in 16 (29.0%) of the patients. Grade ≥3 toxicity occurred in 9 (34.6%) patients in dCRT group, versus 7 (24.1%) in nCRT group. The most common events were neutropenia, followed by esophagitis (Table 5).

Table (4): A multivariate analysis of factors affecting clinical response showed that stage of the disease was the most significant factor ($p$-value=0.025).

| Variable | Number | CR | PR | SD | PD | $p$-value |
|---|---|---|---|---|---|---|
| *Age:* | | | | | | |
| <60 years | 21 | 11 | 4 | 4 | 2 | 0.911 |
| 60 years | 26 | 12 | 7 | 4 | 3 | |
| *ECOG PS:* | | | | | | |
| I | 21 | 11 | 5 | 3 | 2 | 0.959 |
| II | 26 | 12 | 6 | 5 | 3 | |
| *Tumor site:* | | | | | | |
| Upper | 5 | 2 | 1 | 1 | 1 | 0.953 |
| Middle | 17 | 7 | 5 | 3 | 2 | |
| Lower | 25 | 14 | 5 | 4 | 2 | |
| *Histo -pathology:* | | | | | | |
| SqCC | 33 | 16 | 8 | 6 | 3 | 0.945 |
| AC | 14 | 7 | 3 | 2 | 2 | |
| *Pathological grade:* | | | | | | |
| Well Diff. | 6 | 5 | 1 | 0 | 0 | 0.283 |
| Mod. Diff. | 29 | 14 | 8 | 5 | 2 | |
| Poorly Diff. | 12 | 4 | 2 | 3 | 3 | |
| *Stage group:* | | | | | | |
| IIA | 7 | 7 | 0 | 0 | 0 | 0.025 |
| IIB | 11 | 6 | 4 | 1 | 0 | |
| IIIA | 13 | 6 | 1 | 4 | 2 | |
| IIIB | 9 | 4 | 3 | 0 | 2 | |
| IIIC | 7 | 0 | 3 | 3 | 1 | |
| *Radiation dose:* | | | | | | |
| 50.4Gy/28fr | 28 | 16 | 6 | 2 | 4 | 0.116 |
| 60Gy/30fr | 19 | 7 | 5 | 6 | 1 | |
| *Chemotherapy regimen:* | | | | | | |
| Cis/Fu | 25 | 11 | 6 | 5 | 3 | 0.886 |
| Taxel/Carbo | 22 | 12 | 5 | 3 | 2 | |

Table (5): Grade ›_3 Acute toxicity events after chemoradiation therapy in neoadjuvant (nCRT) and definitive chemoradiation treatment (dCRT) groups.

| | dCRT Group (n=26) | nCRT Group (n=29) | All Groups (n=55) |
|---|---|---|---|
| Esophagitis | 4 (15.4%) | 3 (10.3%) | 7 (12.7%) |
| Anorexia | 1 (3.8%) | 1 (3.4%) | 2 (3.6%) |
| Fatigue | 2 (7.7%) | 1 (3.4%) | 3 (5.5%) |
| Neutropenia | 6 (23.1%) | 7 (24.1%) | 13 (23.6%) |
| Diarrhea | 0 (0.0%) | 1 (3.4%) | 1 (1.8%) |

*Late toxicity:* During follow-up; 10 events of grade ›_3 late toxicity were recorded in 7 (12.7%) patients. Severe esophageal stenosis that required endoscopic dilatation occurred in 6 (10.9%) patients.

*Progression free survival (PFS):* Median PFS for dCRT and nCRT was 16 and 18 months respectively, with no statistical significance ($p$-value =0.363). As observed in OS; disease stage at diagnosis and clinical response after radiotherapy are very highly significant factors affecting disease progression (Fig. 2) (Table 6).

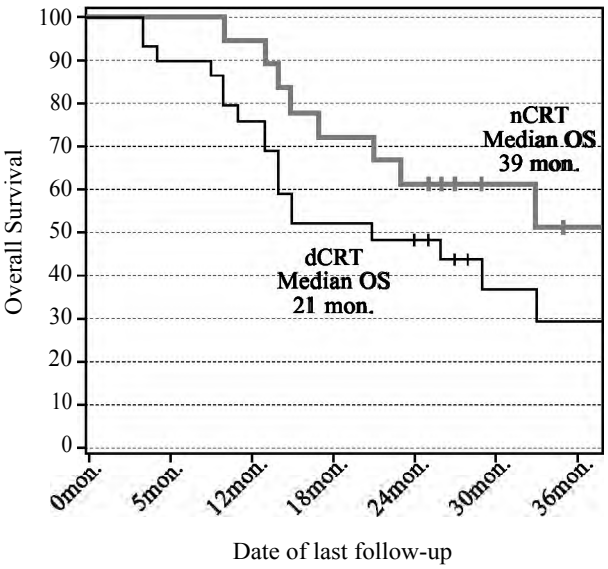


Fig. (2): Overall survival in neoadjuvant (nCRT) and definitive chemoradiation treatment (dCRT) groups in 36 months follow-up was 39 and 21 months respectively, with no statistical significance ($p$-value=0.20).

Table (6): A multivariate analysis of factors affecting progression free survival (PFS), showed that stage of the disease and response to treatment were the significant factor affect the PFS.

| Variable | Number | 2-years PFS | $p$-value |
|---|---|---|---|
| *Age:* | | | |
| <60 years | 21 | 38.1% | 0.877 |
| 60 years | 26 | 31.1% | |
| *ECOG PS:* | | | |
| I | 21 | 42.9% | 0.507 |
| II | 26 | 40.4% | |
| *Tumor site:* | | | |
| Upper | 5 | 60.0% | 0.512 |
| Middle | 17 | 38.5% | |
| Lower | 25 | 28.0% | |
| *Histo -pathology:* | | | |
| SqCC | 33 | 36.7% | 0.283 |
| AC | 14 | 28.6% | |
| *Pathological grade:* | | | |
| Well Diff. | 6 | 33.3% | 0.988 |
| Mod. Diff. | 29 | 34.5% | |
| Poorly Diff. | 12 | 37.5% | |
| *Stage group:* | | | |
| II | 18 | 65.8% | <0.001 |
| III | 29 | 15.0% | |
| *Clinical response:* | | | |
| CR | 23 | 52.2% | <0.001 |
| PR | 11 | 29.1% | |
| SD | 8 | 25.0% | |
| PD | 5 | 00.0% | |
| *Radiation dose:* | | | |
| 50.4Gy/28fr | 28 | 30.4% | 0.518 |
| 60Gy/30fr | 19 | 40.5% | |
| *Chemotherapy regimen:* | | | |
| Cis/Fu | 25 | 28.0% | 0.086 |
| Taxel/Carbo | 22 | 41.4% | |

*Survival analysis:* Median OS for dCRT and nCRT was 21 and 39 months respectively, with no statistical significance (*p*-value=0.20) (Fig. 3). Overall survival was in favor for nCRT group, at 2 and 3 years, but without statistical significance.

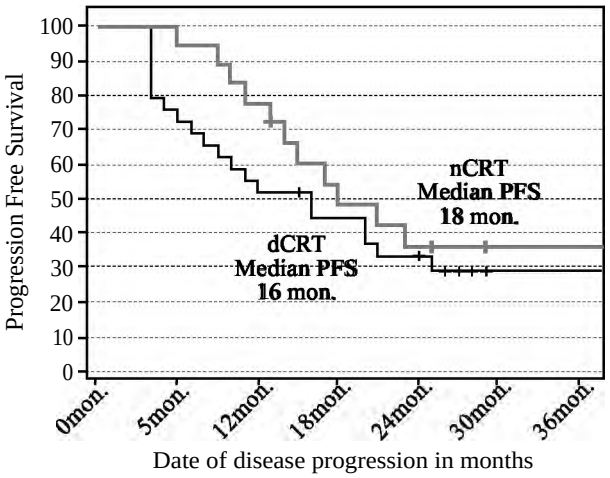


Fig. (3): Progression Survival in neoadjuvant (nCRT) and definitive chemoradiation treatment (dCRT) groups in 36 months follow-up was 18 and 16 months respectively, with no statistical significance (*p*-value =0.363).

Table (7): A multivariate analysis of factors affecting Overall survival (OS) showed that pathological grade, stage of the disease, clinical response to treatment were the most significant factors affecting OS.

| Variable | Number | 2-years OS | *p*-value |
|---|---|---|---|
| *Age:* | | | |
| <60 years | 21 | 57.1% | 0.158 |
| 60 years | 26 | 50.0% | |
| *ECOG PS:* | | | |
| I | 21 | 61.9% | 0.077 |
| II | 26 | 46.2% | |
| *Tumor site:* | | | |
| Upper | 5 | 40.0% | 0.630 |
| Middle | 17 | 58.8% | |
| Lower | 25 | 52.0% | |
| *Histo -pathology:* | | | |
| SqCC | 33 | 60.6% | 0.078 |
| AC | 14 | 35.7% | |
| *Pathological grade:* | | | |
| Well Diff. | 6 | 50.0% | 0.022 |
| Mod. Diff. | 29 | 62.1% | |
| Poorly Diff. | 12 | 33.3% | |
| *Stage group:* | | | |
| II | 18 | 72.2% | 0.014 |
| III | 29 | 41.4% | |
| *Clinical response:* | | | |
| CR | 23 | 73.9% | <0.001 |
| PR | 11 | 54.4% | |
| SD | 8 | 33.3% | |
| PD | 5 | 00.0% | |
| *Radiation dose:* | | | |
| 50.4Gy/28fr | 28 | 53.6% | 0.960 |
| 60Gy/30fr | 19 | 52.6% | |
| *Chemotherapy regimen:* | | | |
| Cis/Fu | 25 | 44.0% | 0.149 |
| Taxel/Carbo | 22 | 62.5% | |

Disease stage at diagnosis and clinical response after radiotherapy are very highly significant factors affecting patients' survival (Table 7) (Fig. 4). Poorly differentiated carcinomas were associated with lower survival.

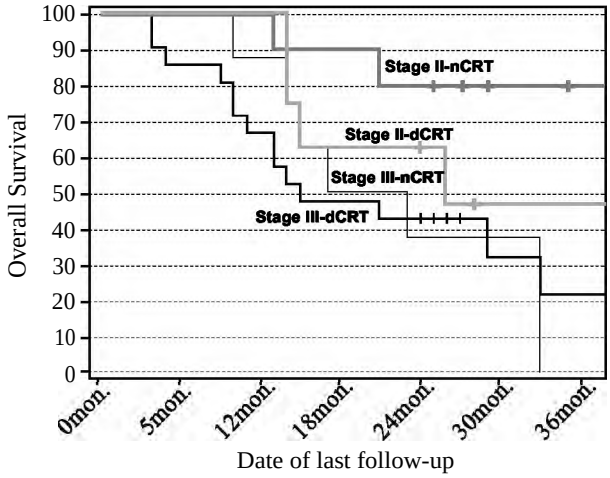


Fig. (4): Overall Survival in neoadjuvant (nCRT) and definitive chemoradiation treatment (dCRT) groups according to disease stage.

## Discussion

In an attempt to improve the outcome of patients with locally advanced esophageal carcinoma multiple studies suggest that no added benefit from surgery after chemo radiation among the complete responder [5,15]. Others tried alternative regimens of chemotherapy rather than the standard one [19]. We retrospectively studied 55 patients presented at South Egypt Cancer Institute whether treated as neoadjuvant chemo radiation followed by surgery or definitive chemo radiation using two different regimens.

The median age of our patients was 61 years with age ranged from 38 to 71 years. This figure is comparable to that reported by Conroy et al., [21] and Bedenne et al., [22] (Median age was 60 and 59 respectively). However, other studies were able to study a group of older patients, with median age of 69 years, the age ranged from 46 to 82 years [18,23]. And that mostly due to better general condition, better available supportive treatment in the developed country rather than our developing one.

As regard pathological types, SqCC was the most common among our studied cases as it diagnosed in 72.7% followed by AC that was diagnosed in 27.3%. This figure is slightly more than that reported by Ben Alexander Fulton [23] (64% SqCC, 36% AC) and less than that reported by Conroy et al., [21] (86% SqCC, 14% AC). We noticed no difference as regard response to treatment among

the two pathological types and regard the overall survival although the Sqcc had better OS but it was not statistically significant, it may requires further studies contain larger number to more accurate results especially among complete responder.

As reported by Kim et al., that almost 50% of patients presented by locally advanced disease at diagnosis, and only 60% of them are resectable [24]. At our study Almost 2/3 of our patients were stage III (67.3%), and the rest were stage II (32.7%). Haisley et al., [25], in their retrospective study, showed patients with stage II or III esophageal carcinoma with percentage of 30% and 62%, respectively. Also, El-Sayed et al., [26] studied definitive chemoradiation in patients with locally advanced esophageal carcinoma with percentage of 33% and 67%, respectively.

After the end of treatment course, treatment response was assessed in all patients using complementary CT and endoscopic ultra sonographic guided biopsy. 46.7% of our patients showed complete response and 24.4% partial response. Among the studied factors that affect the treatment response, only the disease stage at diagnosis was a significant factor affecting clinical response.

That is comparable to Conroy et al., [21], as they reported 43% with complete response and 22% with partial response. Also, Song et al documented treatment responses as general in 73% of their patients [31].

However, we reported better response rates than reported in Noronha et al., [20] and Voncken et al., [27], as they reported rates of 49% and 48%, respectively. These numbers could be explained by; more patients with advanced stage in Noronha et al., (T4 patients were 53%), While in Voncken et al., more patients with adenocarcinoma (75%), and only 72% were evaluated after the end of treatment [27]. However our estimated CR was less than Ilson et al., who reported 35 out of 51 patients (69%) with CR, it might be as a result of more aggressive protocol using induction chemotherapy followed by chemo radiation then surgery [28].

After using multivariate analysis, only the clinical response after chemo radiotherapy were highly significant factors affecting patients' survival, as Rizvi et al., said [29]. So we need further studies including larger number and longer period for follow-up are required to determine who get benefit by further surgery. As Steyerberg et al., mentioned that if we can avoid the morbidity and mortality of additional surgery after achievement a complete response by chemo radiation [30]. Recent analysis have been shown that the addition of esophagectomy to chemoradiotherapy in locally advanced esophageal squamous cell carcinoma probably delays loco regional relapse, but didn't significantly improve OS, and may be associated with higher treatment-related mortality [31].

The median OS in our study was 29 months and 3-year OS was 38%. The median PFS was 17 months and 3-year PFS was 32%. These results were comparable to Song et al., they reported median OS of 23 months (3-year OS=37%), and median PFS of 21 months (3-year PFS=31%), in spite of using different chemotherapy protocol in definitive chemoradiation (Paclitaxel/Oxaloplatin) [33].

On the other hand, Haisley et al., [25] reported better 3-year OS (52%) and 3-year PFS (44%), and Rizvi et al., [29], who reported median OS 44 months, and PFS 66 months. This better result is mostly because they studied retrospectively all patients received neoadjuvant chemoradiation followed by surgery.

However, Conroy et al., [21] reported a lower survival rates with a median OS of 20 months (3-year OS=27%), and median PFS of 10 months (3-year PFS=18%); the authors suggested that this finding could be indicative of the poor baseline characteristics of the included patients. Noronha et al., [20], also, reported lower survival rates; median OS was 19 months, and median PFS of 11 months; the authors explained that by that only patients with extensive disease are considered for definitive CRT (Stage III patients were 83%, T4 patients were 53%).

Regarding the other prognostic factors affecting the survival; the disease stage was a significant factor affecting both OS and PFS, our results were consistent with Haisley et al., [25] who reported a significant impact of disease stage on survival rates. Another investigators were reported that clinical T4 disease and absence of pathologic complete response were independently associated with inferior overall and disease-free survival [33].

Both chemotherapy regimens used with our patients (Cisplatin/Fluorouracil and Paclitaxel/Carboplatin) didn't show any differences regarding the tolerability, clinical and pathological response, although non-statistically significant increase in PFS and OS in Paclitaxel/Carboplatin arm. Honing et al., [19] also reported that OS was not different

between the cisplatin/5-FU and carboplatin/ paclitaxel group. However, Haisley et al., showed a significant difference in pathological response and OS favoring Cisplatin/Fluorouracil over Paclitaxel/Carboplatin, however, they reported a larger number in neoadjuvant setting [25]. Honing et al., was reported significance differences at hematological and nonhematological toxicity (grade 3) in the carboplatin/paclitaxel group (4% and 18%) was significantly lower than in the cisplatin/5-FU (19% and 38%, $p$=0.001) [19].

In our study the most frequent toxicities were esophagitis (13%) and neutropenia (24%). These rates are comparable to that reported by Conroy et al., [21] and Noronha et al., [20]; esophagitis in 9%–12% and neutropenia in 29%–27%, respectively Neutropenia was more frequent when using more toxic agent as reported by Song et al., [32], when they used paclitaxel plus oxaloplatin combined with radiotherapy; as 38% of their patients developed Grade 3 or more of neutropenia.

As regard the late toxicities; esophageal strictures that required endoscopic dilatation was occurred in 11% patients, and that is close to Bedenne et al., who reported endoscopic dilatation in 14% of their patients [22].

We recommended that for patients with resectable Stage II or III esophageal carcinoma and fit for surgery; neoadjuvant chemoradiation followed by surgery is the treatment of choice. For patients with unresectable esophageal carcinoma and/or unfit for surgery; definitive chemoradiation is considered the standard treatment option with accepted outcome. Both chemotherapy regimens (Cisplatin+Fluorouracil or Paclitaxel+Carboplatin) are equally effective with tolerable toxicity profile. So, Cisplatin+Fluorouracil are preferred in our institute for its lower cost, while Paclitaxel+Carboplatin can be reserved for patients with renal impairment in whom Cisplatin is contraindicated.

Further studies are needed to confirm the possibility of omitting surgery after chemoradiation in patients with complete response, especially those with squamous cell carcinoma. Other studies are recommended to evaluate newer chemotherapeutic and targeted agents, and the prognostic factors affecting their efficacy on treatment response and survival rates, in order to improve the outcomes.

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# استخدام العلاج الاشعاعى المصاحب للكيميائى قبل الجراحة أو كعلاج جذرى لحالات سرطان المرئ الموضعى ونتائجه بمعهد جنوب مصر للأورام (دراسة مرجعية)

اشتملت هذه الدراسة المرجعية على ٥٥ مريضاً بسرطان المرئ المرضعى، تمت معالجتهم بالعلاج الاشعاعى المصاحب للكيميائى ما قبل الجراحة أو كعلاج جذرى، بقسم الأشعة العلاجية بمعهد جنوب مصر للأورام جامعة أسيوط فى الفترة ما بين يونيو ٢٠٠٨م حتى يونيو ٢٠١٤م.

من بين هؤلاء المرضى، ٢٩ مريضاً تلقوا العلاج الإشعاعى المصاحب للكيميائى كعلاج جذرى، و ١٨ مريضاً تلقوا العلاج الإشعاعى المصاحب للكيميائى ثم تم الاستئصال الجراحى للورم ، و ٨ مرضى لم يستكملوا العلاج وتم آصاؤهم من التحليل الإحصائى.

كان متوسط عمر المرضى فى هذه الدراسة هو ٦١ عاماً. كانت معظم الحالات من الذكور بنسبة ٦٤٪، و بينما كانت الإناث ٣٦٪.

كانت معظم أعراض المرضى وقت التشخيص هى صعوبة فى بلع الطعام (٩٤٪) ويليها نقص فى الوزن (٨٥٪).

تم تشخيص الورم بالثلث السفلى من المرئ فى معظم الحالات بنسبة ٥٣٪، و كان سرطان الخلية الحرشفية الأكثر حدوثاً بنسبة ٧٣٪. كل المرضى كانوا فى المرحلة الثانية أوالثالثة بنسبة ٣٣٪ و ٦٧٪ على التوالى.

متوسط جرعة العلاج الإشعاعى كانت ٤، ٥٠ جراى على ٢٨ جلسة. تم علاج معظم المرضى (٧١٪) بالتخطيط ثلاثى الأبعاد. تم استخدام العلاج الكيميائى من بروتوكول بلاتينول وفلوروويوراسيل فى ٥٥٪ من المرضى، وبروتوكول تاكسول وكاربوبلاتين فى ٤٥٪ من المرضى. استكمل معظم المرضى جلسات العلاج الإشعاعى والكيميائى فيما عدا ٨ مرضى (٦ لم يستكموا العلاج الكيميائى نتيجة للمضاعفات، و ٢ انقطعوا عن العلاج).

بعد الإنتهاء من العلاج الإشعاعى المصاحب الكيميائى، تم تقييم استجابة الورم للعلاج فى ٤٧ مريضاً. كانت نسبة الاستجابة (الكاملة والجزئية) ٧٢٪، بينما حدث تدهور للورم بنسبة ١١٪.

تم الإستئصال الجراحى فى ١٨ مريضاً بدون حدوث مضاعفات كبرى بعد الجراحة، وحدثت استجابة باثولوجية كاملة فى ٣٣٪ من المرضى.

كان العلاج الإشعاعى المصاحب للكيميائى محتملاً لدى معظم المرضى، حيث حدثت آثار جانبية من الدرجة الثالثة فى ٢٩٪ من المرضى. بينما حدثت المضاعفات المزمنة فى ١٣٪ من المرضى.

كانت متوسط فترة المتابعة للمرضى شهراً، وحدث ارتجاع موضعى للورم فى ٢١٪ وثانويات سرطانية فى ٤٥٪ من المرضى خلال عامين. أما بالنسبة لمتوسط معدل البقاء على قيد الحياة ومعدل البقاء بدون تدهور للمرض كان ٢٩ شهراً و ١٧ شهراً على التوالى.