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Original Article

Sequential versus concomitant chemoradiotherapy in locally advanced head and neck cancer

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Purpose: To test the feasibility of neoadjuvant chemotherapy followed by concomitant chemoradiotherapy regimen versus concomitant chemoradiotherapy in locally advanced squamous cell carcinoma of the head and neck cancer.

Material and Methods: Patients with Stage III and IVA and B squamous cell carcinoma of head and neck excluding nasopharynx with the following criteria were enrolled ; PS 0-2; no prior surgery, chemotherapy or radiotherapy (CT or RT) were prospectively randomly assigned to receive 3 cycles of neoadjuvant TPF(arm A: T (docetaxel) 75 mg/m2,d1; P (platinol) 75 mg/m2,d1; 5-flurourcil 750 mg/m^2 IV ,D1-5) followed the concurrent chemoradiotherapy (CT/RT) (two cycles of cisplatin 20 mg/m^2, days1–4, plus 5-fluorouracil 750 mg/m^2/day IV D1-4during weeks 1 and 6 of radiotherapy).

Concurrent chemoradiotherapy (arm B) consisted of two cycles of cisplatin 20 mg/m^2, days1–4, plus 5-fluorouracil 750 mg/m^2/day IV D1-4 during weeks 1 and 6 of radiotherapy. Basic demographics and clinical characteristics'', overall survival rate, locoregional or systemic relapse rates and time to relapse were recorded.

Results: A total of 49 patients were enrolled in our study between march 2010 and march 2014, with (24 arm A and 25 arm B, four not evaluable in both group. Following CT/RT, The complete response rate was 52.4% and 20 % in arm A and B respectively which was statistically significant (*P* =0.022).

Median follow-up of all patients was 38 months (range 7-42 months). Three year overall survival rates 72.7% in arm A and 68.7% in arm B, respectively which was statistically was insignificant (*P* value=0.4113) . Three year distant disease-free survival rate in group A was 65.8% versus 60% in group B which was statistically insignificant (*P* value=0.3772). The three year progression –free survival was higher in group A than group B 61.1% versus 53.8% which was statistically insignificant (*P* value=0.3345).

The primary endpoint was complete response evaluated 6 weeks after the end of chemoradiotherapy While Secondary endpoints included time to disease progression (TTP), survival and safety.

Conclusion: Induction TPF followed by CT/RT was associated with higher CR in patients with locally advanced SCCHN without unaccepted interruption of the treatment.

Key words: head and neck squamous cell carcinoma, chemoradiotherapy
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Original Article

INTRODUCTION

Head and neck squamous cell carcinomas (HNSCC) are the sixth most common cancers[1], with around two thirds of patients presenting with locally advanced disease[2].

The treatment of advanced disease poses a major challenge in terms of balancing tumor outcomes with acceptable toxicity and maintaining organ function[3,4]. For many years primary surgery and/or radiotherapy have been the mainstay of treatment[5].

Organ preservation using concomitant chemoradiotherapy has been accepted as an alternative to surgery[6-7].

The role of chemotherapy has gradually emerged, and is now taking a more prominent place in treatment algorithms for locally advanced HNSCC. The use of concurrent chemoradiotherapy has improved locoregional control, with optimal results being achieved with cisplatin[6,7]. Induction chemotherapy has been used in an attempt to gain the benefit of full therapeutic doses of chemotherapy via additive clonogen cell kill and spatial cooperation to treat distant micro metastatic disease, whilst avoiding the enhanced toxicity of concurrent treatment[8-9].

Here we present the outcomes for patients with locally advanced stage III-IVA &B HNSCC managed with

induction chemotherapy followed by chemoradiotherapy versus chemoradiotherapy alone.

PATIENTS AND METHODS

From March 2010 to March 2014 forty nine patients with histologically documented locally advanced stage III- IVA& B[10] head and neck squamous cell carcinoma were prospectively randomized (1:1 ratio) this study at Clinical Oncology Department, Faculty of Medicine, Tanta University Hospital. Each patient was required to meet the following criteria: age between 18 and 65 years; Eastern cooperative oncology group (ECOG) status0-2; no previous surgery, chemotherapy or radiotherapy treatment; measurable disease; adequate hematological, hepatic, and renal functions.

Institutional scientific and ethical committees approval was obtained before the start of trial, Patients with severe peripheral neuropathy, symptomatic heart failure, sever arrhythmia, active infection, pregnant or lactating mothers, active peptic ulcer disease, clinical hearing loss, and uncontrolled diabetes mellitus, any other uncontrolled medical illness, were considered as a contraindication for inclusion.

Group A (25patients) was treated with three cycles of chemotherapy followed by concurrent chemoradiotherapy. Group B (24 patients) were treated with concurrent chemoradiotherapy.

Four patients in group A were non evaluable for response, 2 due to protocol violation and 2 for irregular treatment schedule. In group B 4 patients were excluded, one dropped out, 1 due to protocol violation and 2 due to irregular treatment schedule. Evaluable patients for response were 21 in group A and 20 in group B Figure (1)

Treatment Plan

Induction chemotherapy

Induction chemotherapy consisted of 3 cycles of TPF; (Docetaxel) 75 mg/m^2 IV over half an hour, D1; P (Platinol) 75 mg/m^2 IV over one hour, D1; 5-flurourcil 750 mg/m^2 IV over 6 hours, D1-5 every three weeks. Hydration and adequate anti-emetic therapy were ensured for all patients (5HT3 antagonists and dexamethasone). Prophylactic granulocyte colony stimulating factor (G-CSF) was not allowed, but G-CSF was given to patients who experienced grade III neutropenia and febrile neutropenia.

Radiotherapy

Thermoplastic casts with two point stabilization of the head were used to immobilize all patients in suitable anatomic positions. Computed Tomography (CT) simulation was marked on the individual patient. Slice thickness was 3-5 mm. The mask of the patient was marked with radioopac labels with the help of laser beams.

Virtual simulation: The 3D conformal treatment plan was performed in consistency with ICRU (International Committee of Radiation Units and measurements) 50 and ICRU 62 guidelines[11-13]. The findings on clinical examination and CT and/ or MRI before RT were used to constitute the GTV (Gross Tumor Volume), the CTV (Clinical Target Volume) and the PTV (Planning Target Volume). GTV tumor delineation was done to include the primary tumor and GTV node consisted gross lymphatic metastasis. CTV (tumor and node) volumes were constructed by adding margins to GTV volumes as to clinical protocols and experiences for probable microscopic extension of disease. PTV volumes were planned by adding 0.5 cm to the CTV, for possible set-up errors. Internal margin has been neglected in this study

Radiation therapy was given using 3D conformal radiation technique. After casting the customized thermoplastic mold, computerized tomography scan simulation was done. The images were then transferred to planning system. After drawing the target volumes and organs at risk on the planning scans, external beam radiation was delivered to the primary and the nodal areas using 6 MV Linear Accelerator photons. A total dose of 6600-7000 cGy/33-35 fractions ; 200cGy/ fraction five days a week over a period of six to seven weeks was delivered.

The definitive curative radiation dose administered to the primary tumor was between 70 and 74 Gy, administered as fractions of 2 Gy per day 5 days per week. The dose administered to uninvolved lymph nodes was at least 50 Gy. Involved lymph nodes were to receive 60 to 74 Gy, depending on whether an elective neck dissection was indicated after completion of treatment or not.

Concomitant chemotherapy

Two cycles of cisplatin 20 mg/m^2 were given intravenous infusion(one hour), days1–4, plus 5-fluorouracil 750 mg/m^2/day intravenous infusion (4-6 hours), D1-4 during weeks 1 and 6 of radiotherapy.

Primary and secondary endpoints

The primary endpoint was complete response evaluated 6 weeks after the end of chemoradiotherapy While Secondary endpoints included time to disease progression (TTP), survival and safety.

Patients' evaluation

The pretreatment evaluation was conducted before the start of treatment. It consisted of history, physical

examination, dental, dietary, speech assessment, complete blood cell count, routine chemistry measurements, electrolytes, chest x ray, and abdomenoplevis ultrasound. All patients were investigated and staged with endoscopy, biopsy, computed tomographic (CT) scanning and/or magnetic resonance imaging (MRI) of head and neck region.

Laboratory investigations were repeated before every induction chemotherapy, and weekly during concurrent chemoradiation treatment. Radiological imaging procedures were repeated four weeks after completion of induction chemotherapy and 6 weeks after concurrent chemoradiation treatment.

Following completion of induction and concurrent treatment phases, tumor response was routinely evaluated by a detailed clinical examination of the head and neck, endoscopy and CT or MRI imaging of the primary site and the neck. Patients with less than a complete response were evaluated for surgery. Patients who were considered candidate for surgery by the multi-disciplinary team underwent salvage surgery of primary site and/or neck dissection.

Subsequently, patients were followed up by Chest X-ray, and abdominal ultrasonography every 3 months, CT scan and MRI of the primary site, endoscopy and primary site biopsy were done every 6 months.

Response and toxicity assessment:

Tumor was assessed according to WHO criteria[14]. A complete response (CR) was defined as the disappearance of all measurable lesion for ≥ 4 weeks proved by histopathology. A partial response (PR) was defined as a decrease of ≥ 50% of the sum of the products of the greatest perpendicular lesion diameters for≥ 4 weeks with no evidence of new lesions. No change (NC) was defined as a < 50% decrease or < 25% increase in the product of the greatest perpendicular lesion diameters with no evidence of new lesions for ≥ 4 weeks. Progressive disease (PD) was defined as an increase in any measurable lesions by ≥ 25% or the detection of new lesions. Patients with less than a complete response were evaluated for surgery. Patients who were considered suitable for surgery by the multi-disciplinary team underwent salvage surgery of primary site and/or neck dissection.

Toxicity was routinely documented prospectively using the NCIC-version 3.0 grading system for chemotherapy toxicity[15], and the RTOG system for radiotherapy toxicity[16-17].

Statistical analysis

The following endpoints were used for assessment: induction chemotherapy response, overall treatment response, progression-free survival (PFS), disease-free survival (DFS), and overall survival (OS). Survivals were analyzed using Kaplan-Meier curves[18].overall survival (OS) was determined as the time between histological diagnosis and death. Time to local relapse and systemic relapse were determined as time between histological diagnosis and local/systemic relapse, respectively. Distant metastases free survival (DMFS) was defined between the time between histological diagnosis after primary treatment ends that the patient survived without distant metastases. Progression free survival was the time during and after treatment during which cancer treated and doesn't get worse.

Variables compared between patients who received sequential chemoradiotherapy or concurrent chemoradiotherapy using the test or the Fisher exact test, and the log-rank test was used to compare survival curves. A value of <0.05 was regarded as statistically significant in 2-sided tests. Kaplan-Meier methods were used to evaluate time to disease recurrence or death. Cox regression was used for univariate and multivariate analyses to determine the potential risk factors associated with disease-free survival and overall survival. All statistical analyses were performed using SPSS statistical software version 21 (SPSS, Chicago, IL, USA).

RESULTS

From March 2010 to March 2014, 49 patients with stage III and IVA&B head and neck cancer were enrolled in the study. Median age was 53 years in both treatment groups. Group A (25patients) was treated with three cycles of chemotherapy followed by concurrent chemoradiotherapy. Group B (24 patients) were treated with concurrent chemoradiotherapy.

Four patients in group A were non evaluable for response, 2 due to protocol violation and 2 for irregular treatment schedule. In group B 4 patients were excluded, one dropped out, 1 due to protocol violation and 2 due to irregular treatment schedule. Evaluable patients for response were 21 in group A and 20 in group B Figure (1)

In group A, twenty patients were males (83.3%), while in group B eighteen patients (72%) were male.

The main characteristics' of both groups of both groups are shown in table (1) a statistically significant differences between both groups

Treatment Response

After induction chemotherapy, complete response occurred in 8 patients (38.1) , partial response occurred in seven patients (33.3%) with an overall response of 71.4% .

At the end of treatment the overall response was 81% (17/21) and 80% (16/20) in group A & B respectively which was statistically insignificant (*P*=0.064). In group A (TPF+CRT), 11/21 patients (52.4%) achieved complete response (CR) was higher than in group B (CRT) 20% (4/20) which was statistically significant (*P* value=0.0045) Table (2).

In group A, 9 (44.6%) underwent surgery after induction chemotherapy. Five patients with neck residual disease and 2 patients with residual disease both on the neck and primary site and two underwent neck dissection as initially N2–N3.

In group B, surgery was carried out in 13 of the 20 assessable patients (65%) . three patients with neck residual disease and 2 patients with residual disease both on the neck and primary site and 8 because they had initial stage N2–N3 disease.

Survival outcome:

Median follow-up of all patients was 38 months (range 7-42 months). Three year overall survival rates were 72.7% and 68.7% in arm A and B, respectively which was statistically insignificant (*P* value=0.4113) . Three year disease distant free survival rate in group A was 65.8% versus 60% in group B which was statistically insignificant (*P* value=0.3772). The three year progression –free survival was B 61.1% versus 53.8% in group A and B respectively which was statistically insignificant (*P* value=0.3345) Figure (2) Table (3).

Time to disease progression was 21.5 & 12 in group A &B respectively which was statistically significant (0.04).

Prognostic factor

In subgroup analysis, smoker and advanced disease 9 stage IV A & B. Patients had significant lower three PFS and OAS (P value (0.05) Table (4)

In group B, OAS was statistically higher in patients with hemoglobin level > 13 than patients with hemoglobin level less or equal to 13 gm/ dL (*P* value= 0.039), for stage III versus stage IV (*P* value=0.034), for stage III (*P*=0.033) and T2 versus T3 and T4 (*P* value= 0.0007). Cancer larynx than oro or hypopharynx (*P* = 0.03).

We analyzed age, sex, performance status, cigarette smoking, hemoglobin level, treatment line, cancer stage, and primary tumor location as prognostic factors for survival in all patients. Univariate analysis revealed that site (*P* value= 0.023*, hazard ratio [HR]: 1.700, 95% confidence interval [CI]: 1.077–2.683) had a significantly poor 3-year overall survival rate. Multivariate analysis revealed that site (*P* value= 0.001*, hazard ratio [HR]: 3.862, 95% confidence interval [CI]: 1.709–8.726) and T stage (*P* value =0.016*. HR =3.033, 95% CI (1.235-7.449).

In univariate analysis, none of these factors were associated with distant metastases free survival (DMFS), while on multivariate analysis, site is only prognostic factor of poor DMFS (*P* value=0.027*, HR=2.474 , 95% CI(1.106-5.533).

As regard progression free survival, both univariate and multivariate analysis revealed that site (*P* value=0.002*, HR=2.156, 95%CI(1.331-3.491) ;(*P* value=0.003* , HR=3.769 , 95%CI (1.555- 9.271) respectively.

Acute Toxicity

Induction chemotherapy

In group A, Grade 3 neutropenia occurred in 4 patients (26.7%). Two patients (13.3%) experienced grade 3 mucositis.

Chemoradiotherapy

During concurrent chemoradiotherapy, the incidence of hematologic and non-hematologic toxicities was more in the TPF plus chemoradiotherapy arm than in the chemoradiotherapy alone arm. The most common grade 3 hematologic toxicity was leucopenia in both groups (Table 4).The most frequent grade 3 nonhematologic toxicities were stomatitis and dysphagia (Table 4).No grade 4 hematologic or nonhematologic toxicity was reported in either arm.

Late Toxicity

Among15 surviving patients in group A, 2 (13.3%) suffered from late (> 6 months) grade 3 dysphagia. Among 10 surviving patients in group B , one patient had grade 3 dysphagia and 2 had trismus.

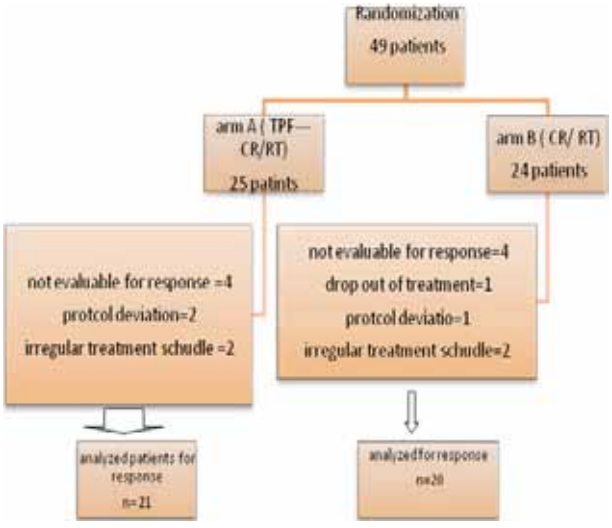

Figure 1: show patient flow chart

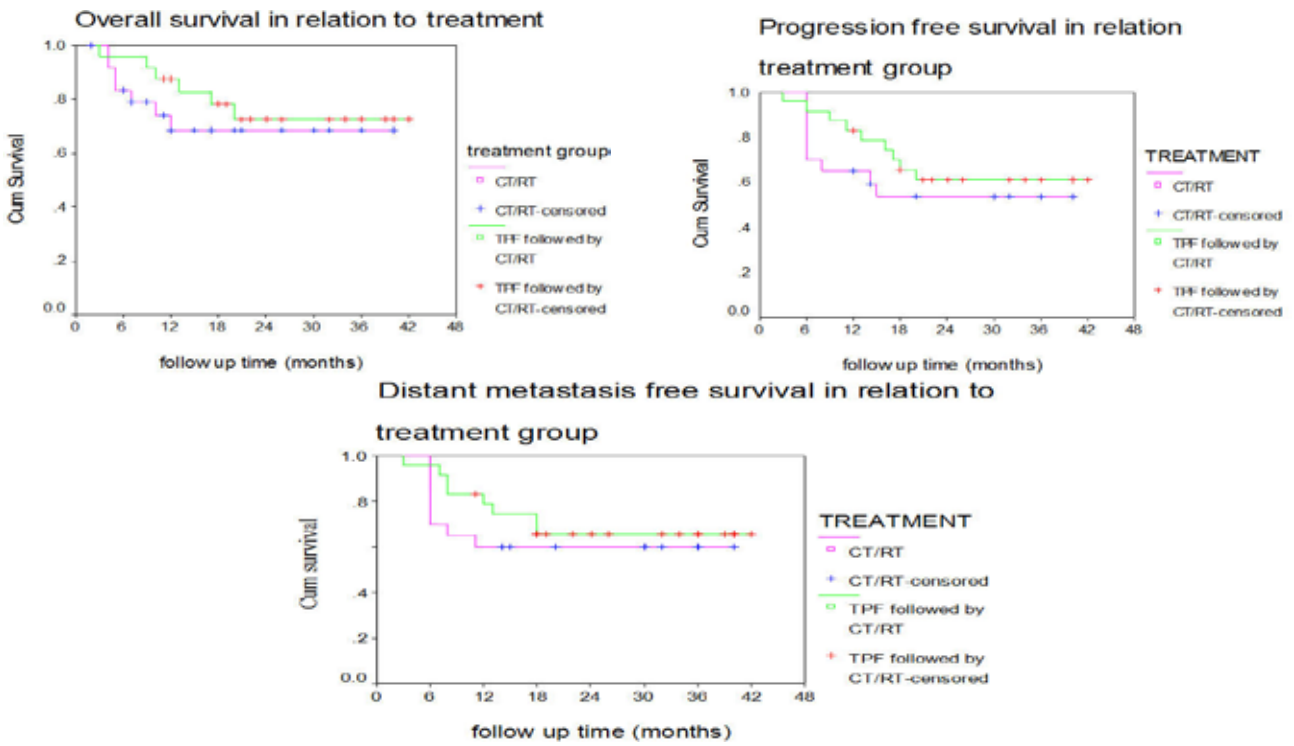

Figure 2: showed the overall, progression-free and distant metastasis free survival rates in relation to treatment group

Table 1: Main characteristics of all patients with locally advanced head and neck cancer in both study groups

Patient characteristics	Treatment group				
	TPF+CRT(24)		CRT(25)		
	No.	%	No.	%	
Age (Range)	37-65y		40-67		
Median	53		53		
Sex					
• Male	20	83.3	18	72	
• Female	4	16.6	7	28	0.273
Cigarette Smoking					
• Smoking	14	58.3	15	60	
• Non-smoking	10	41.7	10	40	0.906
Performance status					
• 0/1	19	79.2	14	56	
• 2	5	20.8	11	44	0.077
Pretreatment Hb-level					
• ≤13g/dL	16	66.7	21	84	
• >13g/dL	8	33.3	4	16	0.158
Tumor site					
• Oropharynx	4	16.7	4	16	
• Larynx	16	66.6	18	72	0.877
• Hypopharynx	4	16.7	3	12	
Clinical stage					
• III	5	20.8	18	72	
• IVA&B	19	79.2	7	28	0.376
T stage					
• T2	2	8.3	7	28	
• T3	10	41.7	9	36	
• T4	12	50	9	36	0.705
N stage					
• N0	3	12.5	2	8	
• N1	8	33.3	4	16	
• N2	11	45.8	12	48	0.474
• N3	2	8.4	7	28	

Table 2: Response after the end of treatment in both groups.

Response	Treatment group				
	TPF+CRT (21) Group A		CRT Group B		
	No.	%	No	%	*P*. value
CR	11	52.4	4	20	0.022*
PR	6	28.6	12	60	0.022*
CR+PR	17	81	16	80	0.064
SD	3	14.3	1	5	0.157
DP	1	4.8	3	15	0.157
Total	21	100	20	100	

Table 3: survival according to treatment group.

Survival	Sequential chemoradiotherapy	Concurrent chemoradiotherapy	*P* value
Three year Overall survival	72.7%	68.7%	0.4113
Three year PFS	61.1%	53.8%	0.3345
Three year DMFS	65.8%	60%	0.3772

Table 4: grade III hematological and non hematological toxicity in both study groups after end of treatment.

Acute toxicity	No of patients (%)	
	TPF+CRT (21)	CRT (20)
Hematologic		
Leucopenia	5(23.8)	3(15)
Neutropenia	3(14.3)	2(10)
Anemia	3(14.3)	2(10)
Nonhematologic		
Mucositis	8(38.1)	6(30)
Dysphagia	5(23.8)	3(15)
Skin reaction	5(23.8)	3(15)
Weight loss	3(14.3)	1(5)

DISCUSSION

Concurrent chemo-radiotherapy has been widely adopted as the standard of care for locally advanced HNSCC[19,20]. Cisplatin is the chemotherapy agent of choice, with studies showing a 5-12% improvement in long term survival with standard or altered fractionation regimens[21-22].

Induction chemotherapy followed by chemoradiotherapy is an alternative approach to concurrent treatment. It has shown a survival benefit in locally advanced HNSCC[23-24].

Although it has only a minimal survival benefit of 2% in a large meta-analysis, the combination of cisplatin and 5-FU was associated with a 5% survival benefit[25-28].

The role of systemic treatment in addition to radiotherapy in locally advanced HNSCC continues to develop. Concurrent chemo-radiotherapy remains a standard of care, while induction chemotherapy may have the same efficacy[22]. However, it remains uncertain whether combining induction with concurrent chemotherapy takes advantage of the benefits of both treatments. Studies are currently underway to investigate the potential superiority of induction chemotherapy followed by concurrent chemoradiotherapy compared with concurrent chemoradiotherapy alone.

This series of 49 patients reported here, demonstrates that induction chemotherapy can be successfully combined with concurrent chemoradiotherapy, without unaccepted toxicity. Radiotherapy commenced four weeks following the administration of the final cycle of chemotherapy. Therefore, induction chemotherapy did not preclude the prompt delivery of radiotherapy. Notably, by contrast with the EORTC/TAX323 trial[26], patients in this series completed radiotherapy as planned.

It should be noted that we used a similar chemotherapy protocol to that reported in ERTOC/TAX323 trial instead of five days) to minimize the expected grade 3 and but with 20% reduction in cisplatin and 5 fluorouracil dose and one day less (4 days instead of 5 days) to minimize the expected grade 3 and 4 toxicities that may interrupt radiotherapy[27]. Our protocol was similar to that reported by paccagnella *et al.*[27].

Concomitant chemotherapy was given to all patients in our series; therefore it can be concluded that induction chemotherapy did not compromise patient fitness to commence definitive concurrent chemoradiation.

The overall toxicity of induction chemotherapy followed by (chemo)-radiotherapy appears acceptable. There were no on-treatment deaths.

In our series, the complete response rate was 52.4% (11/21) and 20 % (4/20) in arm A and B respectively which was statistically significant (*P* =0.022).

Our results are nearly equal to that reported by Paccagnella *et al.*[28], in series of 101 patients were randomized to treatment: 50 patients received chemotherapy (three cycles of docetaxel, 75 mg/m^2, and cisplatin, 80 mg/m^2, on day 1, plus 5-FU, 800 mg/m^2 as a 96-hour continuous infusion every 3 weeks) followed by the same chemoradiotherapy regimen in the other arm and 51 patients received chemoradiotherapy alone (two cycles of cisplatin, 20 mg/m^2 on days 1–4, plus 5-FU, 800 mg/m^2 as a 96-hour continuous infusion, on weeks 1 and 6 during radiotherapy, 66–70 Gy).The complete response was 50% and 21% in group 1&2 respectively.

However our results are lower than that that reported by Ghi *et al.*[29], the CR rate was 62.5% for CRT and 80% for neoadjuvant TPF followed by CRT. This may be due the difference in the regimen given by Ghi *et al.* during the radiotherapy (carboplatin area under the curve 1.5 on Days 1-4 and 5-fluorouracil 600 mg/m^2/d continuous infusion for 96 h) starting on Days 1, 22, and 43 during RT).

Although complete response in the present series was higher in group A compare to group B, the difference in overall survival and disease distant free survival were statistically non significant which was similar to that reported by Paccagnella *et al.*[28]. The PARADIGM trial was a randomized phase III and reached the same conclusion with statistical significant advantage of neoadjuvant chemotherapy over concurrent chemoradiotherapy[30]. The DeCIDE study N2 and 3 disease reached the same conclusion[31].

In our series, time to disease progression was 21.5 & 12months in group A and B respectively which was statistically significant (*P* value =0.04).

The analysis of different prognostic factors with survival (OAS, DMFS, PFS) revealed that the site was the significant prognostic factors on multivariate analysis[25,27]. Also T stage was significant as regard oveall survival on multivariate analysis[32].

The main limitation of the work was the small sample size and relatively short follow up.

Conflict of interest

No conflict of interest was declared.

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